This is a free translation into English of Adocia reference document issued in the French language for informational purposes only

ADOCIA
innovative medicine for everyone, everywhere

A French *société anonyme* (corporation) with €621,187.60 in share capital

Registered office: 115 Avenue Lacassagne, 69003 Lyon

Lyon Trade and Companies Registry no. 487 647 737

2013 REFERENCE DOCUMENT

INCLUDING THE COMPANY'S

ANNUAL FINANCIAL REPORT

AND MANAGEMENT REPORT

AMF AUTORITÉ DES MARCHÉS FINANCIERS

Pursuant to the General Regulation of the French financial markets authority (*Autorité des Marchés Financiers* – "AMF"), in particular Article 212-13 thereof, the AMF filed this reference document on April 24, 2014 under number R14-020. This document may be used in support of a financial transaction only if it is supplemented by an offering circular approved by the AMF. This reference document was prepared by the issuer, and its signatories are liable for its content.

In accordance with Article L. 621-8-1-I of the French Monetary and Financial Code, this reference document was filed after the AMF verified that the document is complete and comprehensible and that the information it contains is coherent. This does not imply that the AMF has verified the accounting and financial information presented.

Copies of this reference document are available free of charge from the company at 115 Avenue Lacassagne, 69003 Lyon. In addition, an electronic version is available on the company's website (www.adocia.com) and the AMF website (www.amf-france.org).

TABLE OF CONTENTS

CROSS-REFERENCE TABLE

The cross-reference table below will facilitate locating in this reference document:

The information contained in the annual financial report (Article L. 451-1-2 of the French Monetary and Financial Code and Article 222-3 of the AMF's General Regulation); and

The information contained in the annual management report (Article L. 225-100 *et seq.* of the French Commercial Code).

Annual financial report	**Reference document**
1. Responsibility statement	§ 1.2
2. Corporate annual financial statements - French GAAP	§ 20.3
3. Corporate annual financial statements - IFRS	§ 20.1
4. Management report	See index below
5. Chairman's report on internal control	Appendix I
6. Annual information document	§ 5.1.6
7. Information on statutory auditors' fees	§ 2.3
8. Statutory auditors' report on the annual financial statements prepared under French GAAP and IFRS	§ 20.2 and 20.4
9. Statutory auditors' report on the chairman's report	Appendix II

Annual management report	**Reference document**
1. Position and business of the company during the past fiscal year	§ 6 and § 20
2. Review of financial statements and results – Appropriation of income – Information on dividends distributed – Non-tax deductible expenses	§ 9 and § 20
3. Information on supplier payment terms	§ 3
4. Progress made and difficulties encountered	§ 6
5. Major risks and uncertainties faced by the company / Use of financial instruments by the company	§ 4
6. Research and development activities	§ 6
7. Foreseeable changes and outlook	§ 6
8. Significant events since the fiscal year-end	§ 20.8
9. Equity interests held by employees	§ 17
10. Executive management of the company	§ 16
11. Information on corporate officers	§ 15.1
12. Acquisition of significant equity interests in, or control of, companies headquartered in France; disposals of such equity interests	§ 7
13. Activities of subsidiaries and controlled entities	§ 7
14. Information on shareholder structure and treasury shares – Share redemption programs	§ 18.1-18.2 and 21.1.4
15. Changes during the fiscal year to the company's shareholder structure	§ 21.1.8
16. Changes in the share price – Risk of price changes	§ 21.1.8
17. Summary of transactions in the company's securities during the past fiscal year by persons referred to in Article L. 621-18-2 of the French Monetary and Financial Code	§ 15.4, p. 134
18. Information required by Article L. 225-100-3 of the French Commercial Code	§ 16.6
19. Employment and environmental information	§ 8.3 – 8.4 et 17.7
20. Table showing the company's results over the last five fiscal years	§ 20.5
21. Authorizations to effect capital increases	§ 21.1.6

Notice

In this reference document, the terms "Adocia" and the "company" refer to Adocia, a French *société anonyme* (corporation) whose registered office is located at 115 Avenue Lacassagne, 69003 Lyon, France, and which is registered with the Lyon Trade and Companies Registry under number 487 647 737.

This reference document presents or incorporates by reference the company's audited financial statements for the fiscal years ended December 31, 2011, December 31, 2012 and December 31, 2013.

In accordance with Article 28 of Commission Regulation (EC) no. 809/2004 of April 29, 2004, the information below is incorporated by reference in this reference document:

- The following information in the reference document filed by the AMF on April 25, 2013 under no. R13-017: information from the board of directors' management report (listed on page 5), the corporate financial statements prepared under IFRS (pp. 173 to 201), the corporate financial statements prepared under French GAAP (pp. 205 to 219), the statutory auditors' report on the corporate financial statements prepared under IFRS, and the corporate financial statements prepared under French GAAP for the fiscal year ended December 31, 2012 (PP. 202 to 204 and 220 to 222);
- The following information in the 2011 annual financial report: the management report (pp. 62 to 103), the statutory auditors' report on pages 127-129 (consolidated financial statements) and pages 122-124 (annual financial statements), the consolidated financial statements prepared under IFRS (pp. 26 to 61), and the corporate financial statements prepared under French GAAP (pp. 5 to 25).

Information included in this reference document, other than the above information, has been, if necessary, replaced and/or updated by information in this reference document.

The corporate financial statements prepared under IFRS for the fiscal year ended December 31, 2013 are presented on pages 173 to 201 of this reference document. The statutory auditors' report on the corporate financial statements prepared under IFRS for the fiscal year ended December 31, 2013 is on pages 202 to 204 of this reference document.

The corporate financial statements prepared under French GAAP for the fiscal year ended December 31, 2013 are presented on pages 205 to 219 of this reference document. The statutory auditor's report on the corporate financial statements prepared under French GAAP for the fiscal year ended December 31, 2013 is on pages 220 to 222.

A glossary containing the definitions of certain technical terms used in this reference document, as well as an index of abbreviations used, can be found in Chapter 26. Terms indicated by an asterisk (*) are defined in the glossary.

Disclaimer

Market and competition information

This reference document contains, in particular in Chapter 6 "Overview of Activities", information about the company's markets and competitive position. This information is taken *inter alia* from studies conducted by external sources. Publicly available information that the company deems reliable has not been verified by independent experts, and the company cannot guarantee that a third party using different methods to collect, analyze or calculate data on these markets would obtain the same results.

Forward-looking information

This reference document contains information on the company's outlook and development priorities. At times, this information is identified by the use of the future or conditional tense or forward-looking words such as "consider", "plan", "think", "have as an objective", "expect", "intend", "should", "aspire to", "estimate", "believe", "wish", "could" or, where applicable, the negative form of these terms, or any variation thereof or similar terminology. This information is not historical data and should not be viewed as a guarantee that the facts and events described will occur. This information is based on data, assumptions and estimates that the company deems reasonable. It is subject to change or amendment due to uncertainties associated with *inter alia* the economic, financial, competitive and regulatory environment. This information is provided in the various sections of this reference document and includes particulars about the company's intentions, estimates and objectives with respect to *inter alia* the market in which it operates and its strategy, growth, results, financial position, cash position and forecasts. The forward-looking information in this reference document is provided only as of the filing date of this reference document. The company operates in a constantly changing competitive environment. Therefore, it cannot anticipate all risks, uncertainties and other factors that may affect its business, the potential impact thereof on its business, or the extent to which the occurrence of a risk or combination of risks could have significantly different results from those implied in any forward-looking information. Lastly, it should be kept in mind that none of this forward-looking information is a guarantee of actual results.

Risk factors

Investors are advised to carefully review the risk factors described in Chapter 4 "Risk Factors" of this reference document before making any investment decision. The occurrence of any or all of these risks may have a material adverse impact on the company's business, financial position, income and outlook. Furthermore, other risks of which the company is not aware or that it does not deem significant as of the filing date of this reference document may also have a material adverse impact.

1. PERSONS RESPONSIBLE FOR THE REFERENCE DOCUMENT

1.1. Person responsible for the reference document

Mr. Gérard Soula, Chairman and Chief Executive Officer

1.2. Responsibility statement

"I hereby certify, after having taken all reasonable measures to this effect, that to my knowledge the information contained in this reference document is accurate and contains no omissions likely to affect its import.

I hereby certify that, to my knowledge, the financial statements have been prepared in accordance with applicable accounting standards and give a true and fair view of the company's assets and liabilities, financial position and income, and that the information cross-referenced from the management report in the table on page 5 gives a true and fair view of the company's business trends, income and financial position, as well as a description of the main risks and uncertainties it faces.

I have obtained a letter from the statutory auditors certifying completion of their work in which they state that they have verified the information in this reference document relating to the company's financial position and financial statements, and that they have read the reference document in its entirety.

The statutory auditors have issued reports on the historical financial information presented in this document. The statutory auditors issued reports, without comments, on the annual financial statements for the fiscal year ended December 31, 2013. The reports are provided on pages 203 to 204 (corporate financial statements prepared in accordance with IFRS) and pages 220 to 222 (corporate financial statements prepared in accordance with French standards) of this reference document.
The statutory auditors issued reports on the financial information for the fiscal year ended December 31, 2012, which is incorporated by reference in this document. The reports are provided on pages 180 to 182 (corporate financial statements prepared in accordance with IFRS) and pages 204 to 206 (corporate financial statements prepared in accordance with French standards) of 2012 reference document no. R13-017, which was filed with the AMF on April 25, 2013.
The statutory auditors issued reports on the financial information for the fiscal year ended December 31, 2011, which is incorporated by reference in this document. The reports are provided on pages 128-129 (consolidated financial statements) and pages 123-124 (annual financial statements) of the 2011 annual report, which is posted on the www.adocia.com website."

Executed in Lyon, on April 24 avril 2014

Gérard Soula
Chairman and Chief Executive Officer

1.3. Person responsible for financial information

Ms. Valérie Danaguezian
Chief Financial Officer
Address: 115 Avenue Lacassagne, 69003 Lyon
Telephone: +33 (0) 4 72 61 06 10
Fax: +33 (0) 4 72 36 39 67
Email: contactinvestisseurs@adocia.com

2. STATUTORY AUDITORS

2.1. Principal statutory auditors

Odicéo
represented by Mr. Sylvain Boccon-Gibod, a partner
115 Boulevard Stalingrad, 69100 Villeurbanne
member of the Lyon regional statutory auditors' association

Appointed by a decision adopted by the sole shareholder on July 31, 2006 until the general shareholders' meeting convened to vote on the financial statements for the fiscal year ended December 31, 2011. This term of office was renewed by the general shareholders' meeting held on June 15, 2012 for a period of six fiscal years, which will expire at the conclusion of the ordinary general shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2017.

Ernst & Young et Autres
represented by Mr. Sylvain Lauria, a partner
41 Rue Ybry, 92200 Neuilly-sur-Seine
member of the Versailles regional statutory auditors' association

Appointed by the combined general shareholders' meeting held on October 24, 2011 for a period of six fiscal years, which will expire at the conclusion of the ordinary general shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2016.

2.2. Alternate statutory auditors

Mr. Pierre Grafmeyer
115 Boulevard Stalingrad, 69100 Villeurbanne
member of the Lyon regional statutory auditors' association

Appointed by a decision adopted by the sole shareholder on July 31, 2006 until the general shareholders' meeting convened to vote on the financial statements for the fiscal year ended December 31, 2011. This term of office was renewed by the general shareholders' meeting held on June 15, 2012 for a period of six fiscal years, which will expire at the conclusion of the ordinary general shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2017.

Auditex
Tour Ernst & Young, Faubourg de l'Arche, 92037 La Défense Cedex,
member of the Versailles regional statutory auditors' association

Appointed by the combined general shareholders' meeting held on October 24, 2011 for a period of six fiscal years, which will expire at the conclusion of the ordinary general shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2016.

During the period covered by the historical financial information, no statutory auditor has resigned or been removed from office.

2.3. Certificate of fees paid to statutory auditors

The table below shows the statutory auditors' fees that the company has paid during the last two years:

(€ thousands)	Ernst & Young		Odicéo	
	2013	2012	2013	2012
Audit services				
* statutory auditor services, certification, review of individual and consolidated financial statements	30	23	30	23
* other services and due diligence directly related to the statutory audit assignment				
Subtotal	30	23	30	23
Other services				
* tax				
* others				
Subtotal				
TOTAL	**30**	**23**	**30**	**23**

The amounts above do not include VAT.

3. SELECTED FINANCIAL INFORMATION

The selected financial information presented in this Chapter 3 is taken from the company's financial statements for the fiscal years ended December 31, 2012 and December 31, 2013, which were prepared in accordance with IFRS and are shown in section 20.1 of this reference document.

This financial information should be read in conjunction with (i) the review of the company's income and financial position presented in Chapter 9 of this reference document and (ii) the review of the company's cash position and equity presented in Chapter 10 of this reference document.

Selected financial information for the fiscal years ended December 31, 2012 and December 31, 2013 (IFRS)

Selected financial information taken from the income statement:

(IFRS - € thousands)	**FY 2013 (12 months)**	**FY 2012 (12 months)**
Revenue from licenses	5 636	2 104
Research and cooperation agreements	(47)	1 892
Sales (a)	**5 588**	**3 995**
Research tax credit	3 215	3 061
Project and other financing	19	180
Other revenue (b)	**3 234**	**3 241**
Operating revenue (a)+(b)	**8 822**	**7 236**
Research and development expenses	(11 475)	(11 784)
General and administrative expenses	(1 649)	(1 522)
Advances	(12 764)	(12 887)
Grants	(360)	(419)
Operating expenses	**(13 124)**	**(13 306)**
OPERATING INCOME / (loss)	**(4 302)**	**(6 070)**
FINANCIAL INCOME	**9**	**75**
NET INCOME / (loss)	**(4 293)**	**(5 995)**

(*) Up-front payment of $10 million (€7.6 million) received from Eli Lilly recognized for an amount of €1.905 million in 2012 and €5.636 million in 2013.

Selected financial information taken from the balance sheet:

(IFRS - € thousands)	FY 2013 (12 months)	FY 2012 (12 months)
NON-CURRENT ASSETS	**1 194**	**1 281**
of which: laboratory equipment	528	555
of which: other fixed tangible assets	418	384
CURRENT ASSETS	**23 535**	**35 345**
of which: cash and cash equivalents	19 415	30 462
TOTAL ASSETS	**24 729**	**36 627**
EQUITY	**19 130**	**23 028**
NON-CURRENT LIABILITIES	**2 066**	**2 244**
of which: long-term financial debts	1 814	2 046
CURRENT LIABILITIES	**3 532**	**11 354**
TOTAL LIABILITIES	**24 729**	**36 627**

Selected financial information taken from the cash flow statement:

(IFRS - € thousands)	FY 2013 (12 months)	FY 2012 (12 months)
Net cash flow generated by the business	(10 796)	919
Net cash flow in connection with investment transactions	57	(1 774)
Net cash flow in connection with financing transactions	(309)	25 413
CHANGES IN NET CASH	**(11 047)**	**24 558**
Cash and cash equivalents at the start of the year	30 462	5 905
Cash and cash equivalents at year-end	19 415	30 462

4. RISK FACTORS

Investors are invited to consider all information contained in this reference document, including the risk factors described in this chapter, before deciding to purchase or subscribe for the company's shares. The company has reviewed the risks that may have a material adverse impact on the company, its business, financial position, income, outlook or ability to achieve its objectives, and it considers that there are no significant risks other than those described herein.

Nevertheless, investors' attention is drawn to the fact that there may or could be other risks that are unknown or have not been considered as of the filing date of this reference document, and which may have a material adverse impact on the company, its business, financial position, income or outlook.

4.1. Risks associated with implementation of the company's strategy

The company may not be able to enter into the partnership agreements on which its medium-term strategy depends.

The company's medium-term strategy depends on its ability to enter into lasting partnership agreements with major players in the pharmaceutical, biotechnology and medical devices industries, on the basis of the results of feasibility studies and clinical trials it conducts.

The company does not plan to produce or market its products and does not have the human and physical resources necessary to develop, manufacture and market therapeutic products using its technology. Therefore, placing such products on the pharmaceutical, biotechnology or orthopedic markets requires entering into partnership agreements with industrial partners that have the human, material and financial resources necessary to conduct and successfully complete the clinical trials required by law.

The company's expansion strategy is therefore to license products derived from its BioChaperone® technology to industrial partners when proof of concept* has been obtained for humans or animals. Accordingly, the company plans to sign partnership agreements, pursuant to which its partners will be responsible for developing, manufacturing and marketing products incorporating the company's technology and will agree to pay royalties to the company on any sales of such products.

However, the company cannot guarantee that it will be successful in finding industrial partners for its projects because it does not control the final decision of each partner that may market its technology as to whether or not to pursue the development of the relevant product to fruition.

Therefore, the company is structurally dependent on its partners' interest in its technology, as well as on their diligence in continuing the development of products incorporating this technology, even if they conclude a license agreement with the company.

Furthermore, the company's current and future partners could encounter difficulties in obtaining technical and clinical approvals for the company's technology. Any resulting delays or refusals may hinder or impede marketing of the relevant products.

Moreover, these partners may not employ all the resources necessary to obtain the results expected from the agreements entered into with the company. In particular, if these partners experience budgetary restrictions or give priority to other development programs, this could delay approval of potential products incorporating the company's technology, which is an indispensable stage for the success of its commercial policy.

In addition, conflicts could arise between the company and certain of its industrial partners. In particular, the company cannot guarantee that none of its partners will design or attempt to set up a commercial business that uses a technology that competes with that of the company, or uses all or part of the company's technology, and which would therefore compete with the company's business (see the section below on risks associated with competition).

The company also cannot rule out that certain partners with which it works or may work pursuant to research contracts, or with which it signs license agreements or plans to sign license agreements in the future, will limit or end their relationships with the company. A conflict of interest could arise between some of their own activities and those they carry out with the company, which would deprive the company of such partners' expertise. This would cause the company to lose know-how and expertise and could even lead to the disclosure of key confidential information derived from the company's research and development program, despite the fact that the relevant partners may be contractually bound to the company by a confidentiality obligation.

It cannot be ruled out that these agreements will not provide the protection expected or that they will be breached (see the section below on risks associated with competition).

Such delays and/or failures and/or competitive actions on the part of the company's partners could materially impact the company's business, financial position, income, expansion and outlook.

4.2. Risks associated with the company's business

4.2.1. The company is dependent on its BioChaperone® and DriveIn® technological platforms

The company does not plan to develop or market therapeutic products directly. Its strategy is to develop innovative formulations for various therapeutic proteins* based on its BioChaperone® and DriveIn® technologies, and then to license use thereof to major players in the pharmaceutical and medical devices industries, which would then develop and market therapeutic products.

Therefore, the company's medium and long-term business, financial position, income, expansion and outlook will depend to a significant extent on its ability to protect and enhance the value of its BioChaperone® and DriveIn® technological platforms.

4.2.2. The research programs that the company and/or its partners undertake with the goal of developing products that incorporate its technologies may be delayed or prove unsuccessful

The research and clinical trials that the company carries out itself may be insufficient to convince major players in the pharmaceutical and medical devices industries to sign license agreements for the company's technologies for the purpose of continuing such work and studies until a product incorporating the company's technologies is placed on the market.

Furthermore, after license agreements are signed, products in the human health field that incorporate the company's technologies must still undergo clinical trials in order to be approved by the regulatory authorities with jurisdiction before such products are placed on the market. The approval process is long and costly, and its outcome is uncertain. Moreover, the fact that the regulatory authorities in one country grant approval does not guarantee that approval will be obtained in other countries.

The company is not assured that the authorizations required to carry out the clinical trials necessary to place on the market products that incorporate its technologies in the countries targeted will be obtained. Similarly, the Company can not predict the time that will be necessary for regulatory authorities to review and approve the files submitted to them, in particular as regards the procedure in India (see paragraph 6.1.3).

The completion of clinical trials will depend on various factors, such as the therapeutic indication in question, the size of the population affected, the nature of the clinical protocols, the proximity of patients to clinical test sites, the eligibility criteria for trials, competition for the recruitment of patients, and compliance with regulatory requirements.

Moreover, the company cannot guarantee that clinical trials that are authorized will be completed within the planned timeframes. In addition, the data obtained from these clinical trials may be subject to differing interpretations, which may delay, restrict or prevent obtaining regulatory authorization, in particular if the clinical data is deemed incomplete.

Lastly, at each stage of a product's progress through the clinical trials, there will be a significant risk of failure that may prevent continued development of a drug candidate, such as intolerance to the product, insufficient therapeutic benefits, or side effects. The company, its relevant partners or the regulatory authorities may suspend or terminate clinical trials if they deem that the subjects participating in the trials are exposed to health risks.

The inability of the company and/or its partners to successfully complete the necessary clinical trials could cause the development of the company's research programs and technologies to fail or be delayed.

The company's medium and long-term business, financial position, income, expansion and outlook could be materially impacted by the occurrence of one or more of these risks.

4.2.3. The company cannot guarantee that products based on its technologies will be marketed at some point, nor can it predict how long it may take to place products on the market

With the exception of research and development, the technologies that the company has developed have not yet led to the marketing of products. It may take several years before products are available to end users, primarily due to the time periods necessary to develop products and obtain marketing authorization.* This is due to the fact that the company's technologies are relatively recent.

Furthermore, the company and its industrial partners may be unsuccessful in developing such therapeutic products for applications in the health field.

The innovative therapeutic protein formulations that the company intends to provide its future industrial partners for incorporation into their own products may also not prove to be effective and/or innocuous enough to justify marketing them.

In any event, the rate at which products incorporating the company's technologies are marketed by its partners and the success thereof depends on various factors, such as:

- the results of ongoing and future clinical trials;
- their acceptance by the relevant medical community; and/or
- the intensity of sales efforts deployed by the company.

The company cannot guarantee that products incorporating its technologies will be placed on the market at all or within the estimated time periods, that the medical community will view them favorably, or that its partners will employ the resources necessary to successfully market such products.

4.2.4. Therapeutic products already exist for the pathologies that the company targets and the emergence of new competing technologies or new therapeutic products cannot be ruled out

The research into products incorporating the company's technologies targets markets in which there already exist therapeutic products, some of which are very widely used. In addition, therapeutic products or competing technologies, whether in existence, in development or unknown to date, could at some point in the future gain significant market share and limit the ability of the company and its partners to successfully market products that incorporate the company's technologies.

The company's competitors may also develop new therapeutic products or new technologies that are more effective, safer and/or less expensive than those that the company has developed, which could result in lower demand for the products incorporating its technologies.

The company's medium and long-term business, financial position, income, expansion and outlook could be materially impacted by the occurrence of one or more of these risks.

4.3. Risks associated with the company's organization

4.3.1. The company may lose key employees and may not be able to attract other qualified persons

To a large extent, the company's success depends on the involvement and expertise of its managers and expert scientific staff.

Despite the fact that the company has taken out a "key person" insurance policy covering its chairman (see section 4.7 entitled "Insurance and risk coverage"), his departure or the departure of other key founders or employees of the company could cause:

- a loss of know-how and be detrimental to certain activities, a risk that would be even greater in the event of a move to the competition; or
- a lack of technical skills that could slow down the business and ultimately compromise the company's ability to achieve its objectives.

Furthermore, in the future, the company will need to recruit expert scientific staff to expand its activities. The company is in competition, in particular with other companies, research organizations and educational institutions, to recruit and retain highly qualified scientific, technical and management staff. Due to the fact that this competition is particularly intense, the company may be unable to attract or retain these key staff members under financially acceptable terms.

The company's inability to attract and retain key staff members could prevent it from achieving its global objectives and could have a material adverse impact on its business, income, financial position, expansion and outlook.

4.3.2. Risks associated with management of the company's internal growth

In connection with its expansion strategy, the company will need to recruit additional staff and expand its operating capacity, which may heavily tax its internal resources.

In this respect, the company will *inter alia* have to:

- train, manage, motivate and retain a growing number of employees;
- plan for the expenses associated with this growth and the corresponding financing requirements;
- anticipate the demand for its products and the revenue they may generate; and
- increase the capacity of its existing operating, financial and management IT systems.

The company's inability to manage its growth, or if it encounters unexpected difficulties during its expansion, could have a material adverse impact on its business, income, financial position, expansion and outlook.

4.3.3. Risks associated with the procurement of specific proteins

The innovative therapeutic protein formulations that the company develops require an association of polymers* developed by the company with specific proteins supplied by third parties. The company cannot guarantee that it will always have access to the specific proteins necessary for the future development of its projects, nor can it guarantee access thereto under acceptable terms.

The company's general policy is to diversify its sources of supply and to identify at least two suppliers for each type of purchase. Nevertheless, in the case of proteins, the various sources of supply are not interchangeable due to the specificities of each protein. Consistently with current practices in the company's business sector, a single source of supply is maintained for each protein. The company has come up with alternative solutions, but implementing them could delay the development of its innovative formulations and generate additional costs.

The inability of the company or its partners to obtain, on financially acceptable terms, one or more specific proteins of sufficient quality necessary for the development of its projects could have a material adverse impact on its business, income, financial position, expansion and outlook.

4.3.4. Risks associated with the outsourcing of clinical trials

The clinical trials indispensable to obtaining proof of concept in order to license the company's technologies have been outsourced to specialized healthcare institutions, which generates risks associated with the choice of such institutions. Operational difficulties could also arise, in particular due to the distance from or geographical distribution of the clinical study centers.

4.4. Regulatory and legal risks

During the 12 months prior to the filing date of this reference document, the company has not been involved in any government, judicial or arbitration proceedings that have had or may have a material adverse impact on the company, its business, financial position, income or outlook and that is not reflected in its financial statements. Furthermore, to the company's knowledge, as of the filing date of this reference document, the company is not threatened with any such proceedings (see section 4.8 of this reference document entitled "Extraordinary events and disputes").

4.4.1. Risks associated with an increasingly strict regulatory environment for the pharmaceutical industry

One of the most significant challenges faced by a growth company such as Adocia is to succeed in developing, with the assistance of its partners, products incorporating its technologies in an increasingly strict regulatory environment.

The statutory and regulatory provisions adopted by the AFSSAPS,* European Commission, EMA,* FDA* and equivalent regulatory authorities in other countries govern research and development work, preclinical trials, clinical trials, the regulation of institutions, and the production and marketing of drugs.

The trend toward stricter statutory and regulatory supervision is worldwide, although requirements vary from one country to another. The health authorities, in particular the FDA and EMA, have imposed increasingly strict requirements to prove the effectiveness and safety of products, in particular with respect to the volume of data requested.

Accordingly, the authorization process is long and costly. It may last several years and its outcome is unpredictable.

Thus, whether in the United States, Europe or other countries, this strict regulatory framework may result in:

- increased costs in connection with the development, testing, production and marketing of products incorporating the company's technologies;
- a restriction as to the indications for which the products incorporating the company's technologies may be marketed;
- significant delays in obtaining marketing authorization for products incorporating the company's technologies and, consequently, in the generation of current revenue for the company.

4.4.2. Specific risks associated with the preclinical and clinical trials that will be necessary to obtain marketing authorizations for therapeutic products that use the company's technologies

Conducting preclinical trials on animals and clinical trials on humans is indispensable for obtaining marketing authorization for products incorporating the company's technologies. In general, these trials are conducted over several years and are very costly.

These studies and trials must be conducted by preclinical and clinical research centers. Therefore, the quality and motivation of such centers will depend to a large extent on the ability of the company and its partners to choose appropriate preclinical and clinical research centers and, in the case of human trials, on the ability to recruit the necessary number of patients within relatively short time periods in order to be able to publish results quickly, as well as on the ability to choose, if applicable, the appropriate service providers to implement the trial protocol designed by the company or its partners. The distance from or geographical distribution of the clinical or preclinical trial centers may also create operating and logistical difficulties, which may generate additional costs and delays.

If the company or its partners are unable to recruit patients as expected, which would delay the clinical trials and the publication of their results, learned societies and professionals in the relevant medical fields may be slow to accept products incorporating the company's technologies, which would affect the marketing thereof, and which could have a material adverse impact on the company, its business, financial position, income, expansion and outlook.

4.4.3. Specific risks associated with obtaining marketing authorization

In Europe, the United States and Japan, as well as in many other countries, access to the drug market is controlled and marketing must be authorized by a regulatory authority.

Obtaining marketing authorization requires compliance with strict rules imposed by the regulatory authorities, as well as providing the authorities with significant quantities of information about the new product, such as its toxicity, dosage, quality, effectiveness and innocuousness. The process to obtain marketing authorization is long and costly, and the result of such process is uncertain.

To obtain marketing authorization for a product incorporating the company's technologies, the partner that the company selects for a particular product may be required to conduct preclinical trials on animals and complete clinical trials on humans in order to prove the safety and effectiveness of the product. If patients are exposed to serious unforeseen risks, the company, the relevant partner or the regulatory authorities may suspend or terminate such clinical trials.

If a partner of the company is unable to obtain marketing authorization for one or more products incorporating its technologies, the marketing thereof would be compromised, which would have a definite impact on the company's income and profitability. Even if marketing authorization is

obtained, the company nevertheless runs the risk that such authorization may be suspended, in particular in the event of non-compliance with manufacturing rules or if undesirable side effects are discovered.

4.4.4. Risks associated with uncertain protection for the company's patents and other intellectual property rights

The company may be unable to adequately protect its intellectual property rights and, consequently, may lose its technological and competitive advantage.

To protect its innovative therapeutic protein formulations and technologies, the company relies on the protection afforded by intellectual property rights, such as patents, patent applications, trademarks and trademark applications, as well as the protection afforded to its trade secrets and know-how by confidentiality agreements and other contracts. However, these means offer only limited protection and may not prevent illicit use of the company's products or technologies.

The patents and patent applications that the company has filed and that protect its technologies are recent. They have been filed only since the company's creation. These patents and patent applications afford protection that varies in duration from one country to another. For example, in France and in Europe, this duration is 20 years from the date patent applications are filed. The company devotes significant financial and human resources to protecting its technologies, and employs the means commonly used in the industry (such as filing additional results that allow expanding one or more patent claims) to extend the protection of its technologies beyond such period, although it cannot guarantee the results thereof. To the company's knowledge, its technologies are well protected by the patents and patent applications it has filed.

In addition, the company regularly files trademarks. These trademarks have been registered or are undergoing examination, and have not been the subject of any disputes, with one exception that was quickly settled. When it files any of its trademarks in a country in which it is not already covered, the company could discover that the trademark in question is not available in that country. In such case, a new trademark would have to be found for such country. The company does not yet use its trademarks because it is still in the development stage. Nevertheless, the trademarks are not yet vulnerable, i.e., subject to revocation for non-use, and no affidavits of use are currently required to maintain them.

The company could experience difficulties in being granted certain of the patents or trademarks for which it has filed applications and that are currently undergoing the examination or registration process.

Furthermore, the fact that a patent or trademark is granted does not guarantee that it will be valid or enforceable. In fact, the company's competitors could at any time successfully challenge the validity or enforceability of the company's patents, patent applications, trademarks and trademark applications before the courts or in other proceedings, which, depending on the outcome of such disputes, may result in their scope being limited, their revocation or their circumvention by competitors. Consequently, the company's rights under its patents, patent applications, trademarks and trademark applications may not afford the expected protection from competitors.

Therefore, the company cannot guarantee with certainty that:

- the company's patent and trademark registration applications undergoing examination will, in fact, result in patents and trademarks being granted; and
- the patents and trademarks granted to the company will not be disputed or revoked.

The exclusive nature of the company's intellectual property rights could be circumvented by third parties or the company's competitors.

The company cannot guarantee that its technologies and the innovative therapeutic protein formulations developed using its technologies, which are closely tied to its know-how and trade secrets, are adequately protected from competitors or that competitors cannot misappropriate or circumvent them. Pursuant to the cooperation and research agreements that the company enters into, the company may be required to provide its contractual partners, in various forms, with certain elements of its know-how, whether or not protected by patents, in particular information, data and facts concerning its research, technologies or products.

The company attempts to limit disclosure of key elements of its know-how to third parties solely to information that is strictly necessary to its collaboration with such third parties and, through contractual provisions, in particular confidentiality clauses, ensures that such third parties undertake not to misappropriate, use or disclose such information. Nevertheless, the company cannot guarantee that such third parties will comply with these agreements, that the company will be aware of a breach of these clauses, or that any compensation that may be subsequently obtained will be sufficient in light of the loss sustained.

Furthermore, the company faces the risk that its contractual partners may claim ownership of intellectual property rights in the company's inventions, knowledge or results, based on these cooperation and research agreements. Lastly, these agreements may lead to the creation of intellectual property rights that are jointly owned or to exclusive rights of use granted to the company on unfavorable terms.

Therefore, the company cannot guarantee with certainty that:

- its know-how and trade secrets cannot be misappropriated or circumvented;
- the company's competitors have not already developed a technology or products similar to those of the company;
- the scope of the protection afforded by patents and trademarks is sufficient to protect the company from the competition or third party patents and trademarks that cover similar products or devices; and
- no contracting partner will claim ownership of intellectual property rights in the company's inventions, knowledge or results.

It cannot be ruled out that the company will bring legal action or that legal action will be brought against it.

The company cannot guarantee that there are no prior patents owned by third parties that may provide grounds for an infringement action against the company.

In addition, the company cannot guarantee that there are no prior third party trademark rights that may provide grounds for an infringement action against it. However, such risks seem limited in light of past examination procedures (in particular, in India, Japan, China and the United States) and opposition proceedings which have been filed and which have been unsuccessful to date.

The company's domain names could also be the subject of Uniform Domain Name Dispute Resolution Policy (UDRP*) proceedings or an infringement action brought by a third party claiming prior trademark rights. To date, no such action has been initiated by a third party, which leads the company to think that these risks are limited.

The company incurs significant costs in protecting intellectual property rights, in particular, filing fees and the costs of maintaining patents in force and managing its other intellectual property rights.

These costs could increase, in particular if the company is obliged to take legal action to protect its rights. In addition to these costs, if legal action becomes necessary to enforce the company's intellectual property rights, protect its trade secrets or know-how, or to establish the validity and scope of its intellectual property rights, this could have an adverse impact on the company's income and financial position and may not provide the protection sought.

Moreover, monitoring unauthorized use of products and technologies is difficult, and the company cannot be sure that it will be able to prevent misappropriation or unauthorized use of its products and technologies, in particular in foreign countries where its rights may be less well protected.

Therefore, the company cannot guarantee with certainty that its products do not infringe patents or trademarks owned by third parties or that the company will not bring legal action to enforce the monopoly granted by its trademarks, patents and domain names.

The occurrence of one or more of these risks could have a material adverse impact on the company's business, financial position, income, expansion and outlook.

4.4.5. Risks associated with the inability to protect the confidentiality of the company's information and know-how

Although the company strives to protect the confidentiality of its information and know-how, in particular by means of clauses in its contracts with third parties, it cannot guarantee that this confidentiality obligation will not be breached by its contractual partners.

Similarly, although the company protects its intellectual property rights, which are closely tied to its know-how, in particular by filing patents, it cannot guarantee that its rights and know-how will not be violated, misappropriated or circumvented by third parties.

4.4.6. Risks associated with potential conflicts with licensees that may impact the company's relationships with current or potential licensees

The company's expansion strategy is to license innovative therapeutic protein formulations developed using its technologies to pharmaceutical, biotechnology and orthopedic companies. Accordingly, entering into license agreements, and the outcome thereof, is essential for the company.

However, conflicts may arise with licensees during the term of their contracts with the company, which may impact the performance thereof and, consequently, the production and marketing of products incorporating the company's technologies. Such conflicts could concern the manner in which the contracts were concluded or proper performance by either party of its obligations under such contracts.

4.4.7. Risks associated with product liability

The company may be held liable to patients or healthy volunteers who take part or have taken part in clinical trials conducted under its direction if they suffer side effects in connection with such trials, despite the fact that the instructions in the protocols have been followed.

The company may also be liable in the event of commercial use of products incorporating its technologies. Criminal or civil actions could be filed or initiated against the company by users (patients, practitioners, researchers and other health care or research professionals), the regulatory authorities, distributors or any other third party that uses or markets products incorporating its technologies.

To date, the company has never been the subject of any such claims of liability. Moreover, it has taken out specific insurance policies to cover the financial risk as a result thereof (see section 4.7 entitled “Insurance and risk coverage”).

4.4.8. Risks associated with price setting and changes in drug reimbursement policies

At the conclusion of the regulatory authorization stage and when marketing authorization has been granted, the process of setting the sale price of drugs and their reimbursement rate begins. In many markets, including France, this process depends on decisions made by public commissions and bodies on the basis of pharmacological and financial data submitted by applicants. In connection therewith, the company’s partners may be requested to carry out additional studies of their products incorporating the company’s technologies. Such studies would generate additional costs for the relevant partners and marketing delays, and would therefore impact the company’s financial position.

The price, as set by public commissions and bodies, will depend on a rate deemed acceptable for the community, applying a policy that seeks to control health costs. The price set will condition the ability of the company’s partners and, indirectly, of the company to earn profits on the sale of the corresponding products. Moreover, if a product of the company is not granted an appropriate reimbursement rate, its profitability will be reduced.

Furthermore, the company’s level of remuneration may change during the period in which products incorporating its technologies are marketed by its partners, in particular due to the reimbursement rate for such products, which may change significantly over time.

4.4.9. Health and safety risks associated with hazardous substance use, technical facilities and the environment

Research and development activities in the biological field require the use of certain hazardous biological or chemical substances. Although the company has adopted a policy appropriate for the types of risks generally identified in biological research laboratories, it cannot rule out all risk of accidents in its laboratories resulting in contamination or injury to its research teams. In the event of an accident, the company could be held liable and be ordered to pay significant damages to affected employees.

Furthermore, the laws currently in force may be amended significantly, which could cause the company to incur considerable expenses to comply therewith.

The company’s medium and long-term business, financial position, income, expansion and outlook could be materially impacted by the occurrence of one or more of these risks.

4.5. Financial risks

4.5.1. History of operating losses – Risks associated with forecast losses

Since its creation in 2005, the company has posted operating losses each year. As of December 31, 2013, its total net losses (including losses carried forward) were €30.3 million, including a net loss of €4.3 million for the fiscal year ended December 31, 2013. These losses are mainly due to internal and external research and development expenses, in particular in connection with the numerous in vivo and clinical trials conducted.

As its research and development activities continue, the company may experience additional operating losses in future years, which may be higher than in the past, in particular due to:

- increased research and development costs associated with the development of its projects as they progress (due, in particular, to the need to conduct clinical trials, without any guarantee as to the point at which such costs may be assumed by the partners with which the company plans to enter into license agreements);
- stricter regulatory requirements governing the manufacturing of its products;
- a larger project portfolio; and
- expanded research and development activities and, perhaps, the acquisition of new technologies, products or licenses.

An increase in such expenses could have a material adverse impact on the company and its business, financial position, income, expansion and outlook.

4.5.2. Uncertain equity resources and uncertain additional financing

In the future, the company will continue to have significant financing needs in order to develop its technologies. The company may be unable to finance its growth itself, which would require it to seek other sources of financing, such as increasing its equity through capital increases and/or taking out bank loans.

The company's financing needs and the timing thereof depend on factors that are largely beyond the company's control, such as:

- higher costs and slower progress than anticipated for its research and development programs and clinical trials;
- the costs of preparing, filing, defending and maintaining its patents and other intellectual property rights;
- the scope of preliminary research work and the time periods necessary to conclude license agreements with industrial partners;
- the costs necessary to deal with technological developments and markets;
- higher costs and longer time periods than anticipated to obtain regulatory authorizations, including the time required to prepare applications to be submitted to the authorities with jurisdiction; and
- new development opportunities for new products or the acquisition of technologies, products or companies.

The company may be unable to procure additional capital when needed, or such capital may not be available on financial terms acceptable to the company. If the necessary funds are unavailable, the company may be required to:

- delay, reduce or cancel research programs;
- obtain funds by entering into partnership agreements, which may oblige it to give up the rights to certain of its technologies or products;
- grant licenses to all or part of its BioChaperone® and DriveIn® technological platforms to partners or third parties; or
- enter into new cooperation agreements, which may be less favorable to the company than those it would have been able to negotiate in a different context.

Furthermore, if the company raises capital by issuing new shares, the stakes of its shareholders may be diluted. In addition, debt financing, if available, could impose restrictive terms on the company and its shareholders.

The occurrence of one or more of these risks could have a material adverse impact on the company and its business, financial position, income, expansion and outlook.

4.5.3. Dilution risk

Pursuant to its policy to motivate its managers, directors and employees, since its creation, the company has issued or granted stock warrants and business founders' stock warrants (BSPCE), and has granted bonus shares. The maximum possible dilution from financial instruments in existence as of December 31, 2013 is 1.50% on a fully diluted capital basis.

In the future, the company may issue or grant additional financial instruments that confer equity rights in the company.

Any grant or issue of additional shares or other financial instruments conferring equity rights would dilute, potentially significantly, the equity stakes of the company's shareholders.

4.5.4. Risks that sums promised under subsidized research programs will not be paid

Since its creation, the company has received grants from the French government, French public and private research assistance organizations, and the European Union. The company plans to request additional grants or advances in the future.

As of December 31, 2013 and since its creation in 2005, the company has received the following financial assistance:

As of December 31, 2013 (€ thousands)	Amount granted	Amount received	Amount refunded
OSEO refundable advances	3 470	3 470	1 120
OSEO - FEDER grants	605	605	
COFACE refundable advances	91	91	
Total financial assistance	**4 166**	**4 166**	**1 120**

The amounts and payment dates of current and future grants depend on various factors beyond the company's control, such as a decision not to distribute or to freeze credits. Delays in paying or the non-payment of these grants, which finance part of the company's growth, could materially impact its business, financial position, income, expansion and outlook.

4.5.5. Risks associated with public subsidies and the research tax credit

To finance its activities, the company has also opted for the research tax credit, pursuant to which the French government grants a tax credit to companies that make significant investments in research and development. Research expenses eligible for the research tax credit include salaries and wages, depreciation of research equipment, services subcontracted to accredited research organizations (public or private) and intellectual property expenditures.

The company has been entitled to the research tax credit each year since its creation, and the amount thereof has been systematically reimbursed to the company upon submission of the corresponding application.

Thus, in 2013, the company received reimbursement of the research tax credit reported for 2012 in the amount of €3.1 million, and it recognized a research tax credit in the amount of €3.2 million for expenses incurred in 2013. With respect to 2013 and subsequent years, it cannot be ruled out that the tax authorities may dispute the methods that the company uses to calculate its research and development expenses, or that the research tax credit may be lost due to statutory amendments or a dispute with the tax authorities, despite the fact that the company feels it is in compliance with the expense documentation and eligibility requirements. Such occurrence could have an adverse impact on the company's income, financial position and outlook.

4.5.6. Risks associated with the loss of or amendments to the "innovative startup" status

For the last time in 2012, the company benefited from "innovative startup" status, which is reserved to small and medium-sized enterprises that incur research and development expenses equal to at least 15% of their total expenses and that meet certain other conditions, in particular workforce and sales requirements.

Due to this status, in 2012, the company obtained a reduction in the employer's share of social security contributions on salaries paid to employees who take part in research. Given the various caps applied, in 2012, this reduction was approximately €180,000. Because these benefits are limited to companies created within the last eight years, the company ceased to be a beneficiary thereof as of January 1, 2013.

4.6. Market risks

4.6.1. Currency risk

The company favors the euro as the currency to be used in connection with contracts it enters into. Moreover, the company's cash is invested in placement products denominated solely in euros. As of December 31, 2013, the company's cash was denominated in euros, except for a portion denominated in US dollars at the end of December 2013, for a total amount of $461,352.

The company has little exposure to fluctuations in the euro-US dollar exchange rate.

However, if the company signs license or cooperation agreements with US pharmaceutical groups, it may, in the future, be required to engage in euro-US dollar currency hedging transactions and to purchase currency forwards.

The company cannot rule out that significant growth in its business may create greater exposure to currency risk. In such case, the company will consider adopting a new policy appropriate to hedging such risk.

4.6.2. Interest rate risk

To date, the company has no loans, other than non-interest bearing reimbursable advances. Therefore, in terms of its liabilities, the company has no exposure to interest rate risk.

Nevertheless, the company is exposed to changes in interest rates in the course of managing its cash and cash equivalents. This item includes term deposits, accounts that pay fixed interest and investments in money market mutual funds. The company's policy is to invest exclusively in liquid products with no risk to capital.

The company strives to reduce the credit risk to which its cash and cash equivalents are exposed by monitoring the quality of the financial institutions with which it deposits its funds.

The company has no guarantee that it will obtain the same interest rates when it renews its time accounts at maturity.

4.6.3. Liquidity risk

Historically, the company has financed its growth primarily by increasing its equity through capital increases. It has never taken out bank loans. Consequently, the company is not exposed to liquidity risks due to the application of early repayment clauses in bank loans.

The company's cash and cash equivalents totaled €30.5 million as of December 31, 2012 and €19.4 million as of December 31, 2013.

The company conducted a specific review of its liquidity risk and considers that it is in a position to meet its financial obligations that will fall due within the next 12 months. Indeed, at the end of March 2014 the cash and cash equivalents of the Company amount to nearly €16 million. Including debts, which mainly relate to OSEO refundable debts for a total €2.4 million, the net cash was €13.6 million. This level of cash enables the company to fund its planed clinical development (see paragraph 6.1.3 Template 1) and the development of its technology platform *DriveIn*.

In particular, the company considers that it is in a position to pay the upcoming reimbursements of OSEO reimbursable advances, being specified that no reimbursement is planed during the 2014 year (see 22.1, 22.2 and 22.3 sections of this reference document, for a breakdown of these various reimbursable advances).

As stated in note 3.10 of the notes to the company's financial statements prepared in accordance with IFRS, which is reproduced in section 20.1 of this reference document, the company's long-term financial debts consist solely of reimbursable advances.

4.6.4. Equity risk

None.

4.6.5. The price of the company's share is subject to significant volatility

The price of the company's share is subject to significant volatility. In addition to the occurrence of the risks described in this chapter, the market price of the company's share could be significantly affected by various factors that may impact the company, its competitors, general economic conditions and the biotechnology sector. In particular, the following factors may have a significant impact on the share price:

- an unfavorable movement in market conditions specific to the company's business sector;
- announcements by the company, its competitors or other companies that engage in similar businesses and/or announcements concerning the biotechnology market, including announcements about the financial and operating performance or scientific results of such companies;
- changes, from one period to another, in the forecasts or outlook of the company or its competitors;
- changes concerning patents or intellectual property rights of the company or its competitors;
- changes in the political, economic and monetary context, in particular unfavorable changes in the applicable regulatory environment in countries or markets specific to the company's business sector or to the company itself;
- announcements concerning changes to the company's shareholder structure;
- announcements concerning the signature of new partnership agreements or the end of existing partnership agreements;
- announcements concerning changes to the company's management team; and
- announcements concerning the scope of the company's assets (acquisitions, sales, etc.).

Furthermore, the stock markets experience significant fluctuations that are not always related to the income or outlook of the companies whose shares are traded. Therefore, such market fluctuations, as well as the economic situation, may also significantly impact the market price of the company's share.

4.7. Insurance and risk coverage

The company has adopted a policy to cover the main risks to which it is exposed by taking out coverage amounts that it deems consistent with its cash consumption requirements.

For all of the insurance policies referred to above, the company's total expenses were €79,400 and €90,900 in the fiscal years ended December 31, 2012 and December 31, 2013, respectively.

The main insurance policies are:

- a "property damage" policy, which generally covers the risks of fire, explosion, lightning, electrical damage, special risks, IT risks, loss of goods in refrigerated chambers, goods in transit, theft, machinery breakdowns and loss of use, with coverage limits of €8.7 million;
- a "business liability" policy, which covers risks in connection with business operations, with maximum coverage limits for all damage, including bodily injury, of €3.5 million per year;
- a "key person" insurance policy that insures against the death of the chairman and chief executive officer due to illness or accident;
- a "directors and officers liability" insurance policy, which covers the liability of the company's senior managers if their liability is alleged in connection with the performance of their duties, with annual coverage limits of €3 million.

The company's liability in connection with clinical trials is covered by specific policies whose rates and coverage amounts depend on the local laws applicable to the relevant clinical research center. The total amount of premiums and coverage taken out for these trials depends *inter alia* on the number of trials, their location and the number of patients to be included in each trial.

The company considers that these insurance policies adequately cover the insurable risks inherent in its business activities, and that its policy with respect to insurance is consistent with practices in its business sector. The company does not foresee any particular difficulty in maintaining adequate insurance levels in the future, subject to market conditions.

Nevertheless, the company cannot guarantee that it will always be able to maintain or, if necessary, obtain similar insurance coverage at an acceptable cost, which may oblige it to take out more expensive insurance policies and/or to assume greater risks, in particular as its business activities expand.

4.8. Extraordinary events and disputes

During the 12-month period preceding the filing date of this reference document, the company has not been involved in any administrative, criminal, judicial or arbitration proceedings that may have a material adverse impact on the company, its business, financial position, income or expansion and that is not reflected in its financial statements. Furthermore, to the company's knowledge, as of the filing date of this reference document, the company is not threatened with any such proceedings.

Moreover, no extraordinary events have occurred during the same period that, to the company's knowledge, impose on it any additional risk or costs for which provisions have not been recognized.

5. INFORMATION ABOUT THE COMPANY

5.1. History and evolution of the company

5.1.1. Legal name and trade name

The company's legal name is Adocia.

5.1.2. Place of registration and registration number

The company is registered with the Lyon Trade and Companies Registry under number 487 647 737.

5.1.3. Date of incorporation and term

The company was incorporated on December 16, 2005 as a French *société à responsabilité limitée* (limited liability company) for a term of 50 years from the date of its registration with the Trade and Companies Registry on December 22, 2005, i.e., until December 22, 2055, unless such term is extended or the company is dissolved before its term expires.

It was converted into a *société par actions simplifiée* (simplified joint stock company) by a decision of the sole shareholder adopted on July 31, 2006, and then into a *société anonyme* (corporation) with a board of directors by a decision adopted by the general shareholders' meeting held on October 24, 2011.

5.1.4. Registered office of the company, legal form, law governing its business

The company is a *société anonyme* governed by French law and, with respect to its operations, is primarily subject to Article L. 225-1 *et seq.* of the French Commercial Code (*Code de Commerce*).

The company's registered office is located at 115 Avenue Lacassagne, 69003 Lyon.

The company's contact information is shown below:

Telephone: +33 (0) 4 72 61 06 10
Fax: +33 (0) 4 72 36 39 67
Email: contactinvestisseurs@adocia.com
Website: www.adocia.com

5.1.5. Significant events in the development of the company's business

End 2005	• Creation of the company by Gérard, Olivier and Rémi Soula, who invest €1.6 million.
2006	• First employees hired. The company moves into Merck's former site at 115 Avenue Lacassagne in Lyon. • OSEO grants a reimbursable advance in the amount of €2.25 million for the Osteoporosis project.
2007	• In a first round of equity financing, €12 million is raised from AGF Private Equity (now IdInvest) as lead investor, Société Générale Asset Management (now Amundi Private Equity), Viveris Management and Bioam Gestion, as well as two private investors, Alain Tornier and Jean Deléage, and the founders.
2009	• In a second round of equity financing, €14 million is raised from the company's historical investors and two new investors: Innobio (CDC Entreprises) and SHAM. • Signature of first research contract (feasibility study). • OSEO provides assistance for the Insulin project totaling €840,000, of which €420,000 is in the form of a reimbursable advance and €420,000 is in the form of a grant from the ERDF.
2010	• Following conclusive preclinical trials, Phase I/II clinical trial of BioChaperone® PDGF-BB begun on diabetic foot ulcer (DFU) patients in India. • Following conclusive preclinical trials, Phase I clinical trial of HinsBet® fast-acting human insulin begun on healthy volunteers. • Signature of new research contract (feasibility studies).
2011	• Positive results from the Phase I clinical trial of HinsBet® fast-acting human insulin on healthy volunteers. • Phase IIa clinical trial of HinsBet® fast-acting human insulin begun on type 1 diabetes patients. • End of the Phase I/II clinical trial of BioChaperone®/PDGF-BB on diabetic foot ulcer (DFU) patients in India. • Signature of a license and cooperation agreement with the US pharmaceutical group Eli Lilly and Company covering the development and marketing of Humalog fast-acting insulin analog, which uses BioChaperone® technology.
2012	• The company's initial public offering on the Euronext regulated market in Paris raises €25.4 million (net of transaction expenses). • Publication of clinical results (Phase I/II trial on diabetic foot ulcer patients and Phase IIa trial on type 1 diabetes patients to study fast-acting human insulin). • Eli Lilly begins Phase I trial of BioChaperone® Lispro. • US and European agencies grant a patent for the Biochaperone® PDGF-BB formulation for the treatment of chronic wounds. • Application filed with the Indian regulatory authorities for authorization to conduct a Phase III clinical trial in India.
2013	• The European Medicines Agency issues a positive scientific opinion for conducting a single Phase III European study for the treatment of diabetic foot ulcers. • Adocia and Lilly end their collaboration. Adocia recovers its rights to develop ultra-fast-acting insulin analogs.

2013	• Clinical trial begun to study the combination of long-acting insulin glargine with a fast-acting insulin analog. • Acquisition of an exclusive license to DriveIn® nanotechnology, which improves the effectiveness of anticancer agents by targeting their action in tumors. • Diabetic foot ulcer treatment patent portfolio expanded (patent granted in Japan for the BioChaperone® PDGF (platelet derived growth factor) composition and patent granted in the US for the BioChaperone® polymer used in the PDGF composition). • Phase IIa clinical trial begun to study an ultra-fast-acting insulin analog formulation.
2014	• Positive clinical results from Phase I/II clinical study of its BioChaperone®Combo, a combination of long-acting insulin glargine and fast-acting insulin lispro. • Postive results from Phase IIa clinical study of ultra-fast acting BioChapreon®Lispro

5.2. Clinical studyInvestments

5.2.1. Major investments

The company's major investments over the last two fiscal years were primarily for purchases of laboratory, IT and office equipment and for parking lots (see notes 3.1, 3.2 and 3.3 of the notes to the company's financial statements prepared in accordance with IFRS for the fiscal years ended on December 31, 2012 and December 31, 2013, in Chapter 20.1 of this reference document).

(IFRS - € thousands)	FY 2013 (12 months)	FY 2012 (12 months)
Intangible assets	11	16
Property, plant and equipment	434	722
Long-term investments		329
TOTAL	**445**	**1 067**

5.2.2. Major current and future investments

No significant investment is currently in progress. At this time, the company does not plan to make any major investments in the coming years and intends to maintain its current investment policy. At this stage, the company's management bodies have not made any firm commitments in this respect.

6. OVERVIEW OF ACTIVITIES

6.1. Presentation of Adocia

Adocia is a French biotechnology company founded in December 2005 by Gérard, Olivier and Remi Soula. It is specialized in the development of best-in-class medicines from approved therapeutic molecules, in particular proteins using its BioChaperone® technology and anticancer drugs using its Drive*In*® technology.

6.1.1. Rekying on the BioChaperone® technological platform to be a major player in the area of insulin therapy and healing of chronic wounds resulting from its

The authorized proteins used by Adocia treat widespread pathologies. Innovations to the formulation of these proteins have led to their improved efficacy, to a simpler and broader therapeutic use and thereby to improved quality of life of patients. Among the main therapeutic areas, Adocia initially focused on two market segments:

1. treatment of diabetes by insulin therapy
2. regenerative medicine*, in particular the treatment of chronic wounds* by a growth factor*, platelet derived growth factor-BB (PDGF-BB).

These two proteins, insulin and PDGF-BB are authorized in the United States and Europe and have proven their superior efficacy in their respective areas. Even so, their efficacy and usage could be significantly improved by better formulations.

To this end, Adocia has designed and developed a technological platform using a new family of polymers called BioChaperone® that have the property of spontaneously combining with these proteins. After combining, BioChaperones provide the proteins with new properties:

- an increase in their solubility;
- protection from enzymatic breakdown*;
- stabilization of therapeutic proteins during storage; and
- stabilization of the activity of therapeutic proteins in the presence of cells.

These important properties result in increased efficacy of the therapeutic protein, in particular by facilitating its absorption in the body, by a faster of onset of action and by an increased duration of action. These properties lead to envisioning a significant improvement of existing medical treatments by improving the expression of the properties of therapeutic proteins, by modifying dosages (reduction of dose, of the number of applications and the duration of the treatment) and/or by changing routes of administration of treatments. These properties also enable new fields of applications for a given therapeutic protein to be considered.

In addition to increasing the efficacy of these formulations in comparison to those currently on the market, these new properties will also improve safety and compliance* with pharmaceutical industry regulations concerning proteins combined with BioChaperone®. By the use of BioChaperone®, Adocia has obtained products that can be considered as best-in-class, i.e. having the best therapeutic effects in their therapeutic class.

The BioChaperone® technological platform can also be used for other therapeutic classes of proteins such as monoclonal antibodies or growth hormones.

The company has decided to use the properties of its collection of BioChaperone® polymers for very large markets in the following areas:

- healing of chronic wounds with the treatment of diabetic foot ulcers and developments planned for the treatment of venous ulcers, bedsores* (bedsores, pressure sores, decubitus ulcer) and burns by the combination of BioChaperone® and the growth factor called PDGF-BB (platelet derived growth factor-BB);
- insulin therapy with the treatment of type 1 and type 2 diabetes by insulin in the form of novel formulations of insulins, so-called second generation ("BioChaperone® Insulins"):
    - a fast-acting BioChaperone®-human insulin complex* with a more rapid onset of action that that of human insulin and similar to that of an insulin analog
    - an ultra-fast acting BioChaperone®-insulin analog complex that starts acting more rapidly than an insulin analog alone
    - a BioChaperone® complex containing a fast acting insulin and the lmong –acting insulin analog glargine, forming a single Combo Insulin reuniting the rapid action of the former and the basal action of the latter
- chronic diseases with the market for monoclonal antibodies having many oncology applications (treatment of leukemias*, lymphomas*, breast cancers, colorectal cancers, etc.) and for the treatment of autoimmune and inflammatory diseases (rheumatoid polyarthritis*, Crohn's disease*, multiple sclerosis*, etc.) resulting from the development of a second generation of formulation of monoclonal antibodies ("BioChaperone® mAbs") that:
    - improves the physical stability of monoclonal antibodies to prevent the formation of aggregates that could reduce efficacy and increase the immunogenicity of products;
    - improves the solubility of monoclonal antibodies to enable the preparation of formulations at high concentrations so they can be administered subcutaneously rather than intravenously when the former mode of administration is compatible with the pathology in question and the monoclonal antibody used.

6.1.2. Relying on Drive*In*® technological platform to become an emerging player in the area of oncology

Starting in December 2013, Adocia began the development of Drive*In*® nanotechnology for the treatment of cancer. Adocia has obtained exclusive rights for the development and marketing of this patented nanotechnology developed by Professor Sebastien Lecommandoux and his team at the Laboratory of Chemistry of Organic Polymers (LCPO, UMR5629 CNRS - University of Bordeaux I - Polytechnic Institute of Bordeaux). This technology has been shown to be very effective in pre-clinical trials for the transport of drug substances and their delivery to solid tumors, thereby increasing the therapeutic index of these drug substances. This work has been described in several publications in benchmark international scientific journals[1].

As a result of elevated efficacy, chemotherapies have been one of the cornerstones of oncology treatment for several decades. These substances nevertheless cause major adverse effects related to the damage they cause to healthy tissues at the same time as destroying cancer cells. This explains why treating cancers with chemotherapy has progressed towards targeted approaches, by using molecules with intrinsic targeting such as monoclonal antibodies, or by developing transporters for chemotherapy molecules that target the treatment of only the tumor and leave healthy tissues intact. Adocia has opted for the second approach with the development of Drive*In*®, an innovative biomimetic nanotechnology for drug delivery in oncology.

1 Upadhyay and al (2009), Biomacromolecules 10:2802-2808; Upadhyay and al (2010), Biomaterials 31: 2882-2892; Upadhyay and al. (2010), Macromol. Biosci., 10:503-512; Upadhyay and al (2012) Nanomedicine: Nanotechnology, Biology and Medicine 8:71-80.

Adocia intends using a dual strategy to develop this nanotechnology. Adocia is planning to develop proprietary products containing doxorubicin and docetaxel, two widely used anti-cancer drugs that could substantially benefit from better penetration in the cells of solid tumors. In addition, Adocia will propose its Drive*In®* technology to pharmaceutical companies in order to optimize the efficacy of their proprietary molecules.

Considerable work is under way by players in this sector in order to discover new oncology treatments but also to improve the performance of authorized products at the same time as attenuating their adverse effects. One of today's major goals of this quest for improvement is to ensure better targeting of solid tumors so the anticancer molecule can concentrate in the tumor, thereby limiting damage to surrounding healthy tissues.

The novelty of Drive*In®* resides in the use of nanoparticles whose surface is composed uniquely of hyaluronic acid, a biopolymer naturally present in the human body, known to interact with the CD44 cell receptor. This receptor is over-expressed in many solid tumors, providing Drive*In®* with its properties of targeting and incorporation in cancer cells. The drug delivered in this way would be more effectively incorporated by cancer cells, whereas existing therapies remain limited for this aspect.

With the acquisition of this new technology platform, the Company is preparing a second generation of innovations in its field of expertise: the delivery of approved therapeutic molecules

6.1.3. Adocia's economic model

The strategy and economic model of the company involves using the BioChaperone® and Drive*In®* technological platforms for the development of innovative formulations for different therapeutic molecules already authorized, with the goal of becoming best-in-class products.

The company will establish proof of concept of medical efficacy of its innovative formulations by phase I-II clinical trials in humans, sometimes remaining limited to preclinical studies with proof of concept in animals. Once the proof of concept is established, Adocia will license products obtained with its technologies to large pharmaceutical or medical device companies. Adocia is also planning on signing joint development contracts, similar to those currently in force for monoclonal antibodies in order to make best use of its technologies for new applications and with the goal of subsequently signing licensing contracts if initial trials are successful.

Adocia does not plan on producing and marketing its products.

The following diagram is a progress report on different Adocia projects under way at the date of registration of this reference document:

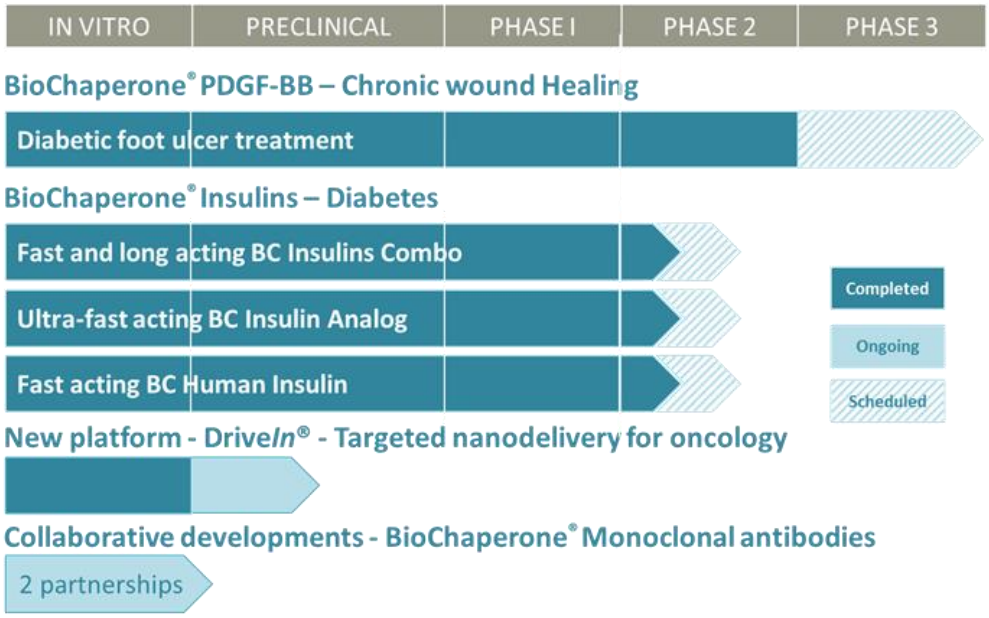


Figure 1: Adocia Pipeline as of April 20, 2014. Source: Adocia

In 2013, Adocia prepared to start three clinical trials for the treatment of diabetes. The first involved the combination a slow acting insulin, glargine, and a fast insulin, lispro. The trial began in mid-November 2013 and the results were published in press release of February 27, 2014 (preliminary results) and in a press release of March 20, 2014 (full results). The other two trials are planned during the year 2014: the first will involve a formulation of an ultra fast acting insulin analog (start of trial had been announced in après release in January 2014, results published on April 9,2014) and the second will involve fast acting BioChaperone® human insulin.

In the area of wound healing, the phase III clinical trial on the treatment of diabetic foot ulcers with BioChaperone® PDGF-BB in India has not started yet because Indian regulatory authorities (DCGI) underwent a reorganization that resulted in substantial delays in reviewing and approving applications.

The following table summarizes the clinical trials planned for 2014.

Indication	Product	Event	Expected dates ***(1)***
Treatment of diabetic foot ulcers	BioChaperone® PDGF-BB	Start of a phase III trial in India	2nd quarter of 2014 *(2)*
BioChaperone® fast acting human insulin	HinsBet®	Project to start a second phase IIa trial	3rd quarter of 2014
BioChaperone® fast acting insulin analog	BC lispro	Start of a phase IIa trial on type 1 diabetics (dose-escalating study)	2nd quarter of 2014
BioChaperone® Combo fast and slow insulins	BioChaperone® Combo	Project to start a phase I-II clinical trial (dose-escalating study)	3rd quarter of 2014

Table 1: Summary of clinical trials planned by Adocia for 2014

(1) As planed at the time of registration of this reference document, provided that the launch of clinical trials is subject to approval from local regulatory authorities
(2) The application for authorization was submitted in September 2012 and is still under review with Indian regulatory authorities

In practice, the above-mentioned clinical trial phases are defined as follows:

The preclinical phase is conducted after laboratory tests *in vitro.* The tests are run on animals with the goal of determining the efficacy and toxicity of the product before its potential administration to humans. In spite of metabolic differences between animals and humans, preclinical studies are an ethical prerequisite before administration of the product to humans. Animal research is conducted according to very strict rules that precisely describe the conditions of the work and related controls. Animal studies most often involve rats, rabbits or dogs. They provide data on the conditions of absorption, diffusion and elimination of the product, and its metabolism in the species in question.

Phase I is conducted on a small number of healthy volunteers. Its goals are to determine (i) the safety of the molecule in humans, (ii) its optimal route of administration (intravenous, subcutaneous, oral) and (iii) the maximal tolerated dose. Phase I trials usually last between 6 months and one year. In the course of development of some projects, however, phase I trials may not be required. This is because the results of phase I clinical trials on healthy volunteers in a therapeutic area with a specific application may enable a phase II clinical trial to be conducted directly for new applications in the same therapeutic area. In addition, in some cases, such as the treatment of wounds, the products can be tested only on patients and so directly enters phase II.

Phase II is conducted on patients. Its objective is to determine effects (efficacy and safety) of the medicine according to the doses and route(s) of administration determined in phase I. This type of trial generally lasts for 1 to 2 years.

Phase III is conducted on a larger patient population. Its goal it to test the efficacy and safety of the product and to determine the optimal dose (posology). This type of trial generally lasts for 2 to 3 years.

If the results of phase II and III trials demonstrate a genuine advantage in terms of benefits compared to risks, the new drug could be granted a Marketing Authorization/Product license from the competent authority (Health Ministry in France).

6.1.4. Considerable advantages over the competition

Using its BioChaperone® and Drive*In*® technology platforms, Adocia is developing new drugs intended to become best-in-class products in new formulations of therapeutic molecules that have demonstrated their value in treating the same or similar indications to Adocia's targeted indication; most of these products have received international Marketing Authorizations. BioChaperone® polymers have no intrinsic biological activity and are therefore registered with regulatory authorities as new excipients*. As a result, the development of new pharmaceutical products from these therapeutic molecules usually requires less time and less money than the development of a new pharmaceutical molecule. In addition, the risk of failure is lower because the therapeutic molecules in question have already proven their safety and acceptability with no harmful adverse effects for humans.

	Development of a new therapeutic protein	Development of a new formulation of an authorized therapeutic protein
Time before Marketing Authorization	10 to 15 years	5 to 8 years
Development cost	800 to 1,400 million dollars*	30 to 50 million dollars

* Tufts Center for the Study of Drug Development - 2007

Adocia has developed a genuine breakthrough technology with its collection of BioChaperone® polymers having multiple applications in the areas of regenerative medicine, the treatment of chronic pathologies and oncology. The strategy of diversification of indications is a lever against the usual risk of product development. In order to meet public health needs, Adocia is focusing on the development of new innovative formulations that provide a better expression of the intrinsic properties of therapeutic molecules that reinforce their efficacy or provide them with new properties resulting from the formation of the BioChaperone® polymer/therapeutic molecule complex. The company aims at mass markets, each representing several billion dollars.

Market	Estimated value
BioChaperone®- Growth factor PDGF-BB complex	
Treatment of diabetic foot ulcers	2.2 billion euros
BioChaperone® Insulins	
Fast acting BioChaperone®-Human insulin	3.9 billion euros
Ultra fast acting BioChaperone®-insulin analog	4.2 billion euros
BioChaperone® combining a fast acting insulin and a slow acting insulin forming Combo Insulin	3.5 billion euros
BioChaperone® mAbs	
Monoclonal antibodies	> 13 billion euros
Oncology	
Drive*In®*	48 billion euros

Table 2: Estimated values of markets concerned by Adocia innovations (Sources: Adocia, Datamonitor Healthcare, Business Insights).

Beyond innovative responses to public health needs, Adocia's strategy has been designed by management so that the global pharma-economic context is taken into account. The development of treatments can no longer be done without taking costs into account. This is because of increases in the prevalence* and incidence* of the pathologies targeted by Adocia, as well as the expansion of the world's population and its aging, in a policy context of controlling public health expenditures in Western countries and the growing demands of emerging economies. Healthy insurance entities, whether public or private, reimbursing patient costs are increasingly protesting the costs of medicines and medical services. These entities examine not only the safety, compliance and efficacy of products, but also their cost/effectiveness ratio. Political, economic and regulatory pressures, the explosion of generic drugs and general globalization have caused a profound change in the pharmaceutical industry. In this context, Adocia provides credible responses:

- to issues of innovations for large pharmaceutical companies that must face the widespread use of generic drugs and the expiration of many patents in the years to come, by proposing new formulations of their therapeutic proteins with new properties (shorter times of action, sustained action, different routes and/or modes of administration) that can provide heightened efficacy or at least equivalent to current treatments; and
- issues of treatment costs in developed and emerging nations (reduction of dosages, of the number of applications and duration of treatment, new routes and/or modes of administration).

This strategy of taking emerging nations into account is new for a French biotechnology company, but is opportune because of the considerable size of developing markets, and because regulatory

requirements for the development of pharmaceutical products remain highly demanding but are not as strict as those of the United States and Europe. Adocia is therefore conducting clinical trials in India for its most advanced product for the treatment of diabetic foot ulcers with the BioChaperone®-Growth factor PDGF-BB complex, before conducting clinical trials in Europe and the United States.

Adocia's economic model is based on signing license contracts for BioChaperone® applications once proof of concept is established in humans, even only in animals. This license model with a system of upfront payments at the moment of signature, of milestones with respect to reaching objectives, and royalties when products are marketed, will enable the company to obtain revenues as projects progress, without having to wait for the products to reach the market. This relatively "low burn-rate" model only requires the company to invest until proof of concept is established, after which the licensee assumes the costs of development and clinical trials.

Adocia has carried out joint development programs with major names in the pharmaceutical industry in the framework of second generation formulations for monoclonal antibodies. These joint work contracts reflect the interest of large pharma companies in BioChaperone® technology and are the first step before signing license contracts if initial studies provide positive results.

In December 2011, Adocia signed a contract for licensing and cooperation with the American pharmaceutical group Eli Lilly and Company (hereinafter **Eli Lilly**) involving the development and marketing of a fast acting insulin analog, Humalog®, with BioChaperone® technology (**BioChaperone®-Humalog®).** This agreement followed promising results of studies *in vivo* conducted by Adocia and presented to Eli Lilly in the summer of 2011.

In July 2013, Adocia announced that, jointly with Eli Lilly, it was decided not to continue the joint research program in the license contract signed in December 2011 giving access to BioChaperone® technology for the formulation of a fast acting insulin analog. The two companies decided to end their cooperation.

Adocia therefore is the holder of all rights for the development of an ultra fast acting insulin analog and intends to pursue the project more actively, a decision prompted by phase I clinical results that reached the clinical objectives set down, therefore confirming the value of BioChaperone® technology.

Adocia's strategy is to remain focused on innovation, the aspect with the highest added value. The company has verified that the formulations it develops are consistent with adapting to the industrial scale of its partners. The signature of license contracts will enable the company to remain focused on its competitive advantages in the field of polymer chemistry and drug delivery. This is the result of the experience of Adocia and its partners, the latter responsible for clinical development, regulatory questions, production, marketing and sale of products. Similarly, for the treatment of diabetic foot ulcers or BioChaperone® insulins, clinical trials conducted were outsourced to recognized and certified service providers. Almost 80% of Adocia's staff, i.e. 65 people, are composed of researchers in varied fields (chemistry, physical chemistry, biology, veterinary specialists) fully dedicated to the development of innovative products based on BioChaperone® and Drive*In®* technologies. The results of Adocia teams have led to a number of patents intended to protect the company's innovations. The company's policy of protection of intellectual property covers BioChaperone® polymers, BioChaperone®/therapeutic molecule complexes and their therapeutic applications.

The company's executive team has solid experience in the management of technological innovation and partnerships with large industrial groups in the fields of both drug delivery technologies for therapeutic proteins and the development of medical devices. Mr. Gérard Soula, founder of Flamel Technologies in 1990 and his sons Olivier and Remi Soula, have actively contributed to the

development of the company specialized in drug delivery and that is listed on the NASDAQ in the United States. In particular, they have demonstrated their know-how in terms of managing scientific projects for the development of new formulations of therapeutic molecules and the signature of partnerships and licenses with major players in the pharmaceutical industry such as GlaxoSmithKline, Novo Nordisk, Merck or Bristol-Myers Squibb.

The company also calls on external consultants, in particular Dr. Bernard Cabane, Research Director at the School of Industrial Physics and Chemistry, Paris (ESPCI), Professor Jacques Descotes, Professor at the Poison Control Centre - Centre of Pharmacovigilance, Dr. Jean-Charles Kerihuel, cardiologist and general manager of the company Vertical, Professor Lecommandoux, Research Director, and Professor François Thomas, oncologist at the Jules Bordet Institute and general manager of the company Thomas Conseil.

6.2. Adocia technologies

6.2.1. BioChaperone®, a single technological platform with many applications

Adocia has designed and developed a technological platform based on novel polymers, called BioChaperone®. These polymers are devoid of intrinsic biological activity and can spontaneously combine with certain therapeutic proteins. This combining increases the solubility and efficacy of the therapeutic protein and protects it from enzymatic breakdown.

6.2.1.1 History of BioChaperone® technology

The capacity of heparin*, a natural polysaccharide*, to form molecular complexes with growth factors was shown about 15 years ago. This combination with heparin led to the identification of three major properties that increase growth factor efficacy: (i) increase in growth factor solubility, (ii) protection of growth factor from enzymatic breakdown and (iii) prolongation of its time of action.

There are many spontaneous formations of complexes between heparin and growth factors, and the same is true for other therapeutic proteins such as hormones. The following table lists the principal proteins that combine with heparin or heparin sulfate:

Morphogenesis and tissue distribution	
Morphogens	**Coagulation**
Activin	Antithrombin III
Bone morphogenesis proteins (BMP-2,- 4)	Factor Xa
Chordin	Leuserpine
Frizzled peptides	Tissue factor pathway inhibitor
Sonic hedgehog (SHH)	Thrombin
Sprouty peptides	**Growth factors**
Wnt (1-13)	Epidermal growth factors (EGF)
Constituents of the extracellular matrix	Amphiregulin
Fibrin	Betacellulin
Fibronectin	Heparin-binding GF
Interstitial collagen	Neuregulins
Laminins	Fibroblast growth factor (FGF 1-15)
Pleiotrophin (HB-GAM)	Insulin-like growth factor (IGF-II)
Tenascin	Platelet derived growth factor (PDGF-AA)
Thrombospondin	Beta transforming growth factor (TGF-β1, 2)
Vitronectin	Vascular endothelial growth factor

Morphogenesis and tissue distribution	
Tissue restructuring factors Plasminogen tissue activator Plasminogen activator inhibitor Vexin protease	(VEGF-165, 189) **Binding proteins of growth factors (BP)** Follistatin Binding proteins (IGFBP-3, -5) TGF-β BP **Proteinases** Neutrophil elastase Cathepsin G

Source: from Bernfield and al. Ann. Rev. Biochem. 1999, 68, 729.

Adocia has developed a first generation of polymers with the goal of mimicking the ability of heparin to interact with growth factors but without the anticoagulation* properties of heparin, while having the possibility of greater versatility in order to act with a larger number of proteins.

These novel polymers, called BioChaperone®, are composed of a sugar backbone, e.g. dextran or pullulan, modified by both anionic groups* (chemical component with a negative electric charge) and hydrophobic amino acids.

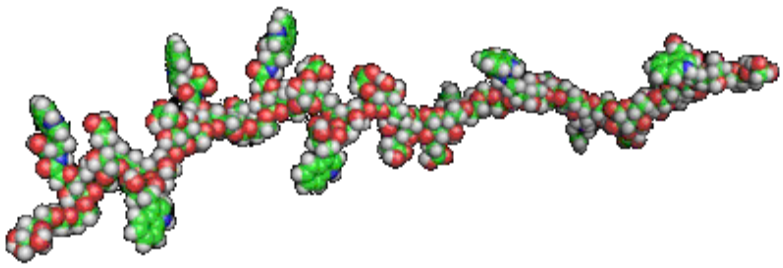
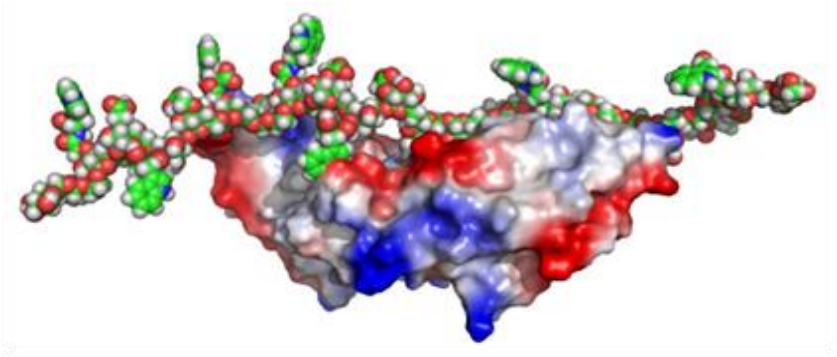


Figure 2: 3D representation of a BioChaperone® polymer with a dextran backbone.

Source: Adocia

BioChaperone® polymers form complexes with proteins by binding to their surface (adsorption). The complex forms spontaneously and is based on hydrophobic and electrostatic interactions, and on the formation of hydrogen bonds. These polymers interact reversibly with proteins and without causing any degradation. The complex forms spontaneously when the two constituents are simply mixed in aqueous solution, in other words the process requires no heating or organic solvent and is immediate.



Source: Adocia

Figure 3: 3D representation of the complex between a growth factor and a BioChaperone® polymer with a dextran backbone. Source: Adocia

It has been shown that there are four original key properties of BioChaperone® technology *via* the formation of a complex with the protein:

- an increase in the solubility of proteins that are relatively insoluble at physiological pH;
- increased stability of proteins during storage;
- protection of proteins against enzymatic breakdown; and
- stabilization of the activity of proteins in the presence of cells.

These properties augment the time the protein is present in the body and thereby increase the resulting cellular activity (prolonged time of action of the therapeutic protein and acceleration of its diffusion in the compartment(s) in question).

In addition, BioChaperone® polymers have no intrinsic biological activity and should therefore be registered with regulatory authorities as new excipients.

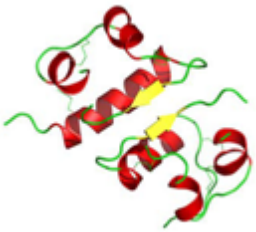
These novel properties will result in higher efficacy of these new formulations with BioChaperone® compared to formulations currently on the therapeutic proteins market, leading to products considered best-in-class, in other words having the best therapeutic effects in their therapeutic class.

Adocia's guiding principle in the development of the BioChaperone® technological platform was to design innovative and easily industrializable formulations of authorized therapeutic proteins with considerable therapeutic value for treating pathologies involving a large number of patients but whose essential properties contain major shortfalls. The intended purposes of pharmaceutical products developed with BioChaperone® technology are to be more efficacious, simpler to use and occasionally even providing new uses consistent with compliance rules of the pharmaceutical industry at competitive costs with respect to existing treatments.

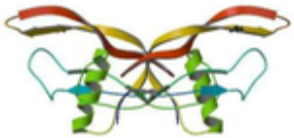
6.2.1.2 BioChaperone®, a unique collection of customized polymers for a large number of therapeutic proteins

At the present time, Adocia research teams have developed more than 250 BioChaperone® polymers, a genuine collection that will grow in size with time. The main distinctions among these polymers are their size, and the type and number of anionic and hydrophobic grafts.

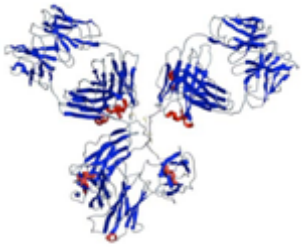
This collection of polymers prepared with the same technological platform and initially developed for growth factors, was rapidly extended to other therapeutic proteins, also authorized, and having considerable therapeutic value, such as insulin, hormones and monoclonal antibodies.



Hormones
Example: Insulin (5.8 kDa)



Growth factors
Example: PDGF-BB (26 kDa)



Monoclonal antibodies
Example: IgG (150 kDa)

BioChaperones are therefore a unique collection of novel customized polymers with a broad range of therapeutic applications.

Adocia first concentrated on the treatment of chronic wounds by growth factor PDGF-BB and the treatment of diabetes by insulin therapy. This scope of application of BioChaperone® has progressively enlarged to other proteins: monoclonal antibodies (refer to section 6.4 "Monoclonal antibodies").

6.2.2. Drive*In*®, an innovative approach to targeted delivery in oncology

In December 2013, Adocia began the development of Drive*In*® nanotechnology for the treatment of cancer after acquiring the exclusive rights for development and marketing in the health field of patents covering this nanotechnology. Drive*In*® technology was developed by the group of Professor Sebastien Lecommandoux of the Laboratory of Chemistry of Organic Polymers of the Polytechnic Institute of Bordeaux (University of Bordeaux I).

6.2.2.1 Chemotherapy, a key cancer treatment

Chemotherapy has been one of the cornerstones of the treatment of cancers for decades as a result of high efficacy. Chemotherapy, however, causes considerable adverse effects because it acts on healthy tissues as well as cancerous tissues. In order to reduce these adverse effects, treating cancers with chemotherapy has progressed towards targeted approaches; this has been done by using intrinsically targeted molecules such as monoclonal antibodies, or by the use of transporters of chemotherapy molecules to target the treatment to only the tumor while sparing healthy tissues. Adocia has adopted the latter approach by developing Drive*In*®, a novel biomimetic nanotechnology for drug delivery in oncology.

6.2.2.2 Nanoparticles: an effective delivery method

Nanoparticles are particles smaller than several hundred nanometers and some can be used as drug transporters. A very special value of nanoparticles in oncology is their capacity to accumulate in tumors by what is call the enhanced permeation and retention effect (EPR). The vascularization of tumors is abnormal, in form and structure, with disorganized formation and blood vessels presenting large fenestrations, enabling blood and what it is carrying to emerge towards the tumor. Nanoparticles of a certain size (in contrast to large molecules) tend to diffuse toward the tumor but the abnormal organization of the tumor's blood vessels and the elevated pressure inside the tumor then prevent the nanoparticles from emerging (in contrast to small molecules that escape). This combination of influx and a lack of efflux leads to the passive accumulation of nanoparticles in the tumor. Several technologies use this passive approach to augment accumulation inside tumors:

- Liposomes: they are lipid-based nano-objets. They can be coated with polyethylene glycol (PEG) to render them "stealthy", i.e. prevent their detection by the immune system. Doxil®

(Johnson & Johnson) is a pegylated liposomal formulation of doxorubicin (adriamycin), one of the most widely used molecules in oncology. The use of doxorubicin is nevertheless limited by is cumulated cardiac toxicity. The liposomal formulation of Doxil® has significantly reduced the cardiac toxicity of doxorubicin. In 2011, global sales of Doxil® were $402 million. Liposomes are nonetheless relatively unstable and their reproducible production is difficult.

- Albumin nanoparticles: Abraxane is the first product containing in a reversible nanoparticle form paclitaxel, a molecule widely used in oncology, and albumin, one of the most widespread proteins in the human body. The combination of paclitaxel with albumin benefits from the EPR effect and remains "stealthy" in the body. Sales of Abraxane, indicated for breast cancer, pancreatic cancer and stomach cancer, reached $427 million in 2012.
- Nanoparticles based on blocks of copolymers: this more recent approach (also that of Drive*In®*) has not yet reached the market.

Passive targeting by EPR leads to the accumulation of the product in the tumor, but tumors themselves are most often very dense objects in which the circulation of therapeutic products is impeded. In addition, the presence of objects in proximity to the tumor does not automatically result in the uptake of the products by the cells to treat, where the product is to be released.

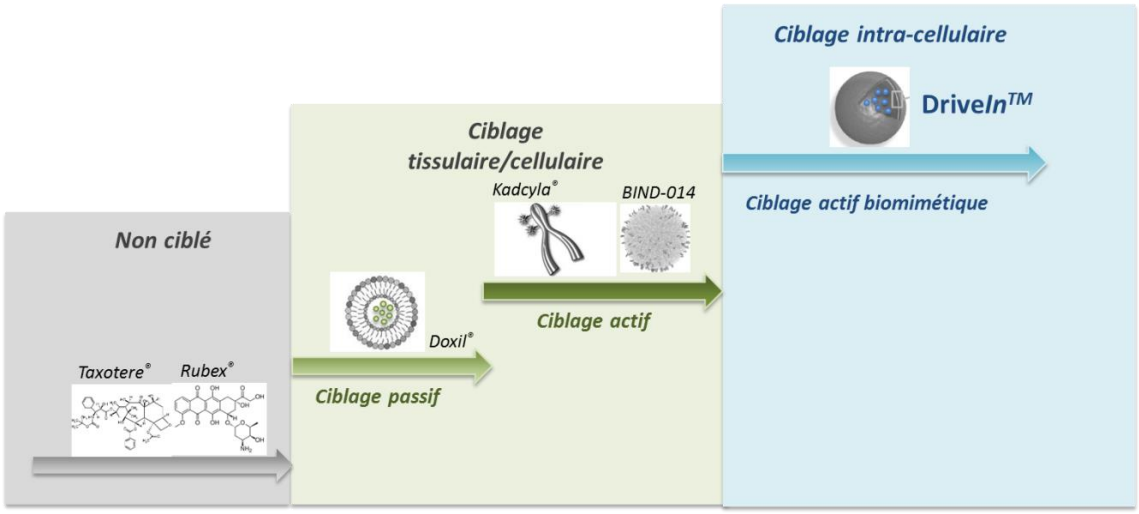


Figure 4: Progress in therapeutic delivery methods towards active targeting and enabling intracellular delivery of the drug.

Drive*In®*, a biomimetic Trojan Horse invading cancer cells

Drive*In®* is an innovative nanoparticle technology for the active delivery of drugs that enables:

- Better cell uptake and better retention of the active chemical molecule in cancer cells, where it must act.
- Effective targeting (active and passive) **towards tumors and cancer cells**.

In order to obtain both better targeting and better cell uptake of therapeutic molecules, Adocia uses a breakthrough technological approach: Drive*In®* nanoparticles are biomimetic, i.e. they are coated with a substance produced naturally by the human body, **hyaluronic acid**. Hyaluronic acid is responsible for the particular properties of Drive*In®*:

- Cell uptake: hyaluronic acid is the natural ligand of CD44, a marker of metastatic stem cells (responsible for the spread (metastasis) of cancers). The normal biological role of CD44 is to

internalize hyaluronic acid and it is over-expressed in many solid tumors2. Drive*In*® nanoparticles are therefore naturally internalized in cancer cells once they have interacted with their receptor. Most nanoparticle products on the market or under development are pegylated. The pegylation process results in a repulsive effect on living matter and thereby prevents detection by the immune system and increases its circulation in the bloodstream, but to the detriment of bioefficacy. Pegylated molecules are internalized to a lower extent and are less likely to interact with their ligand. The use of hyaluronic acid enables Drive*In*® particles to remain invisible to the immune system, but their affinity for their ligand and their uptake capacity remain intact.

- Targeting: the hyaluronic acid-coated surface of Drive*In®* enables active targeting of cells over-expressing CD44. The nanoparticle design of Drive*In®* also benefits from the EPR effect (passive targeting), that concentrates nanoparticles in the environment of the tumor.

Drive*In®* nanoparticles have been designed to act as Trojan Horses that deliver drugs to cancer cells in a targeted and active manner, while preserving healthy tissues.

Drive*In®*, a versatile platform to optimize the delivery of a wide range of molecules

Drive*In®* is a highly effective technological platform that controls all key parameters of nanoparticles (size, shape, encapsulation capacity). In this way, Drive*In®* opens new horizons to a vast array of therapeutic agents, from cytotoxic drugs to targeted inhibitors, and possibly using siRNA[3].

6.3. Competing technologies

6.3.1. Cell therapies

Cell therapies are defined as "cell grafts aiming to restore the functions of a tissue or organ when they are damaged by an accident, pathology or by aging"[2].

Stem cells, one of the great hopes for regenerative medicine research, are undifferentiated cells with three principal characteristics:

- their self-renewal capacity (capacity to divide and produce new identical stem cells);
- their capacity for differentiation (capacity to give rise to specialized cells forming different tissues and organs provided certain conditions of the environment are present); and
- their capacity to proliferate *in vitro* (in culture).

Stem cells are found in the embryo, fetus and umbilical cord blood, as well as after birth in a variety of tissues; the latter type of stem cells, called "adult", have a reduced renewal and differentiation potential.

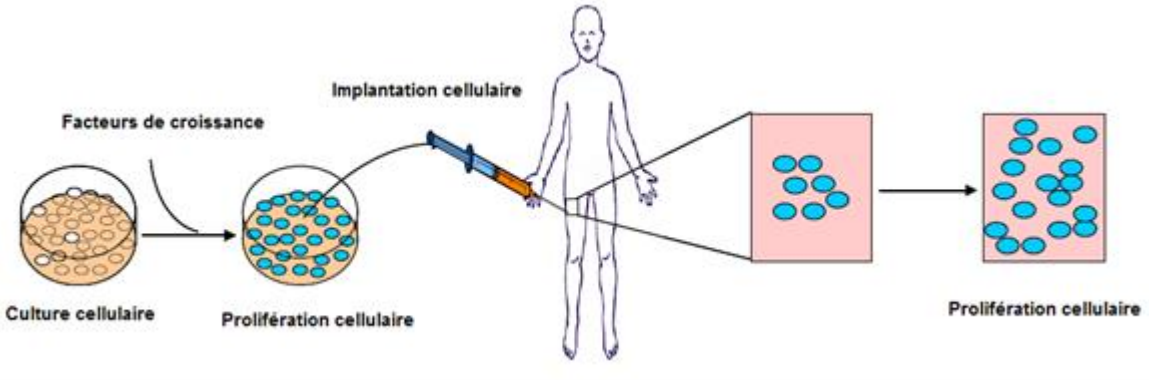
---

[2] Elevated expression of CD44 is a marker of metastatic stem cells (Clinical and Developmental Immunology 2012, 12: Article ID 708036) and a marker of poor prognosis for the course of several cancers, for example cancers of the head and neck (PlosOne 2012; 7: e28776), of the gall bladder, the prostate and ovaries (Int. J. Mol. Sci. 2011; 12: 1009) as well as blood tumors.

3 Upadhyay and al (2010) Biomaterials 31:2882-2892; Upadhyay and al (2010) Macromol. Biosci, 10: 503-512; Upadhyay and al (2012) Nanomedicine: Nanotechnology, Biology, and Medicine 8:71-80; Bui and al (2012) JACS, 134, 20189−20196.

[2] INSERM - Information on Stem Cells and Cell Therapy (in French).

Illustration of the mechanism of cell therapy



Source: Adocia

Very broad fields of therapeutic applications are possible with stem cells:

Cell types	Diseases
Nerve cells	Parkinson's disease, Alzheimer's disease, spinal column injury, multiple sclerosis
Heart muscle cells	Myocardial infarct, kidney failure
Insulin cells	Diabetes
Cartilage cells	Arthritis, arthrosis
Blood cells	Cancer, leukemia, immunodeficiencies, blood diseases genetics
Liver cells	Hepatitis, cirrhosis
Skin cells	Burns, wound healing
Bone cells	Osteoporosis
Retinal cells	Macular degeneration
Skeletal muscle cells	Muscular dystrophy

Table 3: Possible fields of applications of cell therapy, depending on the stem cells used. Source: Veterinary Academy of France, Alain Chapel, 21 February 2008.

There are nevertheless a number of limitations to the development of cell therapies related to:

- phenomena observed in very artificial conditions (transgenic animals, "chimeric" animals bearing genetically modified cells, etc.);
- signals responsible for the differentiation of stem cells and their binding to damaged organs not totally identified;
- risks of immunogenicity and infection; and
- elevated mortality rate of implanted cells …

A far-reaching ethical debate has opened concerning the use of embryonic stem cells and this major aspect must be considered in the future development of cell therapy technologies.

At the present time, about 40 products are marketed globally and the world market for cell and tissue therapies could reach $2.7 billion in 2015[3]. There is also considerable research under way, in particular by American companies such as Advanced Cell Technologies (blindness from degenerative retinopathies, juvenile macular degeneration, age-related macular degeneration), Geron (central

[3] Leem, Cells for Health (in French), 2010. re-edited in Ingenierie cellulaire and tissulaire, Key Technologies 2015, Ministry of Industry, Energy and Digital Economy

nervous system disorders, myocardial infarct, diabetes, arthritis, spinal cord damage) or Stemcells (Alzheimer's disease, arthritis, blindness, burns, multiple sclerosis, heart diseases and more).

In spite of this, clinical results concerning cell therapies are currently limited compared to the number of studies undertaken. The large number of failures can be explained by the elevated immunogenicity and mortality of implanted cells. In the current state of clinical research on markets of interest for Adocia, the BioChaperone® approach involving improved efficacy and safety of formulations of authorized therapeutic proteins is therefore more credible than cell therapy.

6.3.2. Gene therapy

Gene therapy is defined as "the deliberate introduction of genetic material in human somatic cells* in order to correct a genetic defect or compensate for the lack of a protein by providing the gene responsible for its synthesis "[4].

Gene therapy involves introducing a treatment gene in a cell so that it produces a defined protein in the case of deficient cells, or else sends a signal causing the self-destruction of the cell in the case of cancer cells.

Every type of gene therapy is based on three basic aspects:

- a therapeutic gene;
- a vector to transport this gene: a "safe" virus, in other words lacking the sequence of its genetic code that causes its pathogenicity, or else a non-viral vector such as a liposome; and
- a target cell where the gene introduced is to be expressed.

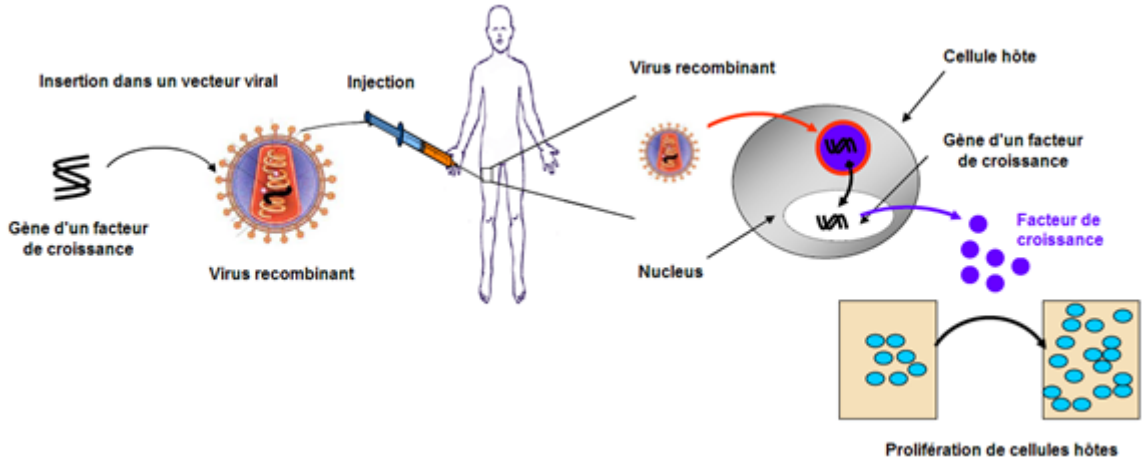


Figure 5: Diagram of the general gene therapy process. Source: Adocia

In 2008, according to the INSERM, there were 1,472 gene therapy trials under way throughout the world, of which 39 were in France. More recently, the Ministry of Industry, Energy and Digital Economy[5] stated that there were 1,644 gene therapy trials under way worldwide in June 2010.

Genetic diseases, whether single-gene diseases (cystic fibrosis, myopathies, Huntington's chorea) caused by the abnormal expression of a single gene, or multi-factor diseases resulting from the combination of several genes or environmental factors, account for only 8.2% of clinical trials started

[4] Gene therapy (in French): results and perspectives, Working group of the Naional Academy of Medicine and the National Academy of Pharmacy) - November 2001

[5] Genetic Engineering (in French), Key Technologies 2015, Ministry of Industry, Energy and Digital Economy

in 2008 and dealing with gene therapy treatments, according to the INSERM. The principal area of gene therapy investigation is the treatment of cancers (melanoma, lung cancer, colon cancer, ovarian cancer, thyroid cancer, liver cancer and more). The vast majority of clinical trials under way in June 2010 were phase I (60.5%) and only 3.5%[6] were phase III trials.

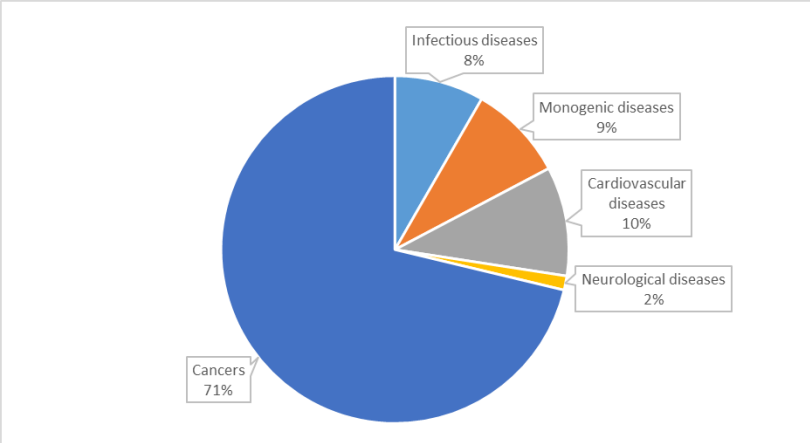


Figure 6: Distribution of gene therapy clinical trials for the indications targeted in 2008. Source: INSERM

The variety of diseases in question and the reproducibility and simplicity of the concept "one disease - one gene" would seem to make gene therapies a genuine therapeutic revolution. It could therefore be a solution to diseases for which no effective treatment has yet been developed. Major scientific issues nevertheless persist:

- the technique for insertion of a gene in a cell is not yet totally controlled and requires a better understanding of the pathways involved in the insertion of vectors and localization of the gene introduced in the genome;
- gene transfer is not yet a safe and effective procedure;
- the stability and expression of the gene introduced are not yet fully ensured.

In order for gene therapy to be safe and effective, it is imperative to fully control the process of transgenesis*, i.e. all techniques used to introduce a foreign gene in the genome of an organism. At the present time practically all gene therapy clinical trials have failed. There exists no gene therapy treatment that is reliable, internationally recognized and used in practice. These treatments could cause serious adverse effects as was the case for neonates born with severe immunodeficiency ("bubble babies"). Work done by Professor Alain Fischer was initially shown to be a total success revealed by the remission and cure of patients: most of the babies emerged from their bubble to live a normal life. Several years later, however, several of the children treated with gene therapy developed leukemia. The data gathered suggest that the type of vector used could be included in sensitive regions of the genome and that the leukemia may have resulted from the deregulation of certain genes. Furthermore, several cases of mortality were reported after injections of high doses of an adenovirus-derived vector.

These cases showed the necessity for total control of the process, in particular because of vectors affecting other genes or inserting elements that are toxic for the person's genome.

---

[6] John Wiley and Sons, The Journal of Gene Medicine, 2010

Ethical aspects may also explain the limitations imposed on gene therapies. The French National Ethics Committee* (CNNE) published a recommendation for limiting research to only somatic cells, i.e. cells that will never give rise to gametes (spermatozoa and ovules).

It has been estimated that the world market for gene therapies will be $484 million in 2015[7] even though no product has yet been granted a Marketing Authorization. The principal parties concerned are American, European (France, Switzerland and the United Kingdom) and Asian (Japan and China) markets.

The elevated risks to patients that currently exist preclude the short- and medium-term development of gene therapy for the treatment of pathologies for which alternative treatments are possible. This technology should therefore not compete with Adocia in its areas of applications.

6.3.3. Monoclonal antibodies

Monoclonal antibodies have become a very effective treatment of cancer, as a complement to chemotherapy. Monoclonal antibodies interfere with a signaling pathway by blocking the targeted receptors or by binding to active molecules. Treatment with a monoclonal antibody is often combined with a companion test to determine beforehand if the patient can or cannot benefit from this treatment. This therapeutic regimen was validated with the development of Herceptin® for patients with HER2-positive breast cancers. The monoclonal antibodies used most often in oncology are listed in Table 4. Monoclonal antibodies are most often administered in a therapeutic regimen including classical chemotherapy.

Name	Target	Name (company)	Global sales (2013)	Indications in oncology
Rituximab	CD20	Rituxan®/Mabthera® (Roche-Genentech)	$6.1 billion	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia
Bevacizumab	VEGF	Avastin® (Roche-Genentech)	$6.3 billion	Metastatic colorectal cancer (mCRC), non-small cell lung cancer (NSCLC), breast cancer, kidney cancer, brain cancer, renal cell carcinoma (RCC), brain tumor
Trastuzumab	HER2	Herceptin® (Roche-Genentech)	$6.45 billion	$HER2^+$ breast cancer, $HER2^+$ stomach cancer
Cetuximab	EGFR	Erbitux® (BMS-Merck-Lilly)	$1.89 billion	$EGFR^+$ mCRC, cancer of the head and neck
Panitunumab	EGFR	Vectibix® (Amgen)	$359 million (2012)	$EGFR^+$ mCRC

Table 4: Best among monoclonal antibodies (Source: Datamonitor Healthcare, 2013)

6.3.4. Gene therapy and cellular immunotherapy

Beyond aiming to directly interfere with cell division in the treatment of cancer, new approaches have been developed over the last decade with the goals of:

- modifying the genetic code of cancer cells (DNA-based gene therapy) or interfering with its expression (RNA-based gene therapies). These DNA and RNA methods are currently limited by

[7] Global Industry Analysts, Gene Therapy: A global strategic Business Report - October 2008.

administration difficulties because the vectors are either viruses or nanoparticles. No RNA-based treatment of cancer has yet reached the market;

- activating the patient's immune system so it directly destroys cancer cells (cellular immunotherapy): these methods are still in an early stage of their development. The only immunotherapy on the market is Provenge® (Dendreon): the method involves harvesting the patient's immune cells and modifying them for their activation so they can present an antigen specific to prostate cancer cells. Once re-injected into the patient, they provoke an immune response of the patient against his(her) own cancer. The theoretical advantage of this approach is that the patient is immunized against his(her) own cancer. In spite of this promise, this technique still remains highly limited by issues of stringent production requirements and treatment costs.

These approaches are all under development and could be complementary methods to chemotherapy to combat cancer.

6.4. Adocia products developed with BioChaperone® technology

6.4.1. The BioChaperone® PDGF-BB combination for the wound healing market

Adocia has perfected an existing treatment for the wound healing market, in particular diabetic foot ulcers. The treatment involves spraying with a complex composed of BioChaperone® and growth factor PDGF-BB (platelet derived growth factor-BB), authorized for this indication with the marketing of Reframe® gel. The treatment developed by Adocia could also be used to treat venous ulcers, bedsores and burns with PDGF-BB. After the phase I-II clinical trial conducted in India, Adocia is planning a phase III trial in India, then in Europe and the United States.

6.4.1.1 The treatment of diabetic foot ulcers

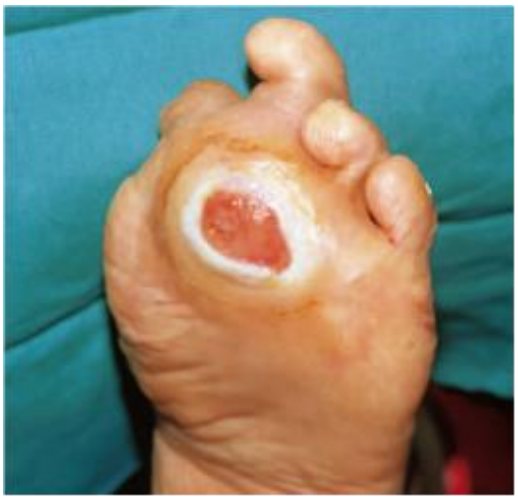
6.4.1.1.1 The pathology

The term "diabetic foot" encompasses all pathological manifestations affecting the foot of a patient, directly related to diabetes. About 20% of hospitalizations for diabetes[8] result from complications to the feet and there are two major causes of these pathologies:

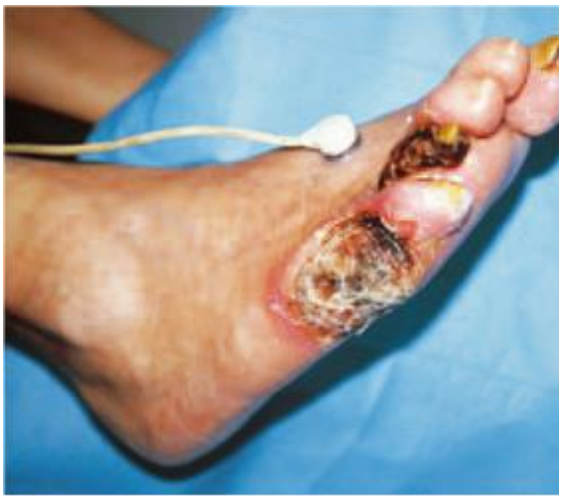
- the involvement of nerves of the foot that can advance all the way to destruction of the nerve fiber*, a condition called neuropathy*; and
- the obstruction of arteries of the leg, called arteriopathy*.

The major risk of this pathology, dominated by the occurrence of an ulceration, is amputation.

[8] CP Fylling (1992) Wound Healing an Update in Comprehensive Wound Management for Prevention of Amputation, Diabetes Spectrum 5: 358-3549 re-edited in Diabetes and Wound healing, Prof. P. Vexiau and Dr. D. Acker (Endocrinology and Diabetes Department, Saint-Louis Hospital, Paris, 2008).



Diabetic foot resulting from neuropathy



Diabetic foot resulting from arteriopathy

Figure 7: Photographs of neuropathic and neuroischemic diabetic feet. Source: L'Observatoire du mouvement - Le pied diabetique

Neuropathy

Neuropathy is a term that includes all disorders of the peripheral nervous system (motor and sensory nerves and nerves of the extremities) and of the autonomic nervous system that controls organs.

The origin of a neuropathy is primarily metabolic. The accumulation of the sugar sorbitol* in nerves creates an edema, in turn causing destruction of nerve fibers[9]. These fibers, whether sensory, motor or vegetative, can be damaged by diabetic neuropathy. Sensory nerve involvement predominates and sensitivity to pain gradually disappears. In the most extreme cases, patients continue walking without being aware that the lesion on the bottom of their feet continues to exacerbate.

[9] JD Ward (1982) The Diabetic Leg, Diabetologia; 22: 141-147 re-edited in Diabetes and Wound healing, Prof. P. Vexiau and Dr. D. Acker (Endocrinology and Diabetes Department, Saint-Louis Hospital Saint-Louis, Paris, 2008).

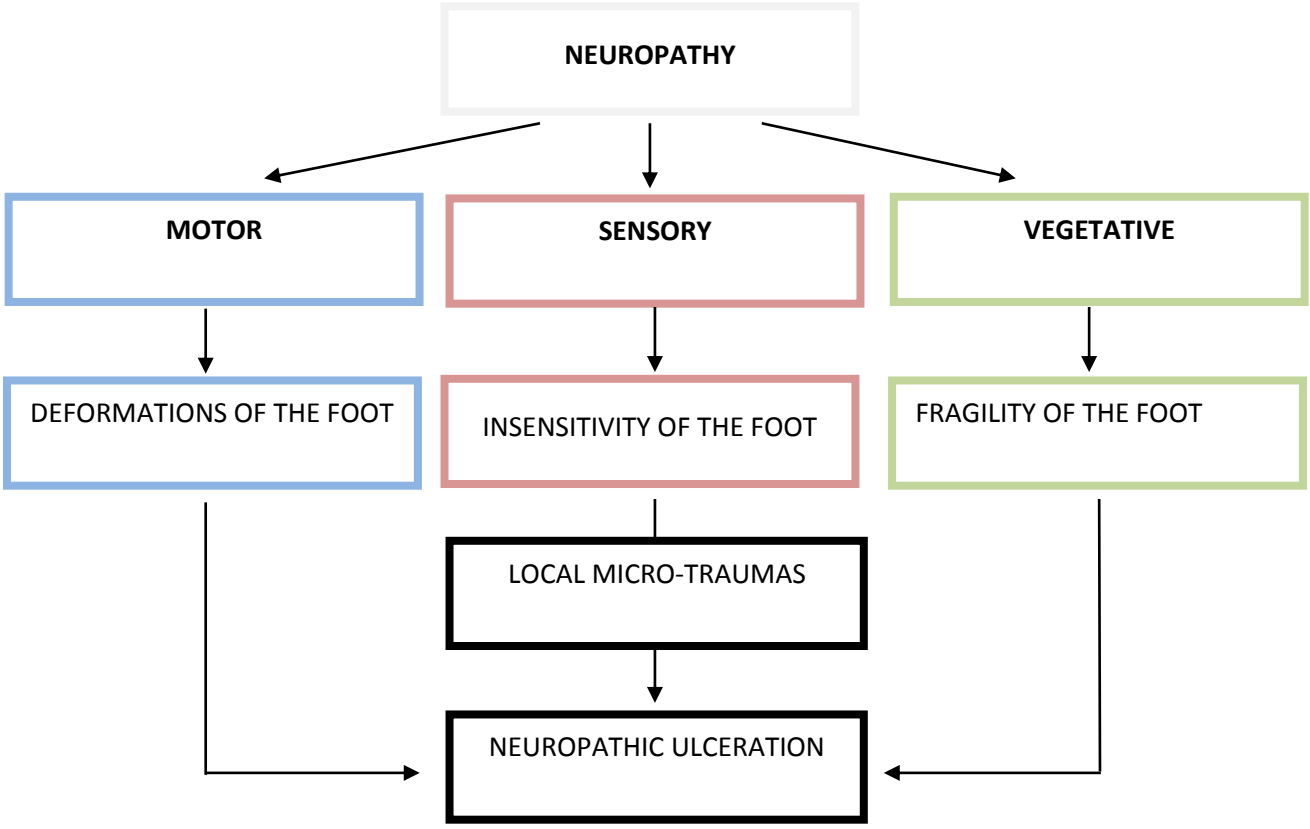


Figure 8: Role of different involvements of the peripheral nervous system in the appearance of diabetic foot ulcers. Source: The Diabetic Foot (in French) - The situation in 2005, Dr. J-L. Richard (Nutritional Diseases and Diabetes Department, Nîmes University Hospital)

Arteriopathy

There are two possible forms of arteriopathy, an obstruction of blood vessels of the lower extremities:

- microangiopathy, the involvement of capillaries, the tiniest blood vessels, with a functional impact on the feet[10] and a negative effect of its wound healing[11];
- macroangiopathy, the involvement of arteries causing a narrowing of their diameter (stenosis) resulting from the deposit of cholesterol on their inner wall (atheroma).

A reduced blood supply or ischemia* becomes chronic and renders the foot vulnerable to the extent that a slight trauma can lead to the formation of a wound. This ischemic state also limits the capacity of blood to circulate, rapidly becoming insufficient to the point of being unable to cope with an infectious phenomenon or to heal wounds. Ischemia is therefore the cause of diabetic foot ulcers and their exacerbation.

Diabetic foot ulcers appear in only about 15% of cases by arteriopathy, whereas 90% of diabetics with an ulceration are also affected by a neuropathy[12].

---

[10] From Took JE, Brash PD, Microvascular Aspect of the Diabetic Foot Disease, Diabet Med 1996; 13 (Suppl): S26-S29

[11] The Diabetic foot - Situation in 2005 (in French), Dr. J-L. Richard (Nutritional Diseases and Diabetes Department, Nîmes University Hospital)

Clinical characteristics of diabetic foot ulcers

Neuropathic ulcers	Ischemic ulcers
Foot arm, pulse intact	No pulse/foot not warm
Reduced sensations/calluses	Reduced sensations
Sites of ulcers: top and extremity of toes/ head of metatarsals on plantar surface	Sites of ulcers: foot contour, extremity of toes, heels
Septicemia	Septicemia
Local necrosis	Necrosis and gangrene
Charcot's arthropathy	Critical ischemia: pallor, pain, absence of pulse, foot cold

Table 5: Clinical characteristics of diabetic foot ulcers. Source: Wesam al Arayedh and Alain Brassard, Mc Gill University Health Center, Montreal - Diabetic foot ulcers

Infection

The development of an infection of diabetic foot ulcers is the aggravating factor of the above-mentioned pathologies and can lead to amputation of the patient's foot and even mortality. The risk of gangrene to a diabetic is 17-fold higher than normal[13].

Epidemiological data

The worldwide prevalence of diabetics who develop a foot ulcer during their lifetimes has been estimated at 15%[14]; there are 10 million[15] diabetics throughout the world with a foot ulcer. In the United States, the number of diabetics has been estimated at 25.8 million[16] and the prevalence of ulcers among these patients has been estimated at 5% every year[17], i.e. more than 1 million ulcers in the United States. This number should be practically the same in Europe because the number of diabetics and the prevalence of diabetic foot ulcers are comparable. The number of amputations every year resulting from diabetes has been estimated to be more than one million[18] and so diabetes is the leading cause of non-traumatic amputation of feet in developed nations.

---

[12] Boulton AJM, The Diabetic Foot: Neuropathy in Aetiology? Diabet Med 1990; 7:852-858 re-edited in The Diabetic foot - Situation in 2005, Dr. J-L. Richard (Nutritional Diseases and Diabetes Department, Nîmes University Hospital)

[13] R. Most & P. Sinnock (1983) The Epidemiology of lower Extremity Amputations in diabetic Individuals, Diabetes Care 10: 764-776 re-edited in Diabetes and Wound healing, Prof. P. Vexiau and Dr. D. Acker (Endocrinology and Diabetes Department, Saint-Louis Hospital)

[14] Reiber GE. Diabetes foot care: financial implications and practical guidelines. Diabetes Care 1992; 15 (Suppl 1): 29-31

[15] Worldwide Wound Management 2005-2014, MedMarket Diligence Report S225, August 2005, p1-23

[16] American Diabetes Association

[17] Vincent Lopez Row, Diabetic Ulcers, Medscape Reference

[18] Diabetes and Wound healing (in French), Prof. P. Vexiau and Dr. D. Acker (Endocrinology and Diabetes Department, Saint-Louis Hospital, Paris, 2008)

[19] The 2007-2010 Entred study (in French) entitled "National control sample of diabetic individuals" was conducted to better understand the health status of diabetics in France.

In metropolitan France, the number of diabetic patients (type 2 diabetes) with foot ulcers has been estimated at 218,000 for a diabetic population of about 2.2 million according to the ENTRED 2007-2010 study[19], i.e. close to 10% of the total number of diabetics. The same study estimated the number of diabetics undergoing amputation of the foot in 2007 in metropolitan France to be 33,000; this number is 80,000 more in the United States[20]. After an initial ulcer, the 5-year risk of recurrence is estimated at 70%[21].

Furthermore, the fact of being diabetic multiplies the risk of amputation by a factor of 10 to 40[22] and a second amputation is required in almost 50% of cases; in the latter situation, the survival rate is only 58%[23]. The consequences of diabetic foot ulcers multiply the risk of patient death by a factor of 2.4[24].

6.4.1.1.2 The market

The global diabetic foot ulcers market has recently been evaluated at $3 billion[25]. This figure was released by the British pharmaceutical company Shire, in its May 17, 2011 announcement of the acquisition of Advanced BioHealing for $750 million. This company owns the rights to DERMAGRAFT®, authorized to treat this pathology.

The goal of all concerned in the treatment of diabetic foot ulcers is evidently to maximally limit amputations.

The three major types of treatment are:

- removing all load to the foot by orthopedic shoes or a plaster cast;
- local treatments (antiseptics, petroleum jelly gauze, etc.); and
- the use of antibiotics in case of infection.

In this context, manufacturers of orthopedic devices are the first concerned by reducing loads on the foot in order to eliminate all physical stress to the wound.

In parallel to reducing load on the foot, local treatments are possible after debridement (excision) of the wound to dry and limit the spread of the necrosis. This local treatment requires not less than

---

[19] The 2007-2010 Entred study (in French) entitled "National control sample of diabetic individuals" was conducted to better understand the health status of diabetics in France. This study was sponsored by the "Institut de veille sanitaire"/Health Watch Institute, that financed the study in partnership with National Health Insurance, the National Institute for Prevention and Health Education, and the National Health Authority.

[20] Evaluation and Treatment of Diabetic Foot Ulcers - Ingrid Kruse and Steven Edelman - Clinical Diabetes • Volume 24, Number 2, 2006

[21] Apelqvist J, Larsson J, Agardh C-D. Long term prognosis of diabetic patients with foot ulcers. J Intern Med 1993; 233: 485-491 re-edited in The Diabetic foot - Situation in 2005, Dr. J-L. Richard (Nutritional Diseases and Diabetes Department, Nîmes University Hospital).

[22] Richard J-L, Parer-Richard C. The Diabetic foot (in French): Epidemiological and economic data, The Diabetic foot. Richard JL, Vannereau D, eds. Paris: Medias Flash. 2002: 23-43.

[23] Apelqvist J, Larsson J, Agardh C-D. Long term prognosis of diabetic patients with foot ulcers. J Intern Med 1993; 233: 485-491

[24] Boyko EJ, Ahroni JH, Smith DG, Davignon D. Increased mortality associated with diabetic foot ulcer. Diabet Med 1996; 13: 967-972

[25] Shire to establish new Regenerative Medicine business unit through cash acquisition of Advanced BioHealing, Inc., including US marketed DERMAGRAFT® Shire - May 17, 2011

primary dressings* even though they have shown no benefit for wound healing[26]. Another treatment that has been developed involves using negative pressure, called vacuum-assisted closure (VAC), continuous aspiration of the wound to facilitate wound healing[27].

Finally, the wound can be treated with Regranex®, a gel whose drug substance, becaplermin, is a genetic recombination of growth factor PDGF-BB (platelet derived growth factor-BB). This gel stimulates granulation* and wound healing of deep, chronic, pathological diabetic ulcers. Regranex® was granted a Marketing Authorization (refer to section 6.4.2.5 "The Competition") in 1997 in the United States and in 1999 in Europe.

An alternative to these treatments could arise from cell therapy by the use of skin replacements composed of human fibroblasts. Adocia believes that these products, some of which are already on the market, remain expensive to produce and so will be used only in the most severe cases. They will therefore account for only a small market share.

A major socio-economic problem

Diabetic foot ulcers are a major socio-economic problem. According to work by a task force led by diabetic foot ulcer specialists[28], the average cost of primary health care for the treatment of this pathology in the United States is between $7,000 and $10.000; the direct cost of amputation caused by a diabetic foot is estimated at between 30 and 60.000 dollars; the cost of three years of post-operative care has been estimated to be between 43 and 63 thousand dollars. The latter, elevated figure is the result of increased home care and social services needs following the amputation. For diabetic patients presenting this complication, the cost of primary care could be estimated to be between 16 and 27 thousand dollars per patient. It is also relevant to take into account indirect costs, those due to productivity losses by these patients. If we therefore take into account reduced quality of life and lost productivity, it has been estimated that the annual costs of diabetic feet is about $4 billion in the United States.

6.4.1.1.3 The first phase II clinical trial in India

Adocia has sponsored a preclinical study using the diabetic rat model with the goal of comparing the effects of Regranex® (1 dose per day for 7 days) and BioChaperone® PDGF-BB complex (1 dose every 2 days for 7 days). The results showed comparable efficacy between the products in terms of wound healing and the quality of granulation tissues.

A phase I/II trial was started in June 2010 in India that included 192 patients in 11 investigation centers. The aim of the trial was to compare the efficacy of the Adocia formulation of PDGF-BB (Platelet Derived Growth factor) combined with BioChaperone® and delivered as a spray, to Regranex® (HealthPoint), a gel containing PDGF-BB that is currently the only available treatment for diabetic foot ulcers.

The 192 patients included were divided into four groups: three received PDGF-BB doses of 14.5, 43.75 and 87.5 µg per cm² and per week and the fourth received Regranex® at 43.5 µg par cm² and per week. BioChaperone® PDGF-BB treatments were administered every other day, while Regranex® was applied daily according to treatment protocols authorized by American and European agencies.

---

[26] Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies and al, Randomised controlled trial of the use of three dressing preparations in the management of chronic ulcerations of the foot in diabetes, Health Technol. Assess. 2009;13:1-86 (iii-iv)

[27] Diabetic foot, O. Tazi and C. Debure, Ed. Elsevier Masson

[28] Dr. K. Bakler, Mme A. Foster, Dr. Z.G. Abbas, Dr. A. Bal, Dr. S. Pensey and Dr. V. Vishwanathan – Improving the treatment of diabetic foot ulcers in developing nations

The study was not blinded because of obvious physical differences between the two preparations, i.e. BioChaperone® PDGF-BB is a spray and Regranex® is a gel. The planned treatment period was 20 weeks or until total wound healing. The aim of the trial was to establish the non-inferiority of BioChaperone® PDGF-BB compared to Regranex® for each dose of the former.

The principal criterion of the trial was the percentage of total wound healing (closure of the lesion) after 20 weeks. The rates of total wound healing were all equal to or greater than that of Regranex®, i.e. 66% after 20 weeks. Criteria of non-inferiority were therefore fulfilled for the three doses of PDGF-BB tested.

One of the outstanding results of this trial is the 80°% rate of wound healing after 20 weeks obtained with the formulation containing only one third of the Regranex® dose, even though the product was applied only once every other day.

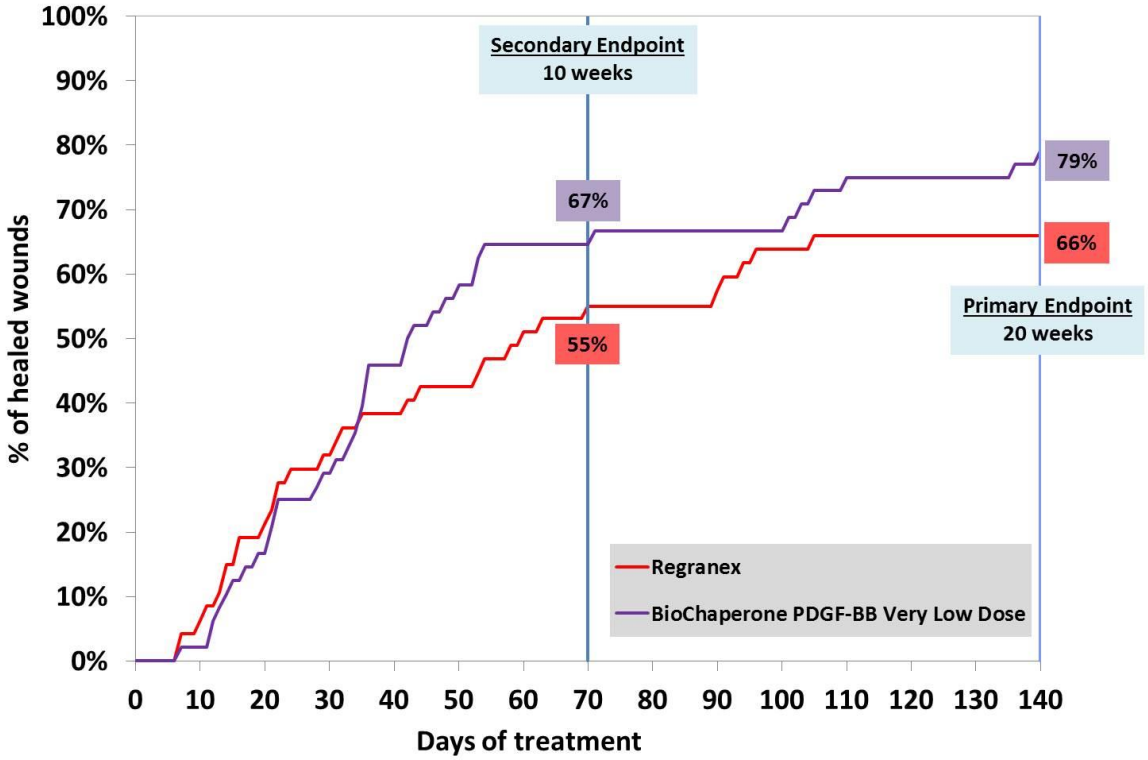


Figure 9: Incidence of total wound healing of diabetic foot ulcers (final results) in the phase II clinical trial of the treatment of diabetic foot ulcers by BioChaperone® PDGF-BB. Source: Adocia

	Principal criterion Incidence of total closure at 20 weeks	Secondary criterion Incidence of total closure at 10 weeks
Very low dose of BioChaperone® PDGF-BB	79% (38/48)	67% (32/48)
Regranex®	66% (31/47)	55% (26/47)

Table 6: Results of the phase II clinical trial of treatment of diabetic foot ulcers by BioChaperone® PDGF-BB. Source: Adocia

These positive clinical results incited the company to continue development of its project and to prepare a phase II clinical trial in India, using the lowest dose of the BioChaperone® PDGF-BB complex, equivalent to one application of 4.2 µg/cm^2 every other day for 20 weeks.

6.4.1.1.4 Future clinical trials

In September 2012, Adocia deposited an authorization application with Indian regulatory authorities in order to continue the clinical development of its product and start a phase II clinical trial. The regulatory authority in question underwent a reorganization and the examination of clinical trial applications was suspended for more than 6 months in 2013. At the time of publication of this reference document, Adocia had not yet received a response from Indian authorities.

The purpose of this trial is to demonstrate the efficacy of the BioChaperone® PDGF-BB complex vs. placebo in 252 patients divided into two groups.

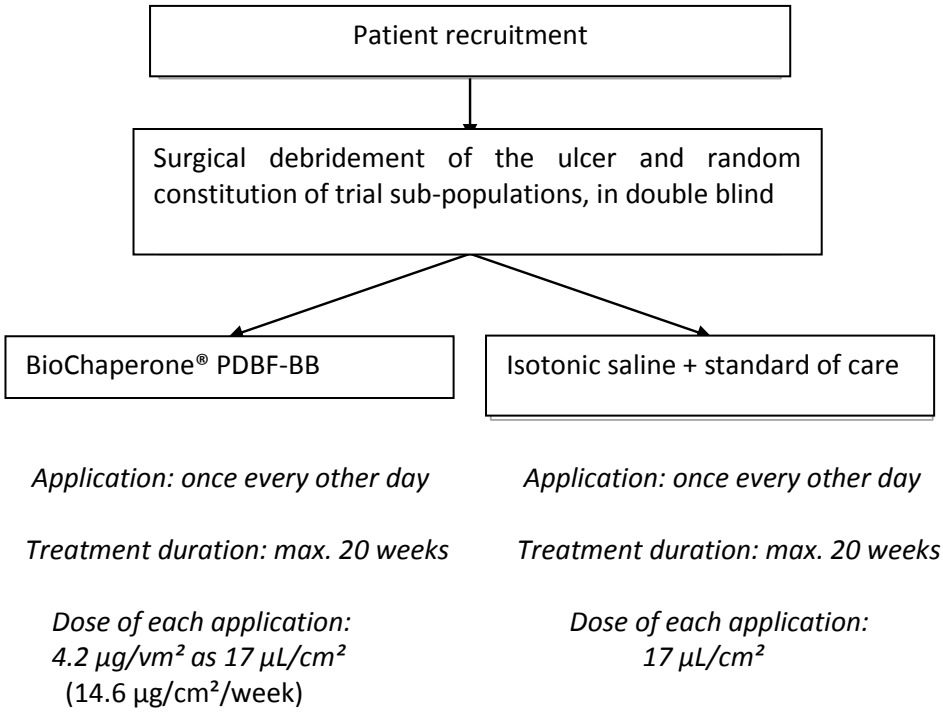


Figure 10: Design of the phase III clinical trial of BioChaperone® PDGF-BB vs. standard of care

The key elements examined involved two levels:

- Primary efficacy of the treatment measured as the percentage of patients for whom total wound healing of the ulcer was obtained after 20 weeks.
- Secondary efficacy of the treatment measured by (i) the percentage of patients for whom total wound healing of the ulcer was obtained after 10 weeks, (ii) the time required for total wound healing of the ulcer, (iii) the extent of reduction of the surface of the ulcer during treatment and (iv) the rate of recurrence of the ulcer after surveillance of 3 months post-wound healing.

The results of this trial will be the basis of the Marketing Authorization (MA) application with local authorities, currently planned for the end of 2015. The trial will be subcontracted to a contract research organization (CRO) working in accordance with Good Clinical Practices (GCP) (refer to section 6.6.3.2 “Controlling subcontracted clinical trials”) to be provided as information for Marketing Authorization applications in Europe and in the United States.

Adocia then plans to start a phase III clinical trial in Europe at the end of 2015. This trial will concentrate on foot ulcers of neuro-vascular origin and for which wound healing is more difficult. As announced in the press release of March 18, 2013 (see chapter 12), the EMA confirmed than only one phase III trial conducted in Europe will be required for the MA, and that clinical data from the phase III trial conducted in India will be admissible for the MA application.

At the date this reference document was registered, Regranex® had not yet been granted an MA for this indication.

6.4.1.1.5 Progress provided by BioChaperone® technology

Adocia has developed a new pharmaceutical product by combining a growth factor, PDGF-BB, authorized since 1997 by the FDA and 1999 by the EMA with one of its BioChaperone® polymers. This new formulation resulted in an increased solubility of PDGF-BB, its protection against enzymatic breakdown and a prolongation of its duration of action.

As a result, for an efficacy at least equivalent, the new product is applied every other day while Regranex® is applied daily; in addition, the dose of PDGF-BB required for wound healing was divided by 3 in comparison to Regranex®. BioChaperone® also led to a change in the method of administration of the growth factor: it is not a non-sterile gel, but a multi-use sterile spray to monitor the dose administered and easier application on the zone to treat.

Another major contribution of the BioChaperone® PDGF-BB complex compared to Regranex®, resulting from the reduction of the growth factor dose required, is a better safety profile for the patient, there have been concerns over a potential increased risk of cancer associated with growth factors therapies.

Finally, the considerable economic advantage of the BioChaperone® PDGF-BB complex involves reduced production costs and the final cost of the product because of the reduced quantity of drug substance used. This assumes more importance since the cost of Regranex® treatment is relatively high, limiting its prescription frequency. Lower cost could lead to widespread use of the treatment and prescription earlier in the course of patient management, which would reduce treatment duration, increase the rate of total wound healing and therefore lower the risk of amputation.

6.4.1.2 Future treatments

6.4.1.2.1 Treatment of venous ulcers

An ulcer of the leg is characterized by a chronic skin lesion that does not heal unassisted. This type of lesion can have several causes, including vascular disorders (venous, arterial or both), infections, blood diseases, cancers or inflammatory diseases. In 80% of cases[30.] ulcers of the leg result from vascular disorders (venous blood reflux, obstruction creating a venous stasis*); in these cases we speak of venous ulcers.

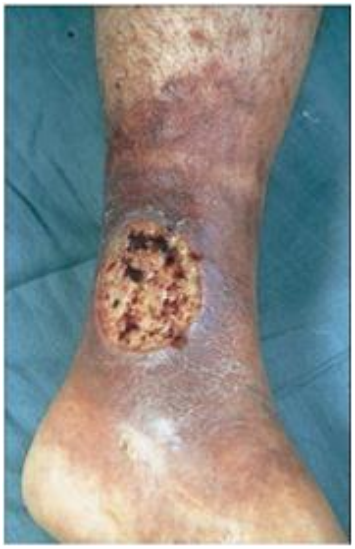


Figure 11: Internal, sub-malleolar venous ulcers on a fibrous substratum. Source: National College of Dermatology Professors

Venous ulcers are generally characterized by their isolated presence on the patient's leg at the level of the internal malleolus, in other words the inner side of the ankle at the lower extremity of the tibia, or above it. Venous ulcers are usually very large but with little or no pain, and their shape may be round, oval of polylobate.

The appearance of the bottom of the ulcer is also variable:

- a bedsore or an adhering fibrinous layer, with a sanious* and purulent bottom if the ulcer is infected;
- red, clean and smooth granulation tissue for ulcers in the course of healing.

The zones around the ulcer are characterized by inflammation of the dermis, the epidermis and/or the hypoderm.

Depending on the study, the prevalence of venous ulcers varies from 0.1% to 0.2%[31]. The percentage of the population having had at least one venous ulcer in a lifetime has been estimated at 1%[32] [33].

---

[31] Phlebologie, 3re edition, A.-A Ramelet, M. Perrin, P. Kern and H. Bounameaux, Ed. Masson
[32] Phlebologie, 3re edition, A.-A. Ramelet, M. Perrin, P. Kern and H. Bounameaux, Ed. Masson
[33] Dale JJ, Callam MJ, Ruckley CV, Herper DR, Berry PN. Chronic ulcers of the leg: a study of prevalence in a Scottish community. Health Bul, 1983; 41: 310-314
[34] Margolis and al.2002 re-edited in Phlebologie, 3rd edition, A.-A. Ramelet, M. Perrin, P. Kern and H. Bounameaux, Ed. Masson
[35] Evans CJ, Fowkes FGR, Ruckley CV, Lee AJ, Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population, Edinburgh Vein Study. J Epidemiol Community Health, 1999; 53: 149-153

Venous ulcers are a pathology that primarily affects the elderly: in a study on this pathology[34], prevalence reached 1.69% in a British sample of 50,000 subjects.

Venous ulcers are predominantly a feminine pathology, with a 1/3 ratio between men and women[35,36].

The rate of relapse is high, sometimes reaching 69%[37] after 12 months.

The basic treatment of venous ulcers involves local care with the goal of drying and delimiting the lesion in order to accelerate wound healing. This is done before treating the causes of venous ulcers, generally involving vascular surgery, occasionally major operations, and before recourse to other surgical treatments such as a skin graft. The initial basic treatment involves different types of wound protection and/or care, such as polyurethane films, hydrocolloids, absorbent polymers, aqueous gels and collagen dressings.

The similarities in the mechanisms of wound healing between diabetic foot ulcers and venous ulcers explain why Adocia is considering the start of a phase III clinical trial in India on the treatment of venous ulcers with the BioChaperone® PDGF-BB complex.

6.4.1.2.2 Bedsores

Similarities also exist between bedsores (eschars), diabetic foot ulcers and venous ulcers (localization in the lower part of the body, ulceration from a vascular cause, role of diabetes as aggravating factor, a lack of novel treatment with growth factors, serious consequences that could lead to amputation, etc). This explains why Adocia considers that wound healing of bedsores with the BioChaperone® PDGF-BB complex could be an interesting axis of development.

A bedsore is the more or less restricted destruction of a tissue resulting from its reduced vascularization. Bedsores are most often seen in bedridden and hospitalized patients, facilitated by the overall lower health status of these subjects (malnutrition, dehydration, etc.) or in a situation of prolonged compression on a limited skin surface, in particular on protrusions, i.e. the heel, sacrum, elbow, shoulder blade, etc.

The prevalence of bedsores in a French population of hospitalized patients has been estimated at 8.9%[38].

The severity of lesions involves simple skin redness, edema of varying hardness, all the way to necrosis of the skin, followed by that of underlying fat (adipose tissue) and muscles. Lesions may progress to the point of bone involvement, sometimes causing osteitis (bone inflammation). In the absence of treatment, the main risk aside from spread of the edema is superinfection that in the most extreme cases could require amputation. Treatment varies with the stage of bedsores, primarily involving local treatment and the use of dressings such as hydrocolloids to facilitate skin regeneration. In the most extreme cases a skin graft may be necessary. The parallel use of pain killers, even morphine-based products, is generally indispensable.

---

[36] Kurz X; Kahn SR, Abenhaim L, and al. Chronic venous disorders of the leg: epidemiology, outcomes, diagnosis and management: summary of an evidence-based report of the VEINES task force, Int Angiol, 1999; 18: 83-102

[37] Nelson EA, Cullum N, Jones J. Venous leg ulcers, Clin Evid, 2004: 2774-2792

[38] Labalette C. and al. Epidemiology of eschars (in French): Results of the national survey of the prevalence of bedsores in hospitalized patients "Perse 2004" L'escarre 2007; 34: 15-17

6.4.1.2.3 Burns

A burn is defined as the partial or total destruction of the skin, of tissues and even of bone. Severity depends on several parameters, in particular localization, depth, extent of the body surface, as well as the cause (heat, caustic substance or product, combustion, radiation, electrocution, extreme cold, etc.). Burns are categorized in four degrees:

- first degree burn: only the epidermis is affected;
- second degree burn: the dermis is affected and in the case of deep burns, regeneration of the dermis may not be possible because of vascular damage or the destruction of stem cells;
- third degree burn: if the burned surface is too large to heal, a skin graft becomes indispensable in light of the destruction of all skin cells; and
- fourth degree burn: muscles and/or bones are also damaged. The treatment of the most severe burns is obligatorily surgical (excision, skin graft).

Superficial (first degree) burns can be treated locally with ointments. In this context of local treatment, many growth factors are used in order to promote all aspects of wound healing.

In 2007 in France, 400.000 burns were reported, of which 10,000 required hospitalization. The number of third and fourth degree victims was estimated at 3,700 among whom about a thousand succumbed to their injuries[39].

6.4.1.3 The competition

6.4.1.3.1 Regranex®

Regranex® is a non-sterile aqueous gel supplied in multi-dose tubes containing 100 µg of rhPDGF-BB per gram (0.01%) marketed (only in the United States at the time of this reference document) by Healthpoint Biotherapeutics that purchased Systagenix in June 2011. Healthpoint Biotherapeutics was acquired by Smith & Nephew in November 2012.

Its Marketing Authorization indication in Europe (1999) and in the United States (1997) is limited to the treatment, combined with suitable care of the lesion, of deep, chronic diabetic ulcers of exclusively neuropathic origin, non-ischemic, and whose surface is smaller than or equal to 5 cm^2. Regranex® is formulated at an acid pH and contains methyl paraben, propyl paraben and m-cresol; the presence of non-resorbable materials such as carboxymethyl cellulose may cause inflammations.

Dosage is one application per day for local treatment of the ulcer. Application and dressing are conducted by a healthcare professional. The maximum treatment period is 20 weeks and requires 3 tubes of Regranex® whose unit cost is about €350 in France. The total cost of treatment is very high in light of the cost of Regranex® and nursing costs.

On June 9, 2008, the FDA required a black box warning concerning the elevated risk of mortality from cancer if more than 3 tubes of Regranex® are used. The FDA nevertheless indicated that Regranex® did not increase the risk of cancer. The European Medicines Agency (EMA) concluded that the data did not demonstrate an effect (positive or negative) of Regranex® on the incidence of cancer or mortality from cancer. Johnson & Johnson, the proprietor of Regranex® at the time, withdrew the product from the European market in 2010. Regranex® then underwent several transfers and acquisitions and has not re-entered the European market since.

[39] DHOS/O4 circular No. 2007-391 of October 29, 2007 concerning the treatment of major burn victims. Ministry of Heath

6.4.1.3.2 Skin replacements

Skin replacements are competitors of the BioChaperone® complex, even if Adocia believes that they should account for only a limited market share as a result of their high costs.

The Dermagraft® technology, authorized by the FDA, seems to be the most advanced treatment. The product is marketed by Advanced Biohealing, acquired in May 2011 by Shire, which estimated the market share at 5% with annual sales of $146 million[29] in the United States in 2010. Other products have also been granted a Marketing Authorization by the FDA, such as Apligraf® (Organogenesis), GraftJacket® (Wright) or Oasis Wound Matrix® (Cook Biotech).

Product (company):	**Dermagraft® (Shire)**	**Apligraf® (Organogenesis)**	**GraftJacket@ (Wright)**	**Oasis Wound Matrix (Smith&Nephew)**
Authorized indications:	Diabetic foot ulcer (>6 weeks)	Diabetic foot ulcer and venous ulcers (>3 weeks)	Diabetic foot ulcer (>3 weeks)	Diabetic foot ulcer and venous ulcers (>4 weeks)
Types of cells:	Dermis	Epidermis and dermis	Dermis	Dermis
Origin of cells:	Human cells	Human cells	Cadaver cell s	Porcine cells
Shelf life:	6 months	2 weeks	2 years	2 years

Table 7: Skin replacements on the market. Source: Reports of the companies mentioned

6.4.1.3.3 Other products under development

The first spray product, Fiblast® is marketed in Japan. Its active substance is fibroblast growth factor 2 (FGF-2) developed by the Japanese company Kaken, a partner of Olympus in the area of wound healing. Fibroblasts produce large quantities of collagen and elastin, proteins located between cells and are the major constituents of connective tissue. The most important role of fibroblasts is to repair traumatic lesions. Fibroblasts can alternatively contract or relax according to a dynamic process mediated by a variety of chemical messengers. In the case of inflammation or any degenerative process, fibroblasts contribute to repair by their contraction capacities and promote wound healing. FGF-2 is authorized and marketed in Japan for several indications such as bedsores, burns and leg ulcers. A phase III clinical trial is under way in Europe for diabetic foot ulcers. The proposed treatment regimen is one application per day for 12 weeks.

Another product under development by Derma Sciences uses an angiotensin analog peptide; angiotensin regulates blood pressure. A phase II clinical trial involving 75 patients showed that the results were comparable to Regranex® in terms of wound healing. The planned treatment regimen is one application per day for 4 weeks. Derma Sciences has started two phase III trials in the United States for the treatment of diabetic foot ulcers. These clinical trials are under way.

Finally, Healor has designed a treatment using a protein kinase-C precursor peptide. A clinical trial involving 22 subjects has terminated. The planned treatment regimen is one application per day for 4 weeks.

[29] Shire press release of May 17, 2011.

6.4.2. BioChaperone® insulins for the treatment of diabetes

Adocia decided to profit from its BioChaperone® technological platform to enter the insulin therapy diabetes treatment market with new innovative insulin formulations. This market accounted for $22.9 billion in 2013[40].

6.4.2.1 The pathology

Diabetes is defined as an increase in the levels of blood glucose. The two major causes of diabetes are the absence of insulin secretion by pancreatic cells (type 1 diabetes) or reduced secretion of insulin in the pancreas and/or poor use of insulin by the body (type 2 diabetes). In addition, type 2 diabetes is often associated with other pathologies such as obesity, cardiovascular diseases and hypertension.

Diabetes is a chronic pathology involving close to 382 million people throughout the world in 2013, according to the International Diabetes Federation (IDF).[41] The IDF also reported that the number of deaths from this pathology was 5.1 million in 2013 and could double by 2030.

The types of diabetes

Type 1 diabetes appears in young subjects and among all diabetics, type 1 has been estimated to affect 10% of this population[42]. The symptoms of this disease are excessive urination (polyuria) occasionally with acetone in the urine, intense thirst (polydipsia), excessive appetite (polyphagia), although the subjects lose weight, their blood glucose levels are high, greater than 1.4 g/L fasting (hyperglycemia) and excessive levels of sugar in the urine (glycosuria). Type 1 diabetes is an autoimmune disease: type 1 diabetics manufacture antibodies that attack the person's own pancreatic cells, in particular those synthesizing insulin in the islets of Langerhans*. Type 1 diabetes becomes unavoidable after the vast majority of these islets are destroyed (about 90%). The link between this autoimmune disease and a hereditary predisposition is not sufficient to explain the occurrence of type 1 diabetes: in 90% of new cases, there was no family history of type 1 diabetes and the risk of developing type 1 diabetes when one of the two parents is afflicted is less than 2 or 3%[43].

Type 2 diabetes is characterized primarily by the resistance of cells to insulin, called insulin resistance, even if the synthesis of this hormone tends to decrease in the elderly. Type 2 diabetes has been estimated to affect 90% of the diabetic population[44]. This metabolic disease prevents what is called glycoregulation (control of blood sugar levels), thereby causing diabetes. The abnormally high production of insulin by the pancreas ultimately damages the islets of Langerhans, leading to an insulin deficiency. Type 2 diabetes is considered to be asymptomatic and is often discovered after blood tests that reveal elevated blood glucose levels, i.e. hyperglycemia. Genetic predisposition is a predominant factor and overweight is an aggravating cause of type 2 diabetes.

---

[40] Source: Novo Nordisk, Full year 2013 presentation Feb 2014
[41] International Diabetes Federation - Diabetes Atlas 2013
[42] Business Insights - The Diabetes Market Outlook to 2016 - May 2011
[43] Diabetology Department, Prof. Altman, Georges Pompidou European Hospital (http://www.hegp.fr/diabeto/causetype1.html)
[44] Business Insights - The Diabetes Market Outlook to 2016 - May 2011

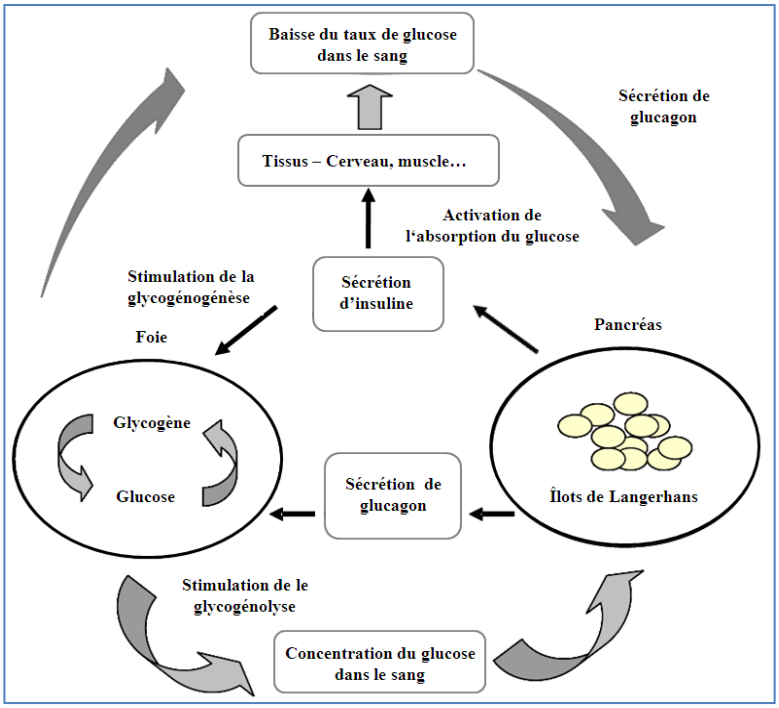


Figure 12: Production and action of insulin. Source: Business Insights/International Diabetes Federation

Other forms of diabetes, called secondary because they are the result of other dysfunctions or pathologies, exist but their prevalence is marginal: genetic defects involving insulin secretion, genetic defects involving insulin sensitivity, diabetes from pancreatitis or pancreatic cancer, diabetes caused by a drug or toxic substance, etc. Pregnancy may also cause diabetes, which could be a type 2 diabetes precursor if is disappears after birth.

Complications of diabetes

Cardiovascular complications are the principal cause of death of type 2 diabetes patients: cardiovascular morbidity and mortality are increased by a factor of 2 to 3 in men and by 4 to 5 in women. About 20% of cerebrovascular accidents (stroke) occur in diabetics. In the long term, diabetes can cause lesions to the heart, blood vessels, eyes, kidneys and nerves, such as [45]:

- diabetic retinopathy, an important cause of blindness resulting from the accumulation of damage to the small vessels of the retina; after 15 years, about 2% of diabetic lose their sight and about 10 % have a severe visual handicap;
- diabetic neuropathies, damage to nerves caused by diabetes; up to 50% of diabetics are afflicted. Diabetic neuropathies can cause a wide variety of problems but usual symptoms are tingling, pain, numbness or weakness of the feet and hands;
- the neuropathy, combined with poor blood flow, can increase the risk of foot ulcer that could require amputation;
- diabetes is among the principal causes of kidney failure and between 10 and 20% of diabetics die from this cause;
- diabetes increases the risk of cardiopathy and cerebrovascular accident and 50% of diabetics die from a cardiovascular disease; and
- the overall risk of death is at least twice as high in diabetics.

[45] Diabetology Department, Prof. Altman, Georges Pompidou European Hospital http://www.hegp.fr/diabeto/causetype2.html)

Treatment of diabetes with insulin

The treatment of diabetes by insulin therapy is broken down into two parts. Initially, prandial treatment (at mealtimes) of diabetes is implemented to control blood glucose after a meal, and secondly the basal treatment of diabetes in order to control continuous blood glucose due to hepatic glucogenesis. Prandial treatment involves so-called fast insulins and basal treatment is with so-called slow insulins.

Prandial treatment

In healthy subjects, a sudden increase in blood glucose is compensated by an equally abrupt increase in the endogenous insulin concentration in the blood. This maintains the blood glucose concentration between 4.4 mmol/L (0.80 g/L) and 7 mmol/L (1.4 g/L). Blood glucose control is considered ideal when the blood glucose concentration remains between these two limits.

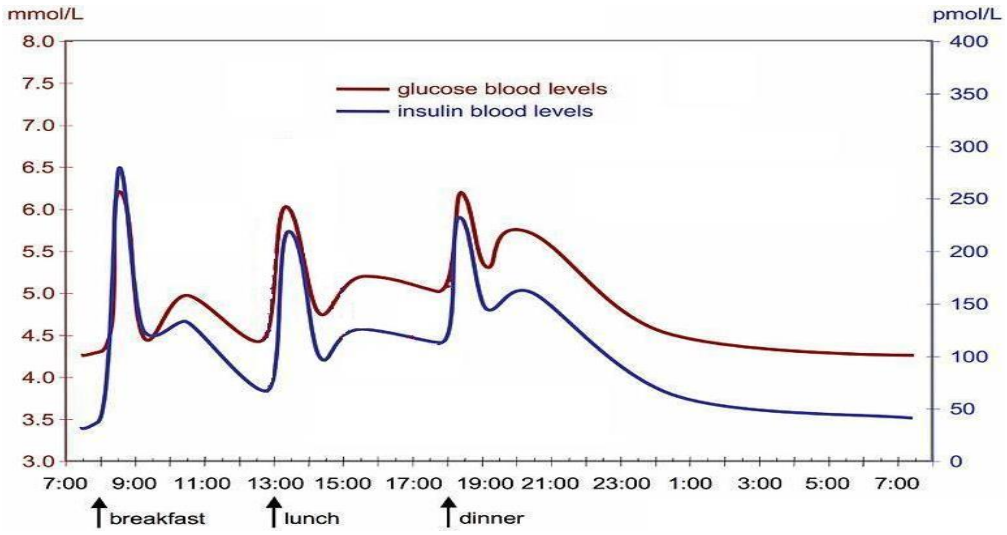


Figure 13: Blood glucose and insulin in healthy subjects. Source: Adocia

If the glucose concentration decreases below 0.80 g/L, the subject is hypoglycemic (exposing the patient to a risk of mortality) and when it rises above 1.4 g/L, the subject is hyperglycemic.

Glucose regulation is defective in diabetic patients, so that the patient is hyperglycemic, in particular after meals. It is therefore of utmost importance to start insulin treatment in order to control blood glucose at levels as close as possible to those of healthy subjects. There are two major types of treatment available that have resulted from recombinant insulin production technology: those using human insulin and those using an analog of human insulin.

Three human insulin products are on the market: Actrapid® (Novo Nordisk), Insuman® (Sanofi-Aventis) and Humulin® (Eli Lilly). The disadvantage of human insulin treatments is that they are relatively slow acting. After the subcutaneous injection of these products, the profile of insulinmia (insulin levels in the blood) is delayed by about 30 minutes compared to healthy subjects. Diabetics therefore have to plan meals and take their injection about 30 minutes before starting the meal. In addition, human insulin treatments do not prevent hyperglycemia and hypoglycemia. These products also tend to make patients overweight and augment cardiovascular risks.

The primary sequence of insulin analogs is modified in comparison to that of human insulin. There are three fast acting insulin analogs currently on the market: NovoLog® (Novo Nordisk), Humalog® (Eli Lilly), and Apidra® (Sanofi-Aventis). Fast acting insulin analogs have the following advantages: improved post-prandial blood glucose regulation, with a reduced risk of hypoglycemia and hyperglycemia, less weight gain and enhanced patient comfort because insulin injection times and dosages are more flexible. Research on new treatments with an even shorter response time is continuing with the goal of reaching normal post-prandial blood glucose control in healthy volunteers. These new insulin treatments are called "ultra fast". The objective in terms of the pharmacokinetic profiles of insulins is shown in the following diagram.

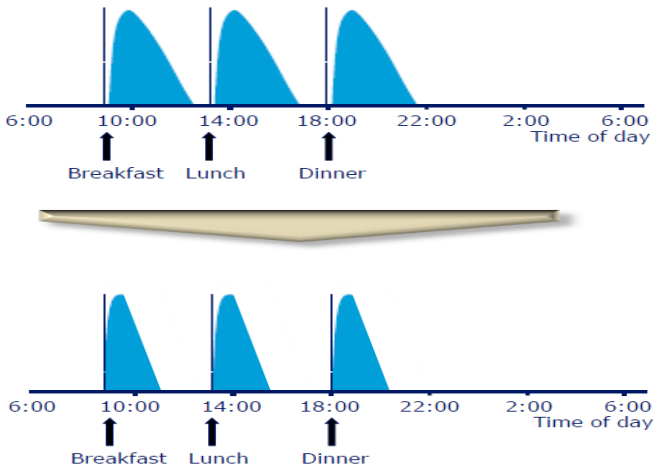


Figure 14: Objectives in terms of pharmacokinetic profile of ultra fast insulin analogs, for better post-prandial blood glucose control. Source: Adocia

The advantage of an ultra fast insulin for patients is that is can be administered at mealtimes, rather than before. In addition, the medical advantages of analogs compared to human insulin could be increased, for example by reducing the number of hypoglycemic episodes and weight gain.

Basal treatment

It is also necessary to use treatments with slow acting insulin (called basal insulin) in addition to prandial treatment of diabetes. This regimen closely reproduces the cycle of endogenous insulin secretion between meals or overnight in patients who no longer produce the hormone or in whom production is abnormal. This insulin class enables sustained release of insulin between meals and therefore maintains an insulin level in the blood sufficient to control blood glucose[46]. There are currently two types of treatment to cover daily basal insulin needs: sustained acting insulins and a fast insulin/crystallized insulin premix.

There are currently two sustained acting insulins on the market to fulfill this need for insulin release over 24 hours: Lantus® (Sanofi Aventis) and Levemir® (Novo Nordisk). One to two injections per day are required to cover patient needs as a complement to insulin taken with meals.

The premixes on the market (Novo Nordisk and Eli Lilly) are a mixture of an insulin and protamine (highly cationic protein) in different proportions. Protamine causes the coacervation* of a portion of the insulin molecules, resulting in the formation of microcrystals that can still be injected. After injection, the free fraction of insulin (not crystallized) retains a rapid profile while the fraction of insulin immobilized as microcrystals dissolves slowly in the subcutaneous environment and so its

[46] Another approach involves insulin infusion with a pump.

profile is one of delayed action. In addition, depending on the proportion of protamine, the action profiles of each fraction can be modulated. Nevertheless, all premix treatments on the market containing NPH (Neutral Protamine Hagedorn) do not enable 24-hour basal insulin needs to be covered with the crystallized delayed acting fraction, or sometimes even 12-hour needs. This is why even two daily injections are sometimes insufficient to cover needs until the next morning. Finally, it is to be noted that this approach involving partial coacervation of human insulin or of a fast insulin analog is associated with a major disadvantage in terms of patient safety. The formation of microcrystals of insulin and protamine may result in partial sedimentation that may be responsible for incorrect injection dosages (risk of hyper- or hypoglycemia accidents) and in some cases can clog the small gauge needles used to inject insulin.

In addition, premixes are not a good medical solution because of the pharmacokinetic profile of insulin (top profile in the following diagram). A patient treated with a premix will be exposed to high levels of insulin over long periods, leading to an extended period of hypoglycemia and considerable weight gain.

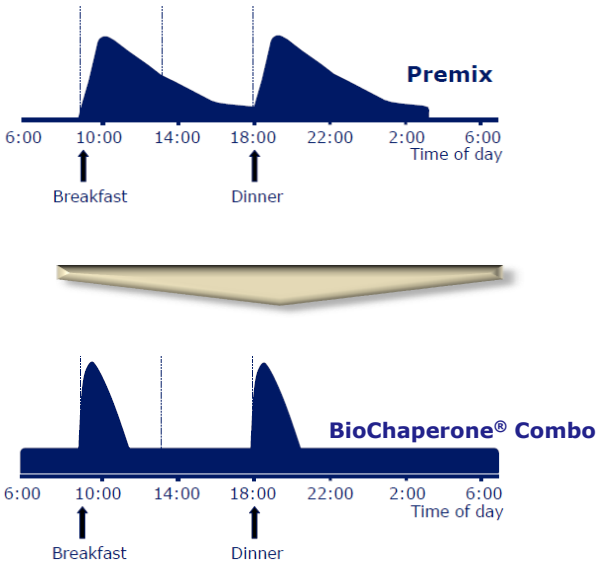


Figure 15: Objectives in terms of pharmacokinetic profiles of insulin Combos. Source: Adocia

This explains the need for a treatment combining a prandial insulin and a basal insulin whose pharmacokinetic profile would be close to that of the lower figure in the above diagram. This combination of insulins called "Combo" would reduce the number of injections and also provide an optimal insulin therapy treatment. This approach of combining two insulins having a basal and prandial action has been validated in a clinical trial comparing the double injection of Lantus® (basal insulin) and Apidra® (prandial insulin).

This double injection leads to better regulation of blood glucose compared to the injection of a premix[47].

[47] Clinical Therapeutics, Vol 33, number 7, 2011.

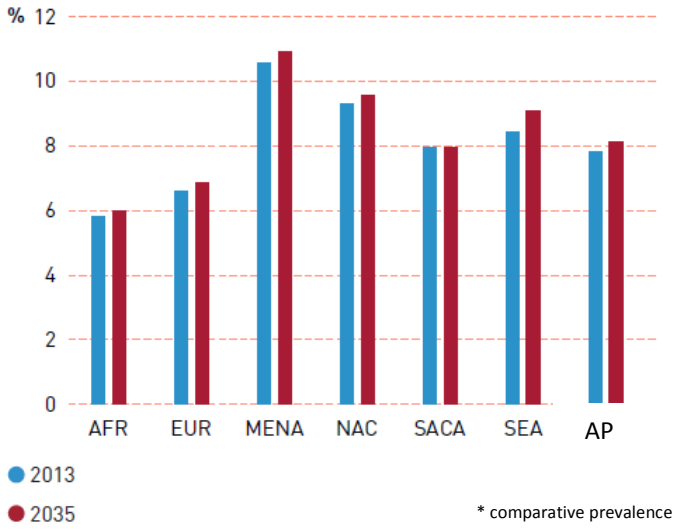
Epidemiology

Diabetes is a chronic disease affecting millions of people all over the world that will increase in emerging nations in the years to come. The International Diabetes Federation[48] has estimated that between 2013 and 2035, the number of diabetics in the world will increase by almost 55% (in the 20 to 79 year-old population), from 382 million people today to 592 million. The increases in Europe (22.4%) and North America (37.3%) are predicted to be lower than the global mean, but emerging nations will without doubt have to face an explosion in the prevalence of diabetes: 109.1% in Africa, 70.6% in Southeast Asia and 69.2% in the Eastern Mediterranean and Middle East.

Geographic zones	Prevalence in 2013	Prevalence in 2035	Rate of increase
Africa	20 million	41.4 million	109%
Eastern Mediterranean and Middle East	35 million	67.9 million	96%
Europe	56 million	68.9 million	22%
North America	37 million	50.4 million	37%
Central and South America	24 million	38.5 million	60%
Southeast Asia	72 million	123.0 million	71%
Asia-Pacific	138 million	201.8 million	46%

Table 8: Estimations of increases in the number of diabetics in the 20 to 79 year-old population in the world. Source: International Diabetes Federation, 2013

This phenomenon will increase the number of diabetics in the same population. By 2035, the percentage of the diabetic population in all regions except Europe and Africa is expected to exceed 8% (Source: International Diabetes Federation, 2013).



[48] Diabetes Atlas 5th edition (2012), International Diabetes Federation

Figure 16: Prevalence of diabetes (in percentage) per region, in the 20 to 79 year-old population in 2013 and predictions for 2035. Source: International Diabetes Federation. AFR: Africa, EUR: Europe, MENA: Middle East and North Africa; NAC: North America and the Caribbean; SACA: South America/Central America; SEA: Southeast Asia, AP: Asia-Pacific

The 2007-2010 ENTRED study[49] provided a qualitative picture of the diabetic population in metropolitan France. The most common form of diabetes is type 2 and concerns 2.2 million patients, i.e. 92% of the total number of diabetics estimated at 2.4 million. The treatment of type 2 diabetes is of long duration because the average time a patient has had the pathology is 11 years. This duration of treatment is even longer, 17 years, for type 1 diabetes patients. Type 2 diabetes is a pathology of the elderly with a mean age of 66 years and one quarter of the diabetic population (type 2) is older than 75. Type 1 diabetes affects a younger population whose men age is 42 years. The sex distribution of diabetes is practically equal for men (54%) and women (46%).

6.4.2.2 The market

According to Novo Nordisk[4], the world market for the insulin treatment of diabetes increased by 13.9% between 2003 and 2013, accounting for more than $2.1 billion, i.e. close to 50% of the total market for antidiabetic drugs. The domination of insulin over other drug classes is explained simply by the fact that insulin is the only way to control blood glucose in type 1 diabetic patients and that the use of insulin will ultimately become as unavoidable as for type 2 diabetic patients.

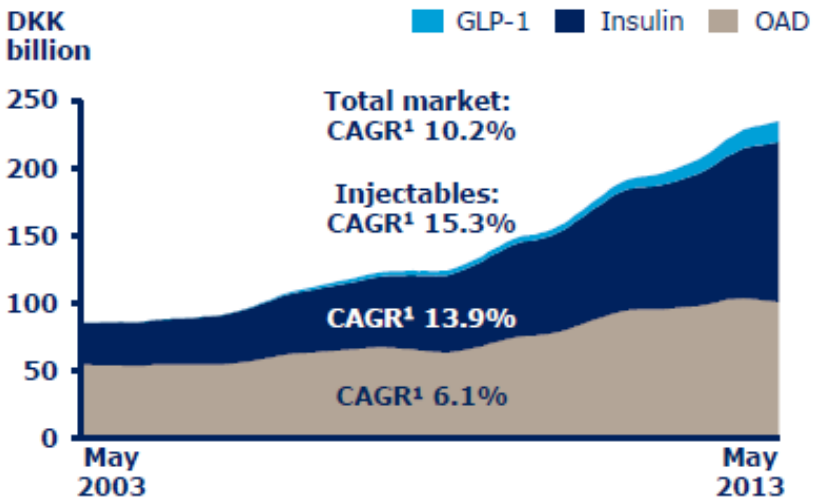


Figure 17: Global diabetes market per therapeutic class and changes between 2003 and 2013 (Source: Novo Nordisk)

Segmentation of the insulin market is conditioned by the time before onset, and duration of action of insulin. In this context, the appearance of human insulin analogs for basal treatment of the disease has transformed the insulin market that is now dominated by Lantus® (Sanofi Aventis), on the market since the early 2000s. This product alone accounts for 30% of the market with sales of more than $6.5 billion in 2012. The sales of its competitor Levemir® (Novo Nordisk) were more than $1.8 billion in 2012.

---

[49] The goal of the 2007-2010 ENTRED study (French acronym of "National representative control study of diabetics") was to extend knowledge on the heath status of diabetics in France. This study was sponsored by the "Institut de veille sanitaire"/Health Watch Institute, that financed the study in partnership with National Health Insurance, the National Institute for Prevention and Health Education, and the National Health Authority.

4 Novo Nordisk, presentation at the Handelsbanken Large Cap Seminar Stockholm, September 2013

The segment of fast acting insulins (prandial treatment) is dominated by human insulin analogs, in spite of the higher cost compared to human insulin, whose post-injection time of action is between 20 and 30 minutes. The two flagship products are NovoLog® (Novo Nordisk) with sales of $2.8 billion in 2012) and Humalog® (Eli Lilly) with sales of $2.4 billion. Eli Lilly with Humulin® dominates the medium term action insulins segment with sales of more than $1.2 billion in 2012. Finally, sales in the premix segment were more than $2.3 billion in 2012 and close to $1.7 billion for NovoMix® from Nordisk.

	Prandial treatment (Fast Acting) Regulate blood glucose after a meal	**Basal treatment (Long Acting)** Regulate blood glucose continuously	**Prandial-basal treatment (Medium term action and/or premix)** Single injection for prandial and basal action
Novo Nordisk	NovoLog® ($2.8 billion/ patent expiration in 2014) Novolin N&R® ($1.5 billion)	Levemir® ($1.8 billion) Tresiba® (authorized in 2012 in Europe and Japan. Patent expiration in 2024	NovoMix® ($1.7 billion)
Eli Lilly	Humalog® ($1.8 billion/ patent expiration in 2013) Humulin® ($1.2 billion)	/	Humalog Mix® ($0.6 billion) Humulin® NPH
Sanofi	Apidra® ($0.3 billion/ patent expiration in 2017) Insuman® ($0.2 billion)	Lantus® ($6.5 billion/patent expiration in 2015)	Insuman® NPH

Table 9: Summary of the insulin market in 2013. Source: Annual corporate reports, Adocia.

During the next five years, the insulin market should be relatively stable (+2.5% anticipated annual growth rate between 2010 and 2016) during which sales of certain flagship products are predicted to decline (-0.7% for Lantus® and -5.8% for Levemir®, as annual growth in the basal treatment segment). Other products, however, should have a rate of annual growth higher than that of the market: +6.8% for NovoRapid® and +3% for NovoMix®.[51]

Anticipated 2010-2016 sales on the market of human insulin and human insulin analogs, in millions of dollars

2010	2011	2012	2013	2014	2015	2016
17,262	18,486	19,425	20,026	20,451	20,017	19,964

Source: Business Insights

In spite of this market size stability, Datamonitor[52] has predicted the emergence of medium-size pharmaceutical companies working to improve the pharmacokinetic profile* or formulation of existing insulins, in contrast to large pharmaceutical companies that will continue their research on new molecules. Research efforts by many companies will probably focus on reducing the adverse effects of insulins, for example hypoglycemia and weight gain. The same study predicted that prandial insulins will be the insulin involved in the largest number of ongoing clinical trials, with 14 trials among a total of 26, of which 6 are phase I, 4 are phase II, 2 are phase III and 2 are post-phase III trials. There are 7 trials on basal insulins (3 are phase I and 3 are phase II, as well as one phase III trial). The other trials involve primarily premixes.

[51] The Diabetes Market outlook to 2016. Business Insights. May 2011.
[52] R&D Trends: Insulin Antidiabetics - The future is analogs. Datamonitor. May 2011

6.4.2.3 Clinical trials conducted by Adocia

6.4.2.3.1 HinsBet human insulin ® (acronym for Human insulin is Better)

A pre-clinical study on pigs (the most widely used animal model for studies of insulin pharmacokinetics and pharmacodynamics*) sponsored by Adocia showed that HinsBet® reduces the time to onset of action of human insulin.

A phase I trial also sponsored by Adocia was carried out by the German contract research organization (CRO) I.K.F.E (refer to section 6.4.3.2 Controlling subcontracted clinical trials) in November and December 2010; the final trial report was published in April 2011. The double-blind randomized crossover study included 12 healthy male volunteers (mean age 27.2 ± 6.6 years) and its general objectives were to establish treatment safety because this was the first exposure of humans to this formulation, and to determine the pharmacodynamic and pharmacokinetic profiles of HinsBet® in comparison to NovoLog® (fast insulin analog produced by Novo Nordisk) and to Actrapid® (human fast insulin produced by Novo Nordisk).

Three consecutive glucose clamp technique cycles* were run: this method involves the injection of glucose via infusion to maintain the patient's blood glucose constant to compensate the hypoglycemia caused by an insulin injection. Each subject received the equivalent of 12 IU* of insulin and was monitored for 6 hours during which the glucose level was held constant by the infusion of glucose to compensate for the drop in levels of insulin injected.

The principal objective of the trial was determining the time required to reach the maximum of infused glucose, called glucose infusion rate (GIR-Tmax). The secondary objectives of the trial were to determine the maximum infused glucose (GIRmax), the time to reach half-GIRmax (GIR-T50), the maximum blood insulin concentration (INSmax), the time required to reach the maximum and half-maximum of the plasma insulin concentration (INS-Tmax and INS-T50) and finally the number and type of adverse effects.

The results were very promising. First, all HinsBet® injections were well accepted and no adverse effect was reported. In addition, changes in the GIR showed that the response time of HinsBet® was similar to that of NovoLog® (insulin analog) and that HinsBet® produced its effect (decreased blood glucose) 20 minutes earlier than Actrapid® (human insulin).

Results of the phase IIa trial on 20 type 1 diabetics (Germany): HinsBet® (BioChaperone® human insulin) compared to a fast acting analog, NovoLog®

After the phase I results were obtained, Adocia decided to continue the clinical development of HinsBet® by conducting a phase II clinical trial in type 1 diabetics.

The double blind, randomized, cross-over trial was conducted in one center on 20 type 1 diabetics using the glucose clamp technique. The aim of the trial was to compare the pharmacokinetic profiles, pharmacodynamic profiles and safety of HinsBet® compared to NovoRapid®, a fast insulin analog, after three consecutive injections of each product to each patient.

The results showed the hypoglycemiant effect of the optimized HinsBet® formulation is just as rapid as that of NovoRapid® (insulin aspart, one of the modern fast insulins). In addition, in the course of the trial no adverse effect and no modification of clinical parameters were found. The local safety of HinsBet® was judged to be very good and comparable to that of NovoRapid®. Finally, repeated administration as three consecutive injections of HinsBet® revealed intra- and inter-individual variabilities of pharmacological parameters similar to those of NovoRapid®.

New optimized formulation of HinsBet®: preclinical results

Adocia decided to rapidly advance the clinical status of HinsBet® in order to obtain proof of concept of the product in humans and validate the use of BioChaperone® as excipient for an insulin formulation. In parallel, the company is continuing to study different BioChaperone® candidates and has developed an optimized HinsBet® formulation, whose preclinical pharmacodynamic profile (pig model) was shown to be better than that of the first HinsBet® formulation, with activity very close to that of NovoLog® (see Figure 18).

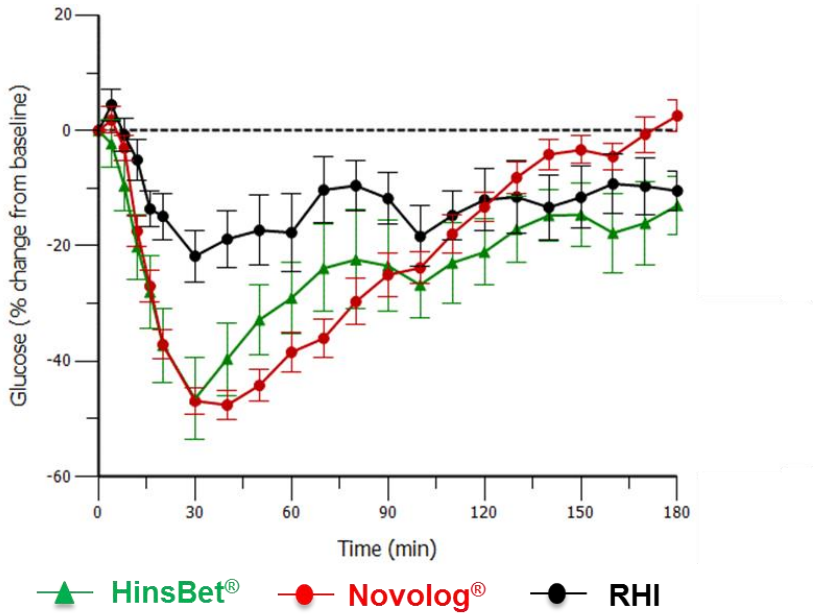


Figure 18 Pharmacodynamic profiles of the new HinsBet® formulation (green), NovoLog® (insulin aspart, red) and recombinant human insulin (RHI, black) in pigs, a preclinical model having good correlations with humans.

Based on phase I results with the first formulation and the very promising results obtained with the new formulation, Adocia plans on continuing development of the second generation of HinsBet® and is preparing a submission for a phase II clinical trial planned to start in 2014.

6.4.2.3.2 Ultra fast insulin analog

A preclinical study in an animal model (pigs) showed the shortened response time of BioChaperone®-Humalog® compared to Humalog® alone, as well as a shorter duration of action of the hypoglycemiant effect, resulting from the more rapid absorption of Humalog® by the body related to the presence of BioChaperone®, and its more rapid elimination.

This preclinical study also showed a reduction in the heterogeneity of action of Humalog® observed in guinea pigs because of the presence of BioChaperone®. The same performance was obtained by applying BioChaperone® to NovoLog®, a fast insulin from Novo Nordisk.

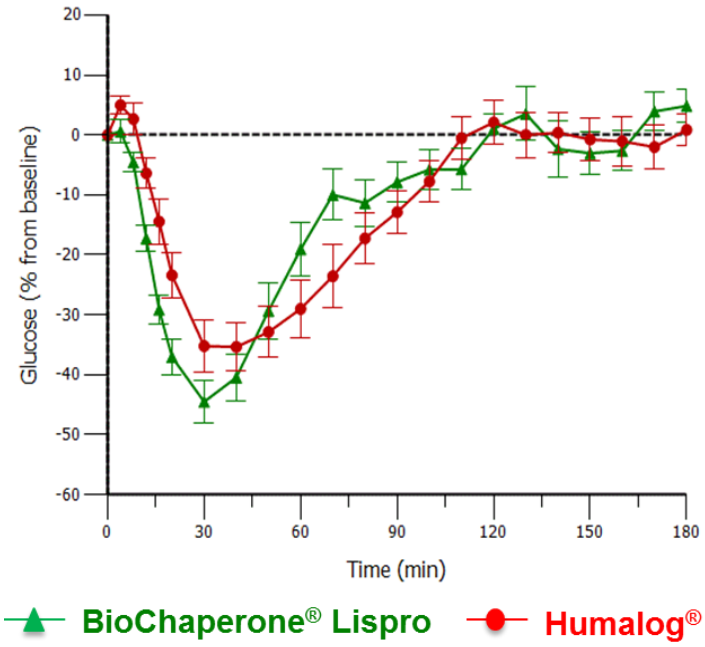


Figure 19: Pharmacodynamic profile of BioChaperone®-lispro vs. Humalog® (insulin lispro, Eli Lilly) in dogs. Source: Adocia

Based on these results, Adocia signed a licensing and joint work contract with the American pharmaceutical group Eli Lilly in 2011. According to the contract, Adocia granted exclusive worldwide rights to Eli Lilly for a BioChaperone® polymer for the development, manufacture and marketing of BioChaperone®-Humalog® and the contract covered all potential indications of BioChaperone®-Humalog®. Eli Lilly financed development of BioChaperone®-Humalog® including clinical trials, and Adocia and Eli Lilly managed joint work by a management committee composed of members of both companies.

In July 2012, Eli Lilly referenced the preparation of a phase I trial of BioChaperone®-lispro (commercial name of Humalog®) on the American website dedicated to clinical trials (clinicaltrials.gov). The trial was a success in that the results fulfilled all the clinical objectives set down. In July 2013, Adocia issued a press release announcing the end of its contract with Eli Lilly.

The results of this clinical trial cannot be presented because it continues to be the subject of certain confidentiality clauses involved in the partnership with Eli Lilly (even though it ended in July 2013).

6.4.2.4 Future clinical trials

6.4.2.4.1 HinsBet®

In parallel to the clinical development of HinsBet®, a version of BioChaperone® optimized for HinsBet® was developed. This optimized formulation of HinsBet® will be tested against NovoLog® in a phase IIa clinical trial on 12 type 1 diabetics in 2014. The clinical trial application was submitted to German regulatory authorities at the end of 2013. The Company has received approval to begin the trial in February 2014. However, and based on recent results on ultra-fast insulin analogue, the Company should review the protocol and submit an amendment to the regulatory authorities. The launch of the study is now scheduled for September 2014

The objective of this clinical trial will be to validate the superior efficacy of this new human insulin formulation in order to continue the clinical development of HinsBet®.

The success of this clinical trial should add value to HinsBet® and open the door to a partnership with a large pharmaceutical group capable of conducting additional clinical trials to obtain a Marketing Authorization for the product.

6.4.2.4.2 Ultra fast insulin analog

Based on the promising results of the phase I trial conducted in partnership with Eli Lilly, Adocia started a phase IIa trial on 36 type 1 diabetics in January 2014. The purpose of this trial is to compare the pharmacokinetic and pharmacodynamic profiles of BioChaperone®-Humalog® complex to those of Humalog® alone. Dated April 9, 2014, Adocia announced the results of this study: BioChaperone Lispro Humalog is significantly faster in patients with type 1 diabetes (onset 30% faster and 69% early metabolic effect higher).

6.4.2.4.3 Combination of prandial insulin and basal insulin

Tests *in vitro* have shown the possibility of using BioChaperone® technology to solubilize insulin glargine (Lantus®) at neutral pH and mix it with any prandial insulin including fast acting insulin analogs (Apidra®, Humalog® and NovoLog®). Adocia combined these two products and established proof of concept in the preclinical dog model that complies with numerous research criteria for the premix: total solubility of both proteins at the same pH, with good stability, with pharmacokinetic and pharmacodynamic profiles showing that the response times of the fast analog (Humalog® in the following figures) were not substantially changed by the presence of Lantus® and a BioChaperone® polymer in the formulation, and that the duration of action of Lantus® was also preserved to a substantial extent.

As shown in the figure below, BioChaperone® provides the same performance as that obtained with the double control injection (Lantus® and Humalog® injected separately).

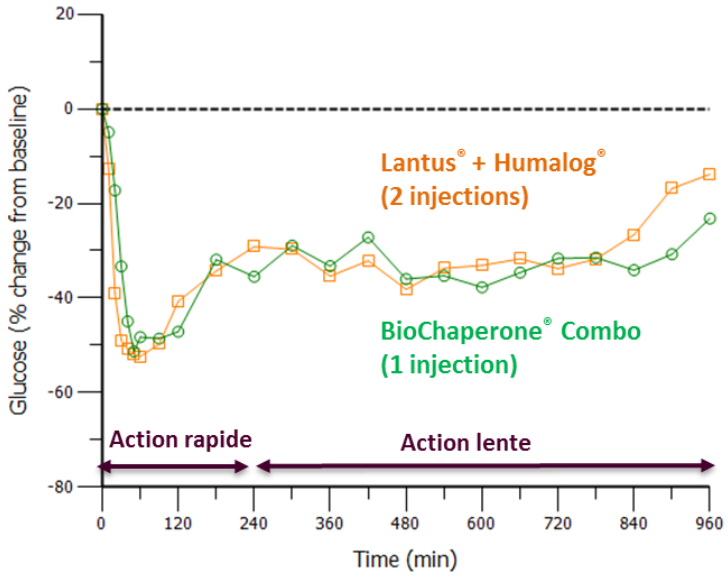


Figure 20: Comparison of the pharmacodynamic profiles of Adocia BioChaperone® glargine-lispro Combo and the double injection of insulin glargine and insulin lispro: preclinical results in dogs (model correlated with humans). Source: Adocia

In this preclinical dog model, which is correlated with humans, it was also shown that the combination of the two insulins using BioChaperone® technology led to an optimized activity profile compared to that obtained with the Premix (Humalog Mix® here), as shown in figure 21.

Concerning the BioChaperone®-Lantus®-Humalog® Combo, the response time of the fast analog (Humalog®) was no longer correlated with that of basal insulin (good transition between the two distinct actions of the two insulins). The premix, however, was characterized by an action of the fast fraction of the premix that acts with a lag time and that risks producing post-prandial hypoglycemias, and also by a duration of action of the slow fraction that does not last long enough and that risks producing hyperglycemia (in particular nocturnal).

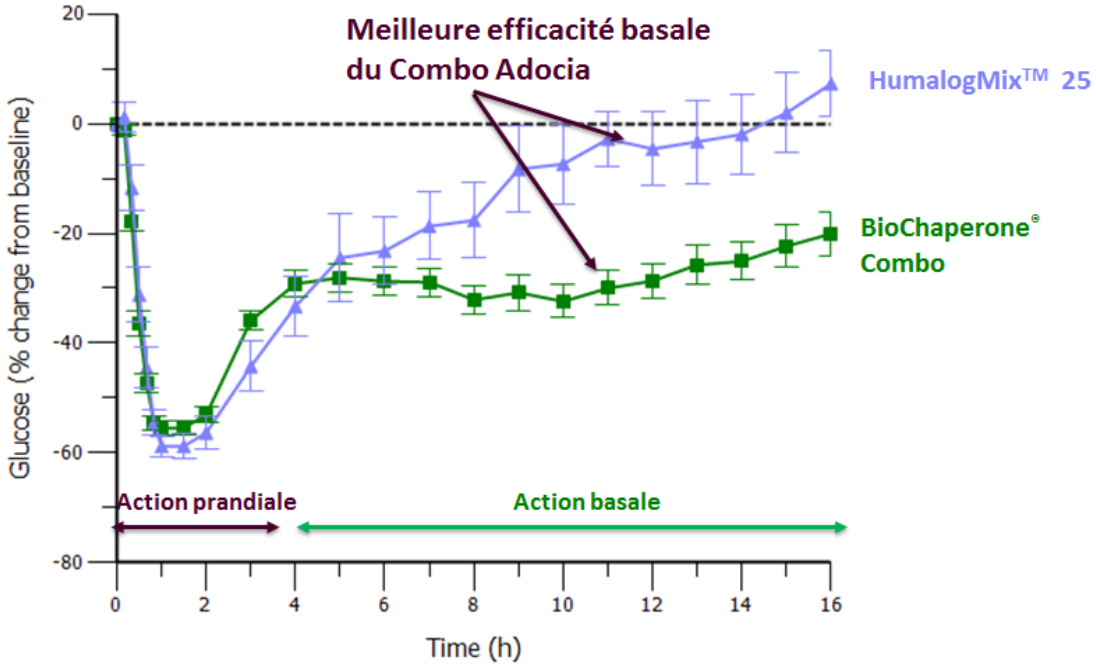


Figure 21: Comparison of the pharmacodynamic profiles of Adocia BioChaperone®-glargine-lispro Combo and of the Humalog Mix®25 premix (insulin-lispro and insulin-lispro-NPH): preclinical results in dogs (model correlated with humans)

Based on these positive results, Adocia started a phase I/II clinical trial in November 2013 on 20 type 1 diabetics. The purpose of the trial was to show that this combination provided diabetic patients with better blood glucose control than that obtained with an insulin analog premix such as Humalog Mix® formulated with insulin lispro (Eli Lilly) or NovoMix® formulated with insulin aspart (Novo Nordisk). The pharmacodynamic and pharmacokinetic profiles of the BioChaperone®-glargine-lispro combination have been compared to those of Humalog Mix® in a crossover trial in 20 type 1 diabetics using the glucose clamp technique.

The preliminary results of this trial were announced on February 27, 2013 and the final results have been published on March 20,2014:
- the onset of action of BioChaperone® Combo is at least 30% more rapid than that of Humalog Mix®,
- the duration of action is more than 30 hours in most patients,
- the BioChaperone® Combo formulation is safe and well accepted.

6.4.2.5 The competition

6.4.2.5.1 The competition for the prandial treatment of diabetes

Novo Nordisk

Novo Nordisk is developing a new formulation of its fast insulin analog (insulin aspart) whose action is believed to be more rapid than that of NovoLog® (FiAsp, ultra fast acting analog). Novo Nordisk started a phase III trial in late 2013 and initial publications on pharmacokinetic and pharmacodynamic profiles have shown a fast-in effect (more rapid onset of action).

Biodel

The American company Biodel, as Adocia, has recognized the value of a human insulin product with an action as rapid as that of analogs. Biodel has developed a formulation of fast acting human insulin called VIAject™ (BIOD-090) whose performance seems to be comparable to that of analogs.

VIAject™ is a formulation of human insulin with ethylenediaminetetraacetic acid (EDTA) and citric acid whose pH is around 4.5. The insulin concentration of VIAject™ is 4 times lower than that of products on the market. VIAject™ has been tested in many phase I, II, and III trials. Phase I results had shown that the BIODEL technology enabled the absorption of human insulin (insulinmia) and regulation of glycemia (blood glucose) that was as rapid as the insulin analog lispro and more rapid than Humulin® human insulin at the same doses[54]. In phase III, VIAject™ had shown its non-inferiority to a commercial human insulin, Humulin® (Eli Lilly)[55]. The administration of VIAject™, however, caused pain at the injection site. Biodel applied for a Marketing Authorization of this formulation (VIAject™) in the United States in October 2010, but the FDA rejected the application. The FDA requested Biodel to conduct a new phase II clinical trial on type 1 and 2 diabetics, based on the judgment that the initial data were insufficient and did not clearly demonstrate superiority of this product.

Biodel conducted new preclinical studies of performance and prepared a new formulation of human insulin, BIOD-123 whose pharmacokinetic and pharmacodynamic profiles were equivalent to VIAject™ but with attenuated reactions at the injection site. BIOD-123 has been tested in phase I and II trials. In September 2013, Biodel announced positive phase II results showing the non-inferiority of BIOD-123 compared to Humalog® in terms of control of prandial blood glucose (level of HbA1C).

BIODEL used the same type of formulation (citrate-EDTA) and also commenced the development of ultra fast insulin lispro formulations (prandial insulin analog, Humalog®, Eli Lilly), BIOD-250 and BIOD-238. BIOD-250 was tested in phase II and showed a more rapid prandial action compared to Humalog®, as well as good acceptability. The stability of this formulation, however, is insufficient for commercial development. In early 2014 BIODEL announced the continuation of development of a new formulation that would comply with stability criteria.

Halozyme Therapeutics

Halozyme Therapeutics recently conducted a clinical trial to demonstrate the increased rate of absorption of human insulin or insulin analogs. Halozyme Therapeutics is developing a recombinant human enzyme, hyaluronidase PH20 that depolymerizes hyaluronic acid in physiological conditions. This polysaccharide is a constituent of the extracellular matrix and is found in a large number of tissues: connective, epithelial and nerve. It is also present in the subcutaneous compartment where the injection of hyaluronidase degrades the matrix. The diffusion of proteins injected with this enzyme is improved, leading to more rapid diffusion of the drug substance from the injection site to the capillary network[57]. This technology is used for monoclonal antibodies to enable their subcutaneous rather than intravenous administration (products authorized in Europe in 2013 and 2014, in partnership with Roche: Herceptin SC® and MabThera SC®).

---

[57] G.I. Frost Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous drug and fluid administration. Expert opinion on drug delivery 2007, 4, 4, 427-440

In a phase I clinical trial[58], the effect of hyaluronidase on the rate of absorption by the blood compartment was demonstrated: there was an increased rate of absorption of human insulin by the combined administration of PH20 with Humulin® and the accelerated absorption of an insulin analog by the combined administration of PH20 with Humalog®.

A phase II clinical trial involving type 1 diabetics also showed the positive effect of PH20 on the pharmacokinetics of human insulin by the combined administration of Humulin® with hyaluronidase. The results also showed a reduction of post-prandial blood glucose and attenuated hypoglycemia in comparison to Humulin® alone.

A phase II clinical trial conducted in 2012 on type 1 diabetics showed the effect of PH20 on the increased absorption rates of two insulin analogs: insulin lispro and insulin aspart. For both insulins, there was improved control of post-prandial blood glucose for analogs formulated with PH20 compared to insulin lispro.

At the present time, however, this enzyme cannot be formulated with insulin because of insulin stability issues. The treatment therefore still involves combined administration, but insulin and hyaluronidase are mixed just before injection. Halozyme is planning to deliver its ultra fast analogs with pumps to resolve this problem, at the same time as taking a position on the future artificial pancreas market.

Mannkind

The company Mannkind was created in 1991 by Alfred Mann. Mannkind acquired Technosphere technology and the Medtone inhaler by purchasing Pharmaceutical Discovery. The acquisition of these technologies resulted in the product Afrezza, a human insulin administered by inhalation. It is an ultra fast human insulin whose concentration peak occurs 12 to 15 minutes after inhalation. Insulin delivered *via* this route has a shorter time of onset of action and the curve lacks a tail, or trailing edge, in contrast to human insulin administered subcutaneously. Its pharmacokinetic profile is very close to that of insulin secreted by the pancreas in healthy subjects. This results in better control of blood glucose after meals and a reduced proportion of glycated hemoglobin, HbA1c.

Based on these results, Mannkind submitted an initial Marketing Authorization application in 2009. The FDA issued an initial response in March 2010, requiring additional information. Following a meeting with the FDA, Mannkind re-submitted its application that the FDA again rejected in January 2011. In a second response, the FDA did not accept the use of Afrezza in type 1 and type 2 diabetic adults, requiring two additional phase III clinical trials with the new inhaler, called Dreamboat.

In August 2013, the company announced the results of these two phase III clinical trials. They established the product's non-inferiority compared to NovoLog® (insulin aspart, Novo Nordisk) in type 1 diabetics and a superiority over oral antidiabetics in type 2 diabetics; there was no negative change in the results concerning safety, the reduction of the number of hypoglycemia episodes and reduction of weight gain. The company resubmitted its MA application based on these results.

On January 10, 2014, Mannkind announced that the Endocrinology and Metabolic Drugs Advisory Committee of the FDA set April 1, 2014 as the date on which the Afrezza application could be reviewed. This date is to be confirmed by a memo (Federal Register notice) from the FDA.

---

[58] D.E. Vaughn, R.C. Yocum, D.B. Muchmore, B.J. Sugarman, A.M. Vick, I.P. Bilinsky and G.I. Frost Accelerated pharmacokinetics and glucodynamics of prandial insulins injected with recombinant human hyaluronidase. Diabetes Technol. Ther 2009, 11(6), 345-352

In 2005, Pfizer received authorization for an inhaled insulin, Exubera, but the product was a commercial failure and was rapidly taken off the market.

6.4.2.5.2 The competition for treating diabetes with Combos

Novo Nordisk

Novo Nordisk is currently developing a Combo formulation of NovoLog® (fast acting analog) and degludec, a slow insulin analog, developed by Novo Nordisk.

Degludec was developed to replace detemir in the next few years to enable Novo Nordisk to have a product whose action is close to that of Lantus, and therefore longer than that of detemir.

Novo Nordisk recently published[59] the results of a 16 week clinical trial on type 2 diabetic patients in which the performance of two degludec/NovoLog® Combos (at two different proportions: 70/30 and 55/45) was compared to that of Lantus®. The results indicate that daily injections of Degludec Combo are well accepted by patients and lead to a control of blood glucose comparable to that of Lantus® with lower extents of hypoglycemia. These Combos also enable a better control of post-prandial blood glucose (after meals) because of the fast action of aspart.

In 2013 Novo Nordisk was granted a Marketing Authorization in Japan and Europe for Tresiba®, (insulin degludec) and for Ryzodeg®, the combination of degludec with NovoLog® (slow insulin-fast insulin Combo). Ryzodeg® is the first product of this type authorized for marketing, but these products have not yet been approved in the United States. The FDA requested Novo Nordisk to conduct additional trials on the potential cardiovascular adverse effects of Tresiba®, which will delay marketing of the product by several years. Adocia's insulins, based on Lantus® (insulin glargine), on the contrary have a large body of positive data available on the safety of insulin glargine.

Biodel

Biodel is currently developing a formulation of ultra concentrated human insulin (400 IU), BIOD-531. The company's desired market position is to be a competitor of premix products and also to treat patients with severe resistance to insulin. In February 2014 Biodel announced the preliminary results of its phase II trial in obese, non-diabetic patients, comparing BIOD-531 to Humulin® R U-500 (concentrated human insulin, Eli Lilly) and to Humalog Mix® 75/25 (Eli Lilly). The acceptability and safety profiles of BIOD-531 are comparable to that of Humalog Mix®. Compared to Humalog Mix®, the results show a significant acceleration of the onset of prandial action of the product, and a prolongation of basal action until about 18 hours post-injection.

6.4.2.6 Progress provided by BioChaperone® technology

The developments under way by Adocia involve all segments of insulin treatment of diabetes (human insulin, insulin analog, Combo). The total value of these markets is more than $7-8 billion and the company could enter them *via* the signature of partnerships (refer to section 6.4.1.2. The market). The company has shown (refer to section 6.4.2.3. Clinical trials conducted by Adocia), using insulins marketed by large pharmaceutical companies, that it is possible to use the BioChaperone® technological platform to eventually produce and market:

---

[59] A New-Generation Ultra-Long-Acting Basal Insulin With a Bolus Boost Compared With Insulin glargine in Insulin-Naive People With Type 2 Diabetes: A randomized, controlled trial, Heise,T., Tack,C.J., Cuddihy,R., Davidson,J., Gouet,D., Liebl,A., Romero,E., Mersebach,H., Dykiel,P., Jorde,R., Diabetes Care, 2011, 34(3), 669-674.

- a BioChaperone®-human insulin complex, HinsBet®, with a time to onset of action more rapid than that of a human insulin and similar to that of an insulin analog in a phase I trial and a phase IIa trial;
- a fast acting BioChaperone®-insulin complex (Humalog® or NovoLog®) with a time to onset of action more rapid than that of the insulin analog alone, currently in phase II; a complex at neutral pH of BioChaperone®-fast acting insulin (Humalog® for example) -slow acting insulin (Lantus). This forms a single Combo retaining the fast action of Humalog® at the same time as enabling the basal action of Lantus® up to 16 hours after its injection in a preclinical study, just as a double injection of Lantus® and Humalog®, currently being tested in phase I/II

Adocia has also received financial support from the OSEO and the Regional European Development Fund (FEDER) in the form of subsidies and upfront loans for a total of €1,640,000 euros (refer to section 22.2 of this reference document Contracts signed with OSEO).

6.4.3. Innovative formulation of monoclonal antibodies

In order to obtain maximal benefit from its BioChaperone® technological platform and ultimately sign license contracts, Adocia is currently working on two joint development programs with major pharma companies to design new formulations of their therapeutic proteins. The goal of these new formulations is to improve efficacy, safety and compliance of the therapeutic proteins of its partners by providing new properties to become best-in-class products. In the framework of these development contracts, Adocia's partners furnish the quantities of therapeutic proteins required for the work and Adocia is reimbursed for costs incurred for research and making BioChaperone® technology available, which have thus far reached €1.18 million.

Monoclonal antibodies were developed in 1975 by Georges Köhler and Cesar Milstein, who received the Nobel Prize in Medicine in 1984 for their work.

Monoclonal antibodies are the products with the highest growth of the pharmaceutical industry. This progress has been rapid because of the number of severe oncology pathologies involved (treatments of leukemias, lymphomas, breast cancers, colorectal cancers, etc.) and their value for the treatment of autoimmune and inflammatory diseases (rheumatoid polyarthritis, Crohn's disease, multiple sclerosis, etc.). An additional reason for rapid growth has been the development of large scale production techniques.

Several monoclonal antibodies have become blockbusters, i.e. with sales over one billion dollars, in particular Remicade® (Johnson & Johnson: $7.7 billion in 2012), Avastin® (Roche: $6.3 billion in 2013), Enbrel® (Amgen & Pfizer: $8.3 billion in 2013), Humira® (Abbott Laboratories: $9.3 billion in 2012), Rituxan®/Mabthera® (Roche, Biogen & Genentech: $6.1 billion in 2013) and Herceptin® (Roche: $6.45 billion in 2013).

These molecules operate primarily as inhibitors, by trapping active proteins or by binding to cell receptors to prevent the binding of ligands. This strategy requires a systemic concentration high enough to block targets and therefore the administration of high doses. In these conditions, stability and formulation issues may predominate and result in therapeutic consequences in terms of efficacy and immunogenicity. In most cases the method of administration involves intravenous infusion after diluting the antibodies in isotonic saline. Some antibodies administered intravenously aggregate during storage and this can cause immune reactions, even reduced antibody activity. The number of subcutaneously administered monoclonal antibodies is increasing. In September 2009, GENMAB and its partner GSK stated that they were re-directing work towards the production of a version for subcutaneous injection of their product Arzerra. This route of administration should be the preferred solution for the pharmaceutical industry but to reach this end, formulations of totally soluble antibodies at high concentrations must be developed.

Adocia is carrying out joint work with two large pharmaceutical companies in order to develop a second generation formulation with the goal of becoming best-in-class products that would improve:

- the physical stability of antibodies to prevent the formation of aggregates that could reduce efficacy and increase immunogenicity of the products;
- the solubility of antibodies to prepare formulations at high concentrations and low viscosity for subcutaneous injection when this route is compatible with the pathology and the antibody used.

The company has also received a subsidy of €63,367 from the OSEO for its research on monoclonal antibodies.

6.5. Adocia oncology products developed with DriveIn® technology

6.5.1. Pathology

Cancers are a pathological cell proliferation in a healthy tissue that threaten the survival of the tissue in question, even the organism itself. This abnormal proliferation results from mutations of cell cycle genes in cancer cells that may arise from hereditary anomalies and/or environmental factors (life style, exposure to carcinogens, infections, etc.).

Cancers are currently one of the leading causes of death in developed nations. The most frequent cancers in the global population are lung cancer, breast cancer and colorectal cancer (see Table 10).

Cancer	Worldwide incidence (number of new cases yearly, in millions)	Worldwide mortality (yearly, in millions)
Non-small cell lung cancer	1.6	1.4
Breast cancer	1.4	0.4
Colorectal cancer	1.2	0.6
Stomach cancer	0.99	0.7
Prostate cancer	0.9	0.3
Liver cancer	0.75	0.69
Cancer of the head and neck	0.74	0.4
Pancreatic cancer	0.28	0.25
Kidney cancer	0.27	0.1
Melanoma	0.2	0.05
Ovarian cancer	0.2	0.14
Multiple myeloma	0.1	0.05

Table 10: Worldwide incidence and mortality from the most frequent cancers (Source: Cancer Research UK)

Mortality rates depend on the type of cancer, its stage of advancement at the time of diagnosis and on available treatments. For example, while the 5 year survival of patients with a stage I ovarian

epithelial cancer is 89%, the rate of the same cancer diagnosed at stage IV (metastatic) is only 18% (Source: National Cancer Institute). Similarly, patients with HER2-positive breast cancers (cancer resulting from the mutation of the HER2 gene) can be effectively treated, for example with Herceptin® (Roche, monoclonal antibody), while patients with so-called triple negative breast cancers (resulting from different genetic mutations) have very few therapeutic options available.

Medical needs vary considerably from one cancer to another and the disease therefore remains difficult to eradicate, explaining why oncology research is very active, with the hope of prolonging the lives of patients and improving their therapeutic management.

6.5.2. Drive*In*® oncology products

6.5.2.1 Types of treatment

The therapeutic oncology arsenal has become greatly diversified over the past several years. The first line of treatment for most solid tumors is surgery that excises accessible and delimited tumors. Surgery may be concomitant with, or followed by chemotherapy at a later time, whose purpose is to make cancer cells enter apoptosis (pre-programmed cell death). In a substantial number of cases, surgery and chemotherapy may, however, be unusable, insufficient or ineffective. Recourse to drug therapy is therefore very important and several types of treatments are available.

6.5.2.1.1 Chemotherapy

Chemotherapy is the treatment of cancer with chemical molecules and remains the lynchpin of therapeutic management in oncology; the first chemotherapy treatments were developed in the 1940s. The principal treatments currently on the market belong to several large families of molecules discovered between the 1950s and 1990s: taxans, platinum derivatives, anthracyclins, alkaloids, and nitrogen mustards in particular (see Table 11). In most cases, the drugs containing these molecules are administered intravenously. Many of them are now in the public domain (patents expired) and are still extensively used as first line treatment (in particular taxans, platinates and anthracyclins).

Molecule (public domain)	Name (company)	Market (year)	Peak of sales (year)
Docetaxel (2010)	Taxotere® (Sanofi)	$742 million (2012)	$3.1 billion (2010)
Pemetrexed (2015-2022)	Alimta® (Eli Lilly)	$2.594 billion (2013)	$2.594 billion (2013)
Temozolomide (2013)	Temodar® (Merck) (Dacarbazine pro-drug)	$2.213 billion (2013)°	2.323 billion (2011)
Oxaliplatin (2013-2016)	Eloxatine® (Sanofi)	$1.229 billion (2013)	$2.17 billion (2006)
Gemcitabin (2010)	Gemzar® (Eli Lilly)	$347 million (2013)	$1.7 billion (2008)
Paclitaxel (2000-2003)	Taxol® (BMS)	$148 million (2011)	$1.6 billion (2000)
Capecitabin (2013)	Xeloda® (Roche Genentech)	$1.435 billion (2013)	$1.624 billion (2012)
Doxorubicin (n.a.) **Liposomal doxorubicin (2009)**	Rubex®, Adriamycin®; Doxil® (J&J)	n.a. $402 million (2011)(*)	n.a. n.a.
Irinotecan	Camptosar® (Pfizer)	$130 million (2013)	$970 million (2007)

Table 11: Chemotherapy best sellers in oncology. Most of these molecules are indicated for the treatment of several types of different cancers. (Source: Datamonitor Healthcare). Sales of Doxil® reported for 2011, before the supply issues encountered by Johnson & Johnson (2012).

These treatments act on cell division, most often with the goal of stopping cell proliferation (treatments called cytostatic) or even killing cells (treatments called cytotoxic). Cancer cells divide to a greater extent and more rapidly than healthy cells and so these treatments preferentially attack rapidly dividing cancer cells. The vast majority of non-cancer cells in the body also divide regularly, however, so chemotherapies also damage healthy tissues. The elevated efficacy of chemotherapies is therefore limited by toxicity to healthy cells that is often extensive. This explains why oncology treatments have progressed to approaches called targeted.

6.5.2.1.2 Targeted therapy

In order to increase the therapeutic index (the efficacy/adverse effects ratio) of oncology treatments, research is being oriented toward development of "targeted" treatments, i.e. preferentially aimed at cancer cells and avoiding possible attack on healthy tissues as much as possible. Targeted therapies block the growth of cancer cells by acting specifically on proteins involved in carcinogenesis and tumor growth, rather than targeting all dividing cells. These therapies may be targeted inhibitors (small molecules), monoclonal antibodies or antibody-drug conjugates (ADC).

Targeted inhibitors

Most marketed targeted inhibitors interfere (by competition or inhibition) with the activity of members of the family of kinases, but their targets may differ. The first targeted inhibitors (Gleevec®, Sutent®) were marketed in the 1990s and had a significant impact on their indications, in particular for leukemia. Most of these products are administered orally. The principal targeted inhibitors on the market are listed in Table 12.

Compound	Target	Name (company)	Worldwide sales (2013)	Indications
Imatinib	Tyr-kinase	Gleevec® (Novartis)	$4.81 billion	Ph+ chronic myeloid leukemia (CML), gastrointestinal stromal tumor (GIST), acute lymphoblastic leukemia (ALL), other rare cancers
Lanalidomide	Immuno-modulator	Revlimid® (Celgene)	$3.77 billion	Myelodysplasic syndrome
Bortezomib	Proteasome	Velcade® (Millenium Pharma-Takeda)	$2.41 billion	Recurrent multiple myeloma, mantle cell lymphoma
Erlotinib	Tyr-kinase	Tarceva® (Roche)	$1.97 million	Non-small cell lung cancer (NSCLC); pancreatic cancer
Dasatinib	Tyr-kinase	Sprycel® (BMS)	$1.37 billion	CML; Ph^+ ALL
Sunitinib	Tyr-kinase	Sutent® (Pfizer)	$1.30 billion	Kidney cancer; GIST; pancreatic cancer
Nilotinib	Tyr-kinase	Tasigna® (Amgen)	$1.12 billion	Ph^+ CML (imatinib-resistant)
Gefitinib	EGFR	Iressa® (AstraZeneca)	$624 million	Breast cancer, NSCLC

Lapatinib	Tyr-kinase	Tykerb® (GSK)	$400 million	HER2+ breast cancer

Table 12: Best sellers of targeted inhibitors. (Source: Datamonitor Healthcare, 2013)

6.5.2.2 Market size and pipeline

The segment of oncology is currently the largest of the pharmaceutical industry market. In 2013, it was estimated at $66 billion (Source: Datamonitor Healthcare). It is also the most active therapeutic area in terms of products under development: in December 2013, Datamonitor inventoried 543 products tested in phase I, 894 products in phase II and 209 in phase III. The vast majority (883) of these molecules under development involves small molecules (chemotherapy and targeted inhibitors).

6.5.3. Drive*In*®, an innovative approach to targeted delivery in oncology

Chemotherapies remain one of the cornerstones of treatment in oncology because of their elevated efficacy. These molecules have harmful effects on healthy cells, however, causing toxicities that may limit the use of these treatments. In order to improve this situation, the active targeting approach is a viable option. Drive*In*® technology is promising for active targeting and cell uptake of drugs thet it transports. These properties are due to the ability of its hyaluronic acid surface to interact with the CD44 receptor, a marker of tumor stem cells.

Adocia has developed two products in-house that use Drive*In*® technology*:* Drive*In*®-doxorubicin and Drive*In*®-docetaxel. Doxorubicin (Adriamycin®, Doxil®, Myocet®, Lipodox®) and docetaxel (Taxotere®) are two of the most widely used drug substances for the treatment of solid tumors. They are now in the public domain but still generate global sales of several hundred million dollars.

Preclinical results

Initial work of Drive*In®* was conducted with the goal of showing:

- *In vitro*, the principle of cell targeting and increased cell uptake resulting from hyaluronic acid
- *In vivo*:
    - non-toxicity of nanoparticles
    - improved treatment safety resulting from enhanced selectivity (preferential accumulation in the tumor compared to healthy tissues) and efficacy of the treatment

Increased intracellular presence of DriveIn®-doxorubicin compared to the active molecule alone

Upadhyay and al (2010)[5] worked *in vitro* on the MCF-7 line of cancer cells (that overexpress CD44, the hyaluronic acid ligand). They compared the cell uptake of doxorubicin and Drive*In*®-doxorubicin when the products were added to the culture medium. The authors showed that the uptake of Drive*In®*-doxorubicin was at least equivalent to that of doxorubicin alone. After 24 hours, doxorubicin levels started to decrease in cells treated with doxorubicin alone, while drug levels were maintained with Drive*In*®-doxorubicin, suggesting better retention of doxorubicin transported and/or better cell uptake of the product (see figure below).

5 Upadhyay and al (2010), Biomaterials 31: 2882-2892

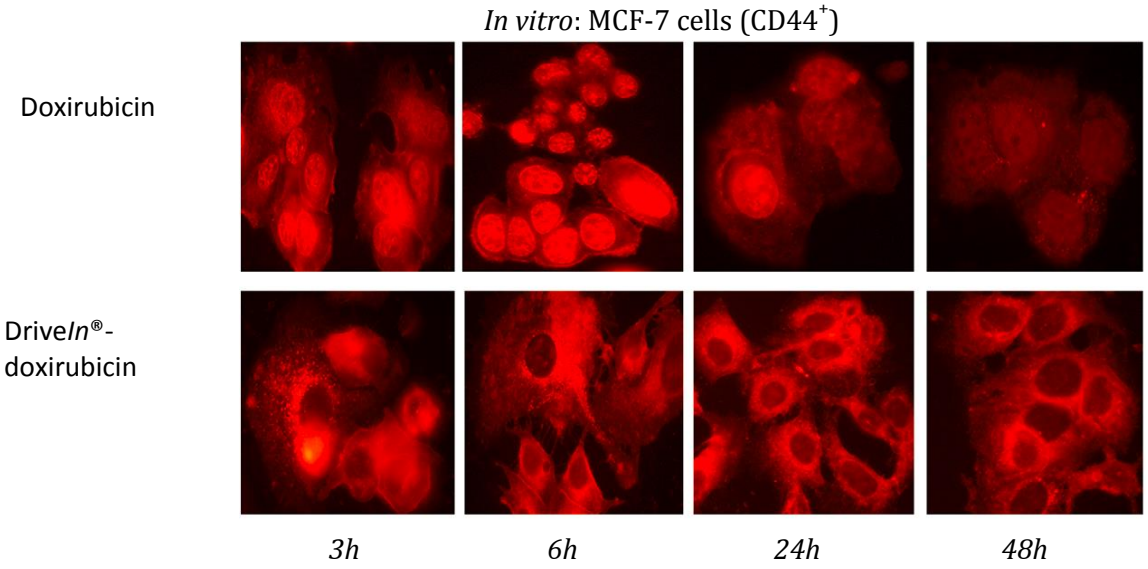


Figure 22: Fluorescence microscopy images of uptake of 10 µM doxorubicin alone by MCF-7 cells (top) and DriveIn®-doxorubicin (bottom) at 3h, 6h, 24h and 48h.

Encapsulation of doxorubicin and mediation of uptake by a hyaluronic acid receptor

Additional experiments[6] showed that adding free hyaluronic acid to the culture medium interferes with the uptake of Drive*In*®-doxorubicin with no effect on that of free doxorubicin. This confirms:

- that doxorubicin is well encapsulated in Drive*In®* molecules,
- that delivery of doxorubicin inside the cell is mediated by an active mechanism involving hyaluronic acid receptors.

Lack of intrinsic toxicity of nanoparticles, even at high doses.

Based on these very promising results *in vitro*, experiments *in vivo* were carried out in mice, using the model of tumors induced by a carcinogen.
The first result was that nanoparticles without doxorubicin show no intrinsic toxicity in this experiment. The comparison of body weight changes of animals between 5 and 25 days, between the placebo (solid circles, black curve) and nanoparticles without doxorubicin (triangles, light blue curve) demonstrate that these changes were the same between 5 and 25 days.

6 Upadhyay et al (2010), Biomaterials 31: 2882-2892

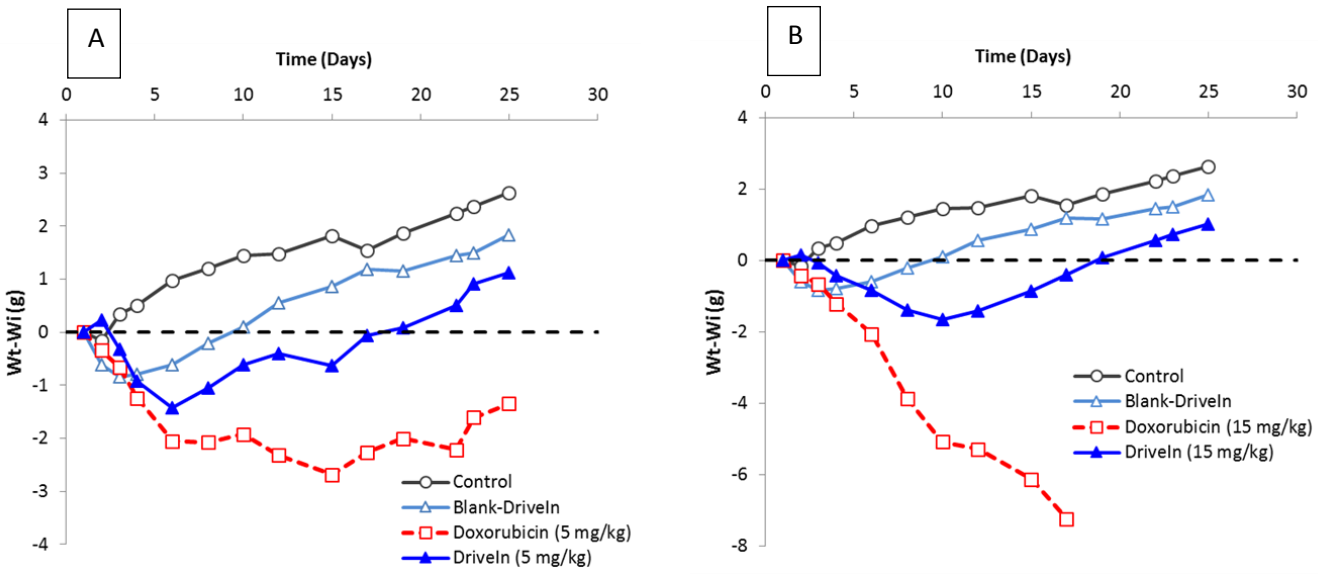


Figure 23: Body weight curves of EAT-Balb-C mice (6 animals/group) injected with saline solution (control, black curve), DriveIn® nanoparticles alone at 20 mg/kg (Blank-DriveIn®, light blue curve), doxorubicin at 5 mg/kg (red curve panel A) or 15 mg/kg (red curve panel B) and DriveIn® particles containing doxorubicin at 5 mg/kg (dark blue curve panel A) or 15 mg/kg (dark blue curve panel B)

Accumulation of DriveIn®-doxorubicin in tumors

The EPR effect (due to the size of Drive*In*® nanoparticles), combined with active targeting by hyaluronic acid, should lead to the accumulation of Drive*In*® nanoparticles in the tumor. This hypothesis was tested on two animal models of cancer with Drive*In*®-docetaxel[7] and Drive*In*®-doxorubicin[8]. In both cases, the results showed the preferential accumulation of Drive*In*® in the tumors compared to the active product alone (see *Figure 24*).

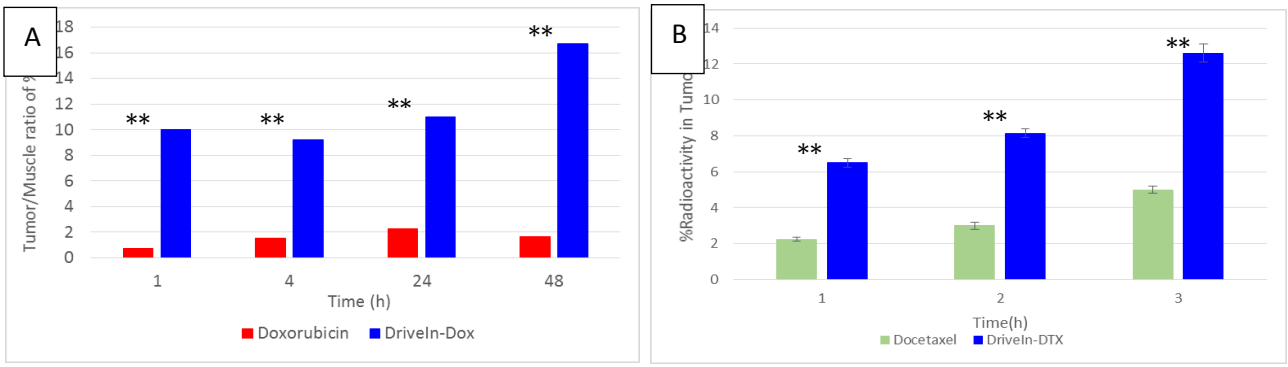


Figure 24: Kinetics of the tumor/muscle ratio of DriveIn® assayed at different times after injection of the product in mice with cancers. A: EAT Balb-C mice, DriveIn®-doxorubicin vs. doxorubicin alone at 5 mg/kg (Dox). B: EAT (CD44+) mice; DriveIn®-docetaxel vs. docetaxel at 2 mg/kg. (: P < 0.05, **; P < 0.001).*

7 Upadhyay et al (2012) Nanomedicine: Nanotechnology, Biology and Medicine 8:71-80
8 Upadhyay et al. (2010), Macromol. Biosci., 10:503-512

Improvement of efficacy in vivo

Improved targeting and uptake of the molecule transported should result in higher efficacy at the same dose, compared to the drug substance in its standard formulation. This increased efficacy has been shown for Drive*In*®-doxorubicin in several murine models of cancer.

In initial work, Upadhyay et al[7] injected Drive*In*®-doxorubicin vs. doxorubicin alone in DMBA mice (model of breast cancer) at 5 mg/kg. The authors reported the decreased progression of tumors over 30 days, as well as the total size of tumors at 30 days in mice treated with Drive*In*®-doxorubicin compared to doxorubicin alone see (*Figure 25*).

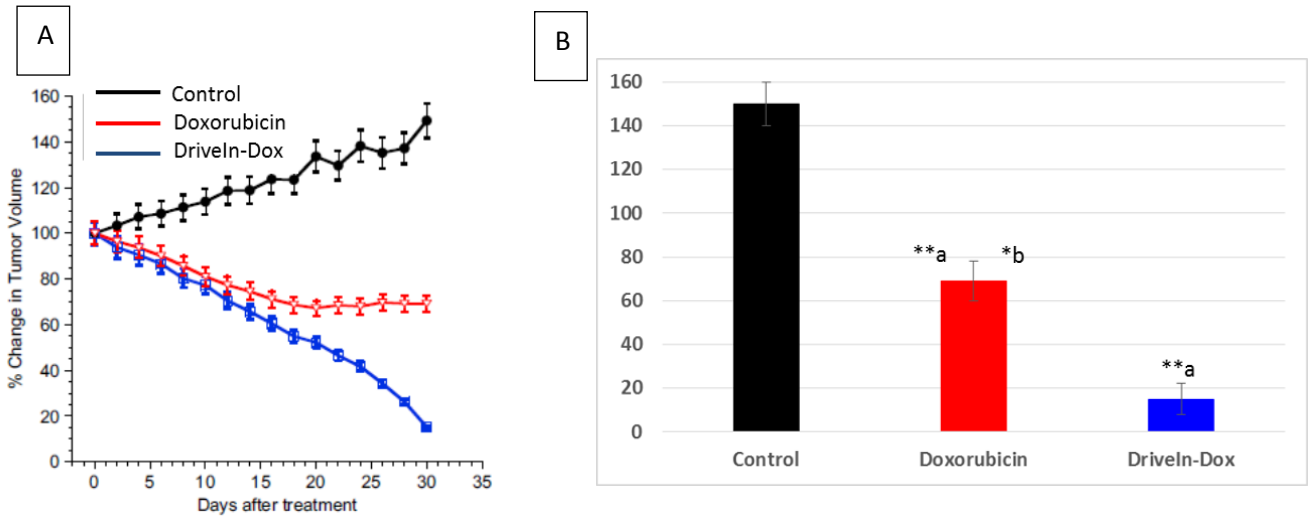


Figure 25: Reduced tumor progression and total tumor volume (A) at 30 days, and as a ratio compared to starting values (B) in DMBA mice after injecting doxorubicin and DriveIn®-doxorubicin at 5 mg/kg, 6 animals per group. (: P < 0.05; P < 0.001; a: vs. control; b. vs. DriveIn®-doxorubicin).*

In a second series of experiments, Upadhyay et al (2012)[9] injected Drive*In*®-doxorubicin vs. doxorubicin alone in EAT-Balb-C mice (murine model of an induced cancer) at 5 mg/kg. The authors reported a significant reduction in the growth of tumors over 30 days, as well as increased survival of mice treated with Drive*In*®-doxorubicin compared to doxorubicin alone (see Figure 26

9 Upadhyay et al (2012), Nanomedicine: Nanotechnology, Biology and Medicine 8: 71-80

7. OVERVIEW OF ACTIVITIES

7.1. Presentation of Adocia

Adocia is a French biotechnology company founded in December 2005 by Gérard, Olivier and Remi Soula. It is specialized in the development of best-in-class medicines from approved therapeutic molecules, in particular proteins using its BioChaperone® technology and anticancer drugs using its Drive*In*® technology.

7.1.1. Rekying on the BioChaperone® technological platform to be a major player in the area of insulin therapy and healing of chronic wounds resulting from its

The authorized proteins used by Adocia treat widespread pathologies. Innovations to the formulation of these proteins have led to their improved efficacy, to a simpler and broader therapeutic use and thereby to improved quality of life of patients. Among the main therapeutic areas, Adocia initially focused on two market segments:

3. treatment of diabetes by insulin therapy
4. regenerative medicine*, in particular the treatment of chronic wounds* by a growth factor*, platelet derived growth factor-BB (PDGF-BB).

These two proteins, insulin and PDGF-BB are authorized in the United States and Europe and have proven their superior efficacy in their respective areas. Even so, their efficacy and usage could be significantly improved by better formulations.

To this end, Adocia has designed and developed a technological platform using a new family of polymers called BioChaperone® that have the property of spontaneously combining with these proteins. After combining, BioChaperones provide the proteins with new properties:

- an increase in their solubility;
- protection from enzymatic breakdown*;
- stabilization of therapeutic proteins during storage; and
- stabilization of the activity of therapeutic proteins in the presence of cells.

These important properties result in increased efficacy of the therapeutic protein, in particular by facilitating its absorption in the body, by a faster of onset of action and by an increased duration of action. These properties lead to envisioning a significant improvement of existing medical treatments by improving the expression of the properties of therapeutic proteins, by modifying dosages (reduction of dose, of the number of applications and the duration of the treatment) and/or by changing routes of administration of treatments. These properties also enable new fields of applications for a given therapeutic protein to be considered.

In addition to increasing the efficacy of these formulations in comparison to those currently on the market, these new properties will also improve safety and compliance* with pharmaceutical industry regulations concerning proteins combined with BioChaperone®. By the use of BioChaperone®, Adocia has obtained products that can be considered as best-in-class, i.e. having the best therapeutic effects in their therapeutic class.

The BioChaperone® technological platform can also be used for other therapeutic classes of proteins such as monoclonal antibodies or growth hormones.

The company has decided to use the properties of its collection of BioChaperone® polymers for very large markets in the following areas:

- healing of chronic wounds with the treatment of diabetic foot ulcers and developments planned for the treatment of venous ulcers, bedsores* (bedsores, pressure sores, decubitus ulcer) and burns by the combination of BioChaperone® and the growth factor called PDGF-BB (platelet derived growth factor-BB);
- insulin therapy with the treatment of type 1 and type 2 diabetes by insulin in the form of novel formulations of insulins, so-called second generation ("BioChaperone® Insulins"):
    - a fast-acting BioChaperone®-human insulin complex* with a more rapid onset of action that that of human insulin and similar to that of an insulin analog
    - an ultra-fast acting BioChaperone®-insulin analog complex that starts acting more rapidly than an insulin analog alone
    - a BioChaperone® complex containing a fast acting insulin and the lmong –acting insulin analog glargine, forming a single Combo Insulin reuniting the rapid action of the former and the basal action of the latter
- chronic diseases with the market for monoclonal antibodies having many oncology applications (treatment of leukemias*, lymphomas*, breast cancers, colorectal cancers, etc.) and for the treatment of autoimmune and inflammatory diseases (rheumatoid polyarthritis*, Crohn's disease*, multiple sclerosis*, etc.) resulting from the development of a second generation of formulation of monoclonal antibodies ("BioChaperone® mAbs") that:
    - improves the physical stability of monoclonal antibodies to prevent the formation of aggregates that could reduce efficacy and increase the immunogenicity of products;
    - improves the solubility of monoclonal antibodies to enable the preparation of formulations at high concentrations so they can be administered subcutaneously rather than intravenously when the former mode of administration is compatible with the pathology in question and the monoclonal antibody used.

7.1.2. Relying on Drive*In*® technological platform to become an emerging player in the area of oncology

Starting in December 2013, Adocia began the development of Drive*In*® nanotechnology for the treatment of cancer. Adocia has obtained exclusive rights for the development and marketing of this patented nanotechnology developed by Professor Sebastien Lecommandoux and his team at the Laboratory of Chemistry of Organic Polymers (LCPO, UMR5629 CNRS - University of Bordeaux I - Polytechnic Institute of Bordeaux). This technology has been shown to be very effective in pre-clinical trials for the transport of drug substances and their delivery to solid tumors, thereby increasing the therapeutic index of these drug substances. This work has been described in several publications in benchmark international scientific journals.

As a result of elevated efficacy, chemotherapies have been one of the cornerstones of oncology treatment for several decades. These substances nevertheless cause major adverse effects related to the damage they cause to healthy tissues at the same time as destroying cancer cells. This explains why treating cancers with chemotherapy has progressed towards targeted approaches, by using molecules with intrinsic targeting such as monoclonal antibodies, or by developing transporters for chemotherapy molecules that target the treatment of only the tumor and leave healthy tissues intact. Adocia has opted for the second approach with the development of Drive*In*®, an innovative biomimetic nanotechnology for drug delivery in oncology.

Adocia intends using a dual strategy to develop this nanotechnology. Adocia is planning to develop proprietary products containing doxorubicin and docetaxel, two widely used anti-cancer drugs that could substantially benefit from better penetration in the cells of solid tumors. In addition, Adocia will propose its Drive*In*® technology to pharmaceutical companies in order to optimize the efficacy of their proprietary molecules.

Considerable work is under way by players in this sector in order to discover new oncology treatments but also to improve the performance of authorized products at the same time as attenuating their adverse effects. One of today's major goals of this quest for improvement is to ensure better targeting of solid tumors so the anticancer molecule can concentrate in the tumor, thereby limiting damage to surrounding healthy tissues.

The novelty of Drive*In®* resides in the use of nanoparticles whose surface is composed uniquely of hyaluronic acid, a biopolymer naturally present in the human body, known to interact with the CD44 cell receptor. This receptor is over-expressed in many solid tumors, providing Drive*In®* with its properties of targeting and incorporation in cancer cells. The drug delivered in this way would be more effectively incorporated by cancer cells, whereas existing therapies remain limited for this aspect.

With the acquisition of this new technology platform, the Company is preparing a second generation of innovations in its field of expertise: the delivery of approved therapeutic molecules

7.1.3. Adocia's economic model

The strategy and economic model of the company involves using the BioChaperone® and Drive*In®* technological platforms for the development of innovative formulations for different therapeutic molecules already authorized, with the goal of becoming best-in-class products.

The company will establish proof of concept of medical efficacy of its innovative formulations by phase I-II clinical trials in humans, sometimes remaining limited to preclinical studies with proof of concept in animals. Once the proof of concept is established, Adocia will license products obtained with its technologies to large pharmaceutical or medical device companies. Adocia is also planning on signing joint development contracts, similar to those currently in force for monoclonal antibodies in order to make best use of its technologies for new applications and with the goal of subsequently signing licensing contracts if initial trials are successful.

Adocia does not plan on producing and marketing its products.

The following diagram is a progress report on different Adocia projects under way at the date of registration of this reference document:

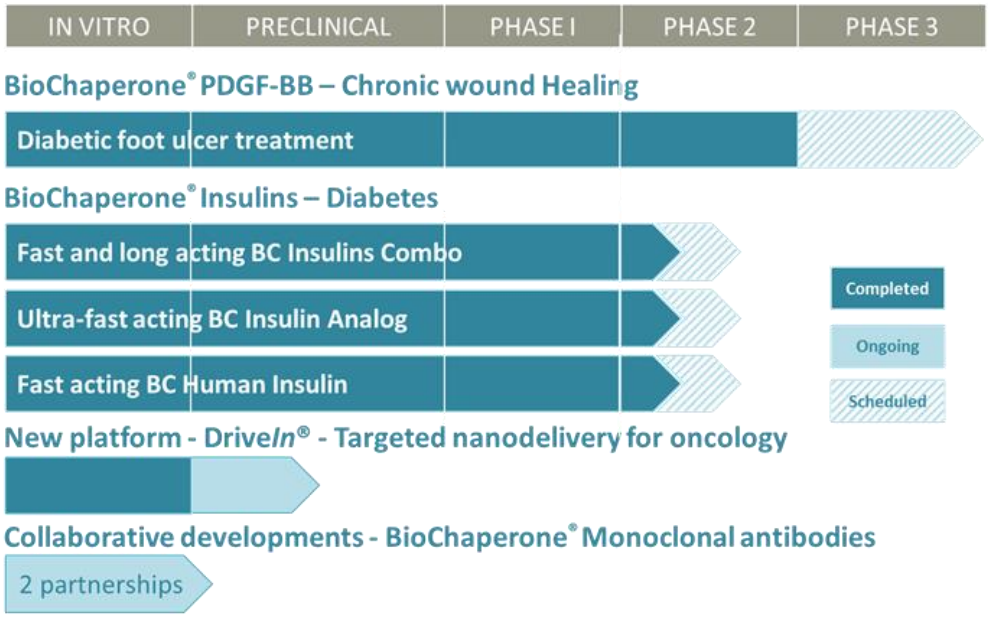


Figure 1: Adocia Pipeline as of April 20, 2014. Source: Adocia

In 2013, Adocia prepared to start three clinical trials for the treatment of diabetes. The first involved the combination a slow acting insulin, glargine, and a fast insulin, lispro. The trial began in mid-November 2013 and the results were published in press release of February 27, 2014 (preliminary results) and in a press release of March 20, 2014 (full results). The other two trials are planned during the year 2014: the first will involve a formulation of an ultra fast acting insulin analog (start of trial had been announced in après release in January 2014, results published on April 9,2014) and the second will involve fast acting BioChaperone® human insulin.

In the area of wound healing, the phase III clinical trial on the treatment of diabetic foot ulcers with BioChaperone® PDGF-BB in India has not started yet because Indian regulatory authorities (DCGI) underwent a reorganization that resulted in substantial delays in reviewing and approving applications.

The following table summarizes the clinical trials planned for 2014.

Indication	Product	Event	Expected dates ***(1)***
Treatment of diabetic foot ulcers	BioChaperone® PDGF-BB	Start of a phase III trial in India	2nd quarter of 2014 *(2)*
BioChaperone® fast acting human insulin	HinsBet®	Project to start a second phase IIa trial	3rd quarter of 2014
BioChaperone® fast acting insulin analog	BC lispro	Start of a phase IIa trial on type 1 diabetics (dose-escalating study)	2nd quarter of 2014
BioChaperone® Combo fast and slow insulins	BioChaperone® Combo	Project to start a phase I-II clinical trial (dose-escalating study)	3rd quarter of 2014

Table 1: Summary of clinical trials planned by Adocia for 2014

(1) As planed at the time of registration of this reference document, provided that the launch of clinical trials is subject to approval from local regulatory authorities
(2) The application for authorization was submitted in September 2012 and is still under review with Indian regulatory authorities

In practice, the above-mentioned clinical trial phases are defined as follows:

The preclinical phase is conducted after laboratory tests *in vitro.* The tests are run on animals with the goal of determining the efficacy and toxicity of the product before its potential administration to humans. In spite of metabolic differences between animals and humans, preclinical studies are an ethical prerequisite before administration of the product to humans. Animal research is conducted according to very strict rules that precisely describe the conditions of the work and related controls. Animal studies most often involve rats, rabbits or dogs. They provide data on the conditions of absorption, diffusion and elimination of the product, and its metabolism in the species in question.

Phase I is conducted on a small number of healthy volunteers. Its goals are to determine (i) the safety of the molecule in humans, (ii) its optimal route of administration (intravenous, subcutaneous, oral) and (iii) the maximal tolerated dose. Phase I trials usually last between 6 months and one year. In the course of development of some projects, however, phase I trials may not be required. This is because the results of phase I clinical trials on healthy volunteers in a therapeutic area with a specific application may enable a phase II clinical trial to be conducted directly for new applications in the same therapeutic area. In addition, in some cases, such as the treatment of wounds, the products can be tested only on patients and so directly enters phase II.

Phase II is conducted on patients. Its objective is to determine effects (efficacy and safety) of the medicine according to the doses and route(s) of administration determined in phase I. This type of trial generally lasts for 1 to 2 years.

Phase III is conducted on a larger patient population. Its goal it to test the efficacy and safety of the product and to determine the optimal dose (posology). This type of trial generally lasts for 2 to 3 years.

If the results of phase II and III trials demonstrate a genuine advantage in terms of benefits compared to risks, the new drug could be granted a Marketing Authorization/Product license from the competent authority (Health Ministry in France).

7.1.4. Considerable advantages over the competition

Using its BioChaperone® and Drive*In*® technology platforms, Adocia is developing new drugs intended to become best-in-class products in new formulations of therapeutic molecules that have demonstrated their value in treating the same or similar indications to Adocia's targeted indication; most of these products have received international Marketing Authorizations. BioChaperone® polymers have no intrinsic biological activity and are therefore registered with regulatory authorities as new excipients*. As a result, the development of new pharmaceutical products from these therapeutic molecules usually requires less time and less money than the development of a new pharmaceutical molecule. In addition, the risk of failure is lower because the therapeutic molecules in question have already proven their safety and acceptability with no harmful adverse effects for humans.

	Development of a new therapeutic protein	Development of a new formulation of an authorized therapeutic protein
Time before Marketing Authorization	10 to 15 years	5 to 8 years
Development cost	800 to 1,400 million dollars*	30 to 50 million dollars

* Tufts Center for the Study of Drug Development - 2007

Adocia has developed a genuine breakthrough technology with its collection of BioChaperone® polymers having multiple applications in the areas of regenerative medicine, the treatment of chronic pathologies and oncology. The strategy of diversification of indications is a lever against the usual risk of product development. In order to meet public health needs, Adocia is focusing on the development of new innovative formulations that provide a better expression of the intrinsic properties of therapeutic molecules that reinforce their efficacy or provide them with new properties resulting from the formation of the BioChaperone® polymer/therapeutic molecule complex. The company aims at mass markets, each representing several billion dollars.

Market	Estimated value
BioChaperone®- Growth factor PDGF-BB complex	
Treatment of diabetic foot ulcers	2.2 billion euros
BioChaperone® Insulins	
Fast acting BioChaperone®-Human insulin	3.9 billion euros
Ultra fast acting BioChaperone®-insulin analog	4.2 billion euros
BioChaperone® combining a fast acting insulin and a slow acting insulin forming Combo Insulin	3.5 billion euros
BioChaperone® mAbs	
Monoclonal antibodies	> 13 billion euros
Oncology	
Drive*In®*	48 billion euros

Table 2: Estimated values of markets concerned by Adocia innovations (Sources: Adocia, Datamonitor Healthcare, Business Insights).

Beyond innovative responses to public health needs, Adocia's strategy has been designed by management so that the global pharma-economic context is taken into account. The development of treatments can no longer be done without taking costs into account. This is because of increases in the prevalence* and incidence* of the pathologies targeted by Adocia, as well as the expansion of the world's population and its aging, in a policy context of controlling public health expenditures in Western countries and the growing demands of emerging economies. Healthy insurance entities, whether public or private, reimbursing patient costs are increasingly protesting the costs of medicines and medical services. These entities examine not only the safety, compliance and efficacy of products, but also their cost/effectiveness ratio. Political, economic and regulatory pressures, the explosion of generic drugs and general globalization have caused a profound change in the pharmaceutical industry. In this context, Adocia provides credible responses:

- to issues of innovations for large pharmaceutical companies that must face the widespread use of generic drugs and the expiration of many patents in the years to come, by proposing new formulations of their therapeutic proteins with new properties (shorter times of action, sustained action, different routes and/or modes of administration) that can provide heightened efficacy or at least equivalent to current treatments; and
- issues of treatment costs in developed and emerging nations (reduction of dosages, of the number of applications and duration of treatment, new routes and/or modes of administration).

This strategy of taking emerging nations into account is new for a French biotechnology company, but is opportune because of the considerable size of developing markets, and because regulatory

requirements for the development of pharmaceutical products remain highly demanding but are not as strict as those of the United States and Europe. Adocia is therefore conducting clinical trials in India for its most advanced product for the treatment of diabetic foot ulcers with the BioChaperone®-Growth factor PDGF-BB complex, before conducting clinical trials in Europe and the United States.

Adocia's economic model is based on signing license contracts for BioChaperone® applications once proof of concept is established in humans, even only in animals. This license model with a system of upfront payments at the moment of signature, of milestones with respect to reaching objectives, and royalties when products are marketed, will enable the company to obtain revenues as projects progress, without having to wait for the products to reach the market. This relatively "low burn-rate" model only requires the company to invest until proof of concept is established, after which the licensee assumes the costs of development and clinical trials.

Adocia has carried out joint development programs with major names in the pharmaceutical industry in the framework of second generation formulations for monoclonal antibodies. These joint work contracts reflect the interest of large pharma companies in BioChaperone® technology and are the first step before signing license contracts if initial studies provide positive results.

In December 2011, Adocia signed a contract for licensing and cooperation with the American pharmaceutical group Eli Lilly and Company (hereinafter **Eli Lilly**) involving the development and marketing of a fast acting insulin analog, Humalog®, with BioChaperone® technology (**BioChaperone®-Humalog®).** This agreement followed promising results of studies *in vivo* conducted by Adocia and presented to Eli Lilly in the summer of 2011.

In July 2013, Adocia announced that, jointly with Eli Lilly, it was decided not to continue the joint research program in the license contract signed in December 2011 giving access to BioChaperone® technology for the formulation of a fast acting insulin analog. The two companies decided to end their cooperation.

Adocia therefore is the holder of all rights for the development of an ultra fast acting insulin analog and intends to pursue the project more actively, a decision prompted by phase I clinical results that reached the clinical objectives set down, therefore confirming the value of BioChaperone® technology.

Adocia's strategy is to remain focused on innovation, the aspect with the highest added value. The company has verified that the formulations it develops are consistent with adapting to the industrial scale of its partners. The signature of license contracts will enable the company to remain focused on its competitive advantages in the field of polymer chemistry and drug delivery. This is the result of the experience of Adocia and its partners, the latter responsible for clinical development, regulatory questions, production, marketing and sale of products. Similarly, for the treatment of diabetic foot ulcers or BioChaperone® insulins, clinical trials conducted were outsourced to recognized and certified service providers. Almost 80% of Adocia's staff, i.e. 65 people, are composed of researchers in varied fields (chemistry, physical chemistry, biology, veterinary specialists) fully dedicated to the development of innovative products based on BioChaperone® and Drive*In®* technologies. The results of Adocia teams have led to a number of patents intended to protect the company's innovations. The company's policy of protection of intellectual property covers BioChaperone® polymers, BioChaperone®/therapeutic molecule complexes and their therapeutic applications.

The company's executive team has solid experience in the management of technological innovation and partnerships with large industrial groups in the fields of both drug delivery technologies for therapeutic proteins and the development of medical devices. Mr. Gérard Soula, founder of Flamel Technologies in 1990 and his sons Olivier and Remi Soula, have actively contributed to the

development of the company specialized in drug delivery and that is listed on the NASDAQ in the United States. In particular, they have demonstrated their know-how in terms of managing scientific projects for the development of new formulations of therapeutic molecules and the signature of partnerships and licenses with major players in the pharmaceutical industry such as GlaxoSmithKline, Novo Nordisk, Merck or Bristol-Myers Squibb.

The company also calls on external consultants, in particular Dr. Bernard Cabane, Research Director at the School of Industrial Physics and Chemistry, Paris (ESPCI), Professor Jacques Descotes, Professor at the Poison Control Centre - Centre of Pharmacovigilance, Dr. Jean-Charles Kerihuel, cardiologist and general manager of the company Vertical, Professor Lecommandoux, Research Director, and Professor François Thomas, oncologist at the Jules Bordet Institute and general manager of the company Thomas Conseil.

7.2. Adocia technologies

7.2.1. BioChaperone®, a single technological platform with many applications

Adocia has designed and developed a technological platform based on novel polymers, called BioChaperone®. These polymers are devoid of intrinsic biological activity and can spontaneously combine with certain therapeutic proteins. This combining increases the solubility and efficacy of the therapeutic protein and protects it from enzymatic breakdown.

7.2.1.1 History of BioChaperone® technology

The capacity of heparin*, a natural polysaccharide*, to form molecular complexes with growth factors was shown about 15 years ago. This combination with heparin led to the identification of three major properties that increase growth factor efficacy: (i) increase in growth factor solubility, (ii) protection of growth factor from enzymatic breakdown and (iii) prolongation of its time of action.

There are many spontaneous formations of complexes between heparin and growth factors, and the same is true for other therapeutic proteins such as hormones. The following table lists the principal proteins that combine with heparin or heparin sulfate:

Morphogenesis and tissue distribution	
Morphogens	**Coagulation**
Activin	Antithrombin III
Bone morphogenesis proteins (BMP-2,- 4)	Factor Xa
Chordin	Leuserpine
Frizzled peptides	Tissue factor pathway inhibitor
Sonic hedgehog (SHH)	Thrombin
Sprouty peptides	**Growth factors**
Wnt (1-13)	Epidermal growth factors (EGF)
Constituents of the extracellular matrix	Amphiregulin
Fibrin	Betacellulin
Fibronectin	Heparin-binding GF
Interstitial collagen	Neuregulins
Laminins	Fibroblast growth factor (FGF 1-15)
Pleiotrophin (HB-GAM)	Insulin-like growth factor (IGF-II)
Tenascin	Platelet derived growth factor (PDGF-AA)
Thrombospondin	Beta transforming growth factor (TGF-β1, 2)
Vitronectin	Vascular endothelial growth factor

Morphogenesis and tissue distribution	
Tissue restructuring factors Plasminogen tissue activator Plasminogen activator inhibitor Vexin protease	(VEGF-165, 189) **Binding proteins of growth factors (BP)** Follistatin Binding proteins (IGFBP-3, -5) TGF-β BP **Proteinases** Neutrophil elastase Cathepsin G

Source: from Bernfield and al. Ann. Rev. Biochem. 1999, 68, 729.

Adocia has developed a first generation of polymers with the goal of mimicking the ability of heparin to interact with growth factors but without the anticoagulation* properties of heparin, while having the possibility of greater versatility in order to act with a larger number of proteins.

These novel polymers, called BioChaperone®, are composed of a sugar backbone, e.g. dextran or pullulan, modified by both anionic groups* (chemical component with a negative electric charge) and hydrophobic amino acids.

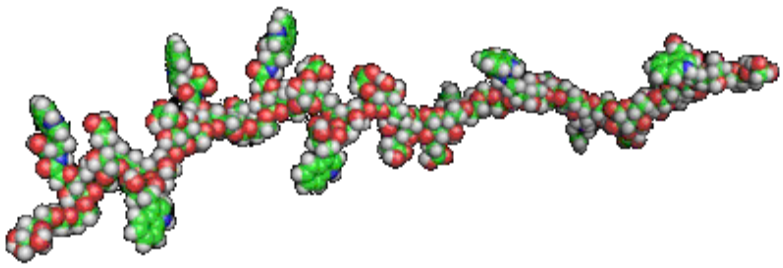
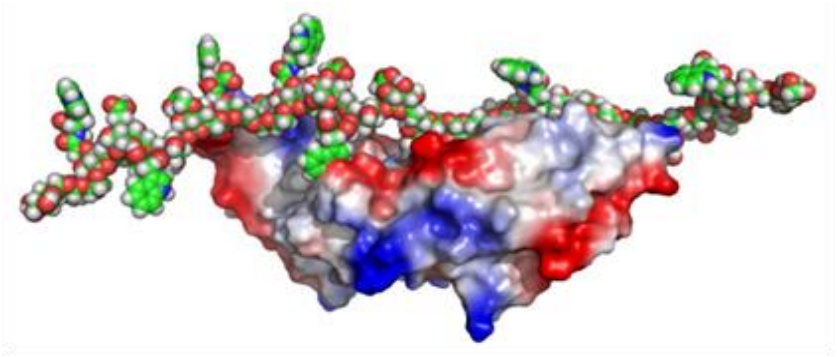


Figure 2: 3D representation of a BioChaperone® polymer with a dextran backbone.

Source: Adocia

BioChaperone® polymers form complexes with proteins by binding to their surface (adsorption). The complex forms spontaneously and is based on hydrophobic and electrostatic interactions, and on the formation of hydrogen bonds. These polymers interact reversibly with proteins and without causing any degradation. The complex forms spontaneously when the two constituents are simply mixed in aqueous solution, in other words the process requires no heating or organic solvent and is immediate.



Source: Adocia

Figure 3: 3D representation of the complex between a growth factor and a BioChaperone® polymer with a dextran backbone. Source: Adocia

It has been shown that there are four original key properties of BioChaperone® technology *via* the formation of a complex with the protein:

- an increase in the solubility of proteins that are relatively insoluble at physiological pH;
- increased stability of proteins during storage;
- protection of proteins against enzymatic breakdown; and
- stabilization of the activity of proteins in the presence of cells.

These properties augment the time the protein is present in the body and thereby increase the resulting cellular activity (prolonged time of action of the therapeutic protein and acceleration of its diffusion in the compartment(s) in question).

In addition, BioChaperone® polymers have no intrinsic biological activity and should therefore be registered with regulatory authorities as new excipients.

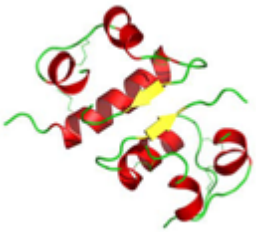
These novel properties will result in higher efficacy of these new formulations with BioChaperone® compared to formulations currently on the therapeutic proteins market, leading to products considered best-in-class, in other words having the best therapeutic effects in their therapeutic class.

Adocia's guiding principle in the development of the BioChaperone® technological platform was to design innovative and easily industrializable formulations of authorized therapeutic proteins with considerable therapeutic value for treating pathologies involving a large number of patients but whose essential properties contain major shortfalls. The intended purposes of pharmaceutical products developed with BioChaperone® technology are to be more efficacious, simpler to use and occasionally even providing new uses consistent with compliance rules of the pharmaceutical industry at competitive costs with respect to existing treatments.

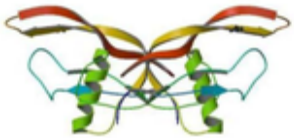
7.2.1.2 BioChaperone®, a unique collection of customized polymers for a large number of therapeutic proteins

At the present time, Adocia research teams have developed more than 250 BioChaperone® polymers, a genuine collection that will grow in size with time. The main distinctions among these polymers are their size, and the type and number of anionic and hydrophobic grafts.

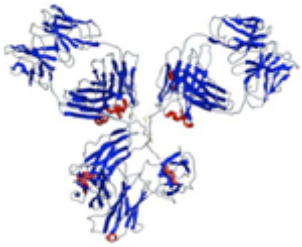
This collection of polymers prepared with the same technological platform and initially developed for growth factors, was rapidly extended to other therapeutic proteins, also authorized, and having considerable therapeutic value, such as insulin, hormones and monoclonal antibodies.



Hormones
Example: Insulin (5.8 kDa)



Growth factors
Example: PDGF-BB (26 kDa)



Monoclonal antibodies
Example: IgG (150 kDa)

BioChaperones are therefore a unique collection of novel customized polymers with a broad range of therapeutic applications.

Adocia first concentrated on the treatment of chronic wounds by growth factor PDGF-BB and the treatment of diabetes by insulin therapy. This scope of application of BioChaperone® has progressively enlarged to other proteins: monoclonal antibodies (refer to section 6.4 "Monoclonal antibodies").

7.2.2. Drive*In*®, an innovative approach to targeted delivery in oncology

In December 2013, Adocia began the development of Drive*In*® nanotechnology for the treatment of cancer after acquiring the exclusive rights for development and marketing in the health field of patents covering this nanotechnology. Drive*In*® technology was developed by the group of Professor Sebastien Lecommandoux of the Laboratory of Chemistry of Organic Polymers of the Polytechnic Institute of Bordeaux (University of Bordeaux I).

7.2.2.1 Chemotherapy, a key cancer treatment

Chemotherapy has been one of the cornerstones of the treatment of cancers for decades as a result of high efficacy. Chemotherapy, however, causes considerable adverse effects because it acts on healthy tissues as well as cancerous tissues. In order to reduce these adverse effects, treating cancers with chemotherapy has progressed towards targeted approaches; this has been done by using intrinsically targeted molecules such as monoclonal antibodies, or by the use of transporters of chemotherapy molecules to target the treatment to only the tumor while sparing healthy tissues. Adocia has adopted the latter approach by developing Drive*In*®, a novel biomimetic nanotechnology for drug delivery in oncology.

7.2.2.2 Nanoparticles: an effective delivery method

Nanoparticles are particles smaller than several hundred nanometers and some can be used as drug transporters. A very special value of nanoparticles in oncology is their capacity to accumulate in tumors by what is call the enhanced permeation and retention effect (EPR). The vascularization of tumors is abnormal, in form and structure, with disorganized formation and blood vessels presenting large fenestrations, enabling blood and what it is carrying to emerge towards the tumor. Nanoparticles of a certain size (in contrast to large molecules) tend to diffuse toward the tumor but the abnormal organization of the tumor's blood vessels and the elevated pressure inside the tumor then prevent the nanoparticles from emerging (in contrast to small molecules that escape). This combination of influx and a lack of efflux leads to the passive accumulation of nanoparticles in the tumor. Several technologies use this passive approach to augment accumulation inside tumors:

- Liposomes: they are lipid-based nano-objets. They can be coated with polyethylene glycol (PEG) to render them "stealthy", i.e. prevent their detection by the immune system. Doxil®

(Johnson & Johnson) is a pegylated liposomal formulation of doxorubicin (adriamycin), one of the most widely used molecules in oncology. The use of doxorubicin is nevertheless limited by is cumulated cardiac toxicity. The liposomal formulation of Doxil® has significantly reduced the cardiac toxicity of doxorubicin. In 2011, global sales of Doxil® were $402 million. Liposomes are nonetheless relatively unstable and their reproducible production is difficult.

- Albumin nanoparticles: Abraxane is the first product containing in a reversible nanoparticle form paclitaxel, a molecule widely used in oncology, and albumin, one of the most widespread proteins in the human body. The combination of paclitaxel with albumin benefits from the EPR effect and remains "stealthy" in the body. Sales of Abraxane, indicated for breast cancer, pancreatic cancer and stomach cancer, reached $427 million in 2012.
- Nanoparticles based on blocks of copolymers: this more recent approach (also that of Drive*In®*) has not yet reached the market.

Passive targeting by EPR leads to the accumulation of the product in the tumor, but tumors themselves are most often very dense objects in which the circulation of therapeutic products is impeded. In addition, the presence of objects in proximity to the tumor does not automatically result in the uptake of the products by the cells to treat, where the product is to be released.

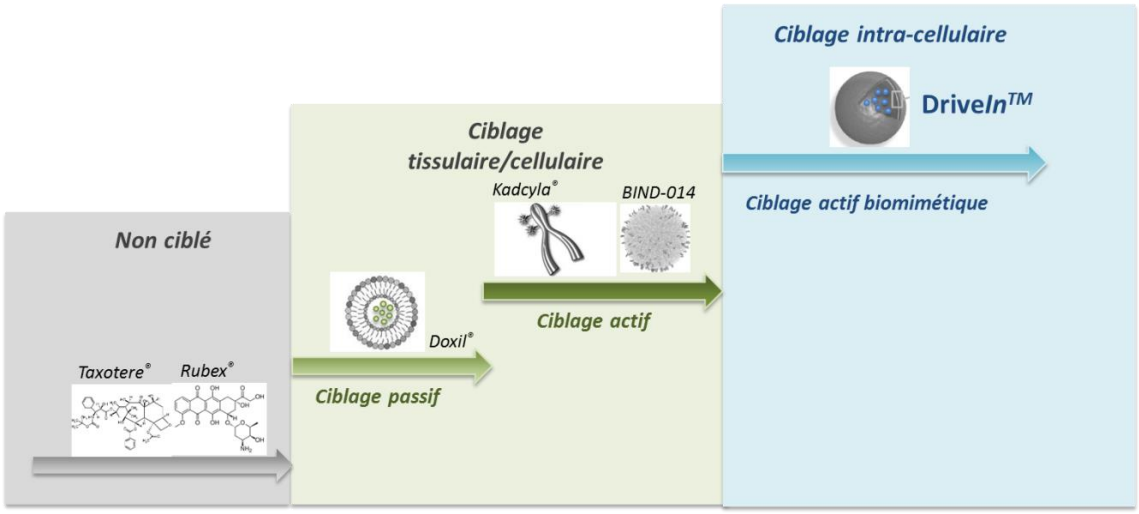


Figure 4: Progress in therapeutic delivery methods towards active targeting and enabling intracellular delivery of the drug.

Drive*In®*, a biomimetic Trojan Horse invading cancer cells

Drive*In®* is an innovative nanoparticle technology for the active delivery of drugs that enables:

- Better cell uptake and better retention of the active chemical molecule in cancer cells, where it must act.
- Effective targeting (active and passive) **towards tumors and cancer cells**.

In order to obtain both better targeting and better cell uptake of therapeutic molecules, Adocia uses a breakthrough technological approach: Drive*In®* nanoparticles are biomimetic, i.e. they are coated with a substance produced naturally by the human body, **hyaluronic acid**. Hyaluronic acid is responsible for the particular properties of Drive*In®*:

- Cell uptake: hyaluronic acid is the natural ligand of CD44, a marker of metastatic stem cells (responsible for the spread (metastasis) of cancers). The normal biological role of CD44 is to internalize hyaluronic acid and it is over-expressed in many solid tumors. Drive*In®* nano-particles are therefore naturally internalized in cancer cells once they have interacted with their receptor.

Most nanoparticle products on the market or under development are pegylated. The pegylation process results in a repulsive effect on living matter and thereby prevents detection by the immune system and increases its circulation in the bloodstream, but to the detriment of bioefficacy. Pegylated molecules are internalized to a lower extent and are less likely to interact with their ligand. The use of hyaluronic acid enables Drive*In*® particles to remain invisible to the immune system, but their affinity for their ligand and their uptake capacity remain intact.

- Targeting: the hyaluronic acid-coated surface of Drive*In*® enables active targeting of cells over-expressing CD44. The nanoparticle design of Drive*In*® also benefits from the EPR effect (passive targeting), that concentrates nanoparticles in the environment of the tumor.

Drive*In*® nanoparticles have been designed to act as Trojan Horses that deliver drugs to cancer cells in a targeted and active manner, while preserving healthy tissues.

Drive*In*®, a versatile platform to optimize the delivery of a wide range of molecules

Drive*In*® is a highly effective technological platform that controls all key parameters of nanoparticles (size, shape, encapsulation capacity). In this way, Drive*In*® opens new horizons to a vast array of therapeutic agents, from cytotoxic drugs to targeted inhibitors, and possibly using siRNA.

7.3. Competing technologies

7.3.1. Cell therapies

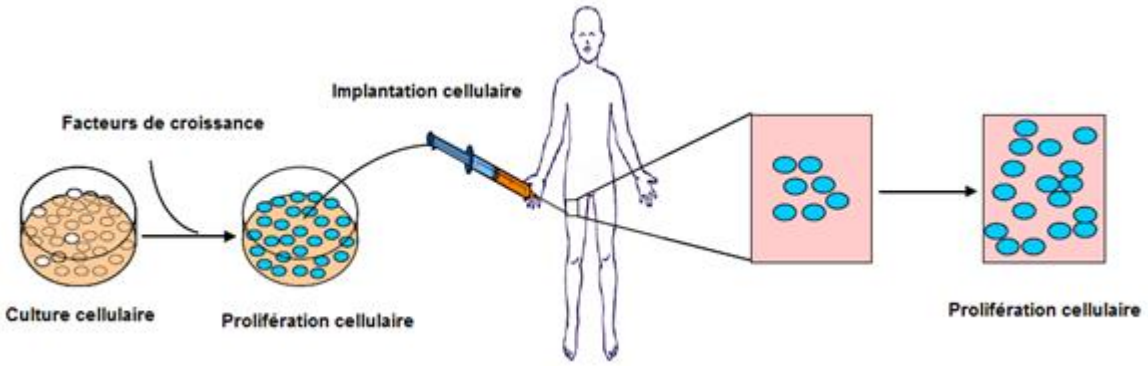
Cell therapies are defined as "cell grafts aiming to restore the functions of a tissue or organ when they are damaged by an accident, pathology or by aging".

Stem cells, one of the great hopes for regenerative medicine research, are undifferentiated cells with three principal characteristics:

- their self-renewal capacity (capacity to divide and produce new identical stem cells);
- their capacity for differentiation (capacity to give rise to specialized cells forming different tissues and organs provided certain conditions of the environment are present); and
- their capacity to proliferate *in vitro* (in culture).

Stem cells are found in the embryo, fetus and umbilical cord blood, as well as after birth in a variety of tissues; the latter type of stem cells, called "adult", have a reduced renewal and differentiation potential.

Illustration of the mechanism of cell therapy



Source: Adocia

Very broad fields of therapeutic applications are possible with stem cells:

Cell types	Diseases
Nerve cells	Parkinson's disease, Alzheimer's disease, spinal column injury, multiple sclerosis
Heart muscle cells	Myocardial infarct, kidney failure
Insulin cells	Diabetes
Cartilage cells	Arthritis, arthrosis
Blood cells	Cancer, leukemia, immunodeficiencies, blood diseases genetics
Liver cells	Hepatitis, cirrhosis
Skin cells	Burns, wound healing
Bone cells	Osteoporosis
Retinal cells	Macular degeneration
Skeletal muscle cells	Muscular dystrophy

Table 3: Possible fields of applications of cell therapy, depending on the stem cells used. Source: Veterinary Academy of France, Alain Chapel, 21 February 2008.

There are nevertheless a number of limitations to the development of cell therapies related to:

- phenomena observed in very artificial conditions (transgenic animals, "chimeric" animals bearing genetically modified cells, etc.);
- signals responsible for the differentiation of stem cells and their binding to damaged organs not totally identified;
- risks of immunogenicity and infection; and
- elevated mortality rate of implanted cells …

A far-reaching ethical debate has opened concerning the use of embryonic stem cells and this major aspect must be considered in the future development of cell therapy technologies.

At the present time, about 40 products are marketed globally and the world market for cell and tissue therapies could reach $2.7 billion in 2015. There is also considerable research under way, in particular by American companies such as Advanced Cell Technologies (blindness from degenerative retinopathies, juvenile macular degeneration, age-related macular degeneration), Geron (central nervous system disorders, myocardial infarct, diabetes, arthritis, spinal cord damage) or Stemcells (Alzheimer's disease, arthritis, blindness, burns, multiple sclerosis, heart diseases and more).

In spite of this, clinical results concerning cell therapies are currently limited compared to the number of studies undertaken. The large number of failures can be explained by the elevated immunogenicity and mortality of implanted cells. In the current state of clinical research on markets of interest for Adocia, the BioChaperone® approach involving improved efficacy and safety of formulations of authorized therapeutic proteins is therefore more credible than cell therapy.

7.3.2. Gene therapy

Gene therapy is defined as "the deliberate introduction of genetic material in human somatic cells* in order to correct a genetic defect or compensate for the lack of a protein by providing the gene responsible for its synthesis ".

Gene therapy involves introducing a treatment gene in a cell so that it produces a defined protein in the case of deficient cells, or else sends a signal causing the self-destruction of the cell in the case of cancer cells.

Every type of gene therapy is based on three basic aspects:

- a therapeutic gene;
- a vector to transport this gene: a "safe" virus, in other words lacking the sequence of its genetic code that causes its pathogenicity, or else a non-viral vector such as a liposome; and
- a target cell where the gene introduced is to be expressed.

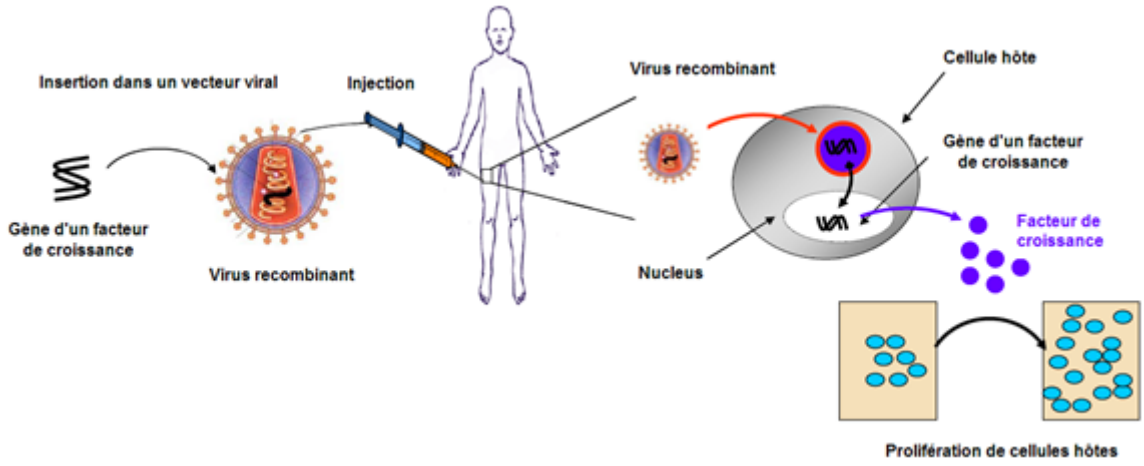


Figure 5: Diagram of the general gene therapy process. Source: Adocia

In 2008, according to the INSERM, there were 1,472 gene therapy trials under way throughout the world, of which 39 were in France. More recently, the Ministry of Industry, Energy and Digital Economy stated that there were 1,644 gene therapy trials under way worldwide in June 2010.

Genetic diseases, whether single-gene diseases (cystic fibrosis, myopathies, Huntington's chorea) caused by the abnormal expression of a single gene, or multi-factor diseases resulting from the combination of several genes or environmental factors, account for only 8.2% of clinical trials started in 2008 and dealing with gene therapy treatments, according to the INSERM. The principal area of gene therapy investigation is the treatment of cancers (melanoma, lung cancer, colon cancer, ovarian cancer, thyroid cancer, liver cancer and more). The vast majority of clinical trials under way in June 2010 were phase I (60.5%) and only 3.5% were phase III trials.

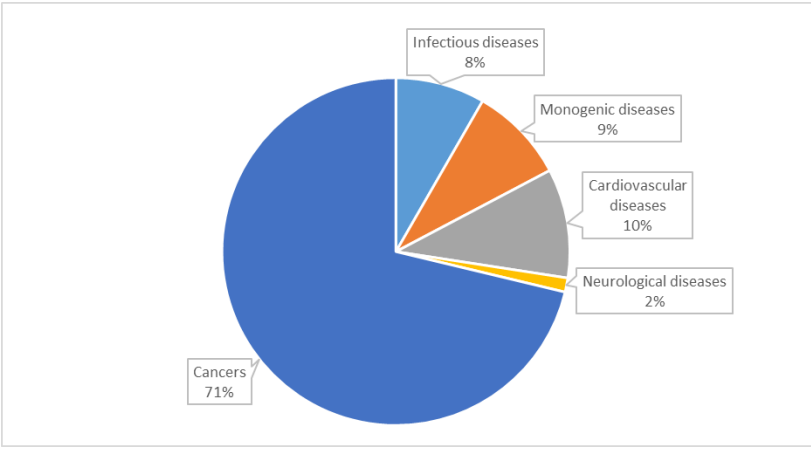


Figure 6: Distribution of gene therapy clinical trials for the indications targeted in 2008. Source: INSERM

The variety of diseases in question and the reproducibility and simplicity of the concept "one disease - one gene" would seem to make gene therapies a genuine therapeutic revolution. It could therefore be a solution to diseases for which no effective treatment has yet been developed. Major scientific issues nevertheless persist:

- the technique for insertion of a gene in a cell is not yet totally controlled and requires a better understanding of the pathways involved in the insertion of vectors and localization of the gene introduced in the genome;
- gene transfer is not yet a safe and effective procedure;
- the stability and expression of the gene introduced are not yet fully ensured.

In order for gene therapy to be safe and effective, it is imperative to fully control the process of transgenesis*, i.e. all techniques used to introduce a foreign gene in the genome of an organism. At the present time practically all gene therapy clinical trials have failed. There exists no gene therapy treatment that is reliable, internationally recognized and used in practice. These treatments could cause serious adverse effects as was the case for neonates born with severe immunodeficiency ("bubble babies"). Work done by Professor Alain Fischer was initially shown to be a total success revealed by the remission and cure of patients: most of the babies emerged from their bubble to live a normal life. Several years later, however, several of the children treated with gene therapy developed leukemia. The data gathered suggest that the type of vector used could be included in sensitive regions of the genome and that the leukemia may have resulted from the deregulation of certain genes. Furthermore, several cases of mortality were reported after injections of high doses of an adenovirus-derived vector.

These cases showed the necessity for total control of the process, in particular because of vectors affecting other genes or inserting elements that are toxic for the person's genome.

Ethical aspects may also explain the limitations imposed on gene therapies. The French National Ethics Committee* (CNNE) published a recommendation for limiting research to only somatic cells, i.e. cells that will never give rise to gametes (spermatozoa and ovules).

It has been estimated that the world market for gene therapies will be $484 million in 2015 even though no product has yet been granted a Marketing Authorization. The principal parties concerned are American, European (France, Switzerland and the United Kingdom) and Asian (Japan and China) markets.

The elevated risks to patients that currently exist preclude the short- and medium-term development of gene therapy for the treatment of pathologies for which alternative treatments are possible. This technology should therefore not compete with Adocia in its areas of applications.

7.3.3. Monoclonal antibodies

Monoclonal antibodies have become a very effective treatment of cancer, as a complement to chemotherapy. Monoclonal antibodies interfere with a signaling pathway by blocking the targeted receptors or by binding to active molecules. Treatment with a monoclonal antibody is often combined with a companion test to determine beforehand if the patient can or cannot benefit from this treatment. This therapeutic regimen was validated with the development of Herceptin® for patients with HER2-positive breast cancers. The monoclonal antibodies used most often in oncology are listed in Table 4. Monoclonal antibodies are most often administered in a therapeutic regimen including classical chemotherapy.

Name	Target	Name (company)	Global sales (2013)	Indications in oncology

Rituximab	CD20	Rituxan®/Mabthera® (Roche-Genentech)	$6.1 billion	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia
Bevacizumab	VEGF	Avastin® (Roche-Genentech)	$6.3 billion	Metastatic colorectal cancer (mCRC), non-small cell lung cancer (NSCLC), breast cancer, kidney cancer, brain cancer, renal cell carcinoma (RCC), brain tumor
Trastuzumab	HER2	Herceptin® (Roche-Genentech)	$6.45 billion	$HER2^+$ breast cancer, $HER2^+$ stomach cancer
Cetuximab	EGFR	Erbitux® (BMS-Merck-Lilly)	$1.89 billion	$EGFR^+$ mCRC, cancer of the head and neck
Panitunumab	EGFR	Vectibix® (Amgen)	$359 million (2012)	$EGFR^+$ mCRC

Table 4: Best among monoclonal antibodies (Source: Datamonitor Healthcare, 2013)

7.3.4. Gene therapy and cellular immunotherapy

Beyond aiming to directly interfere with cell division in the treatment of cancer, new approaches have been developed over the last decade with the goals of:

- modifying the genetic code of cancer cells (DNA-based gene therapy) or interfering with its expression (RNA-based gene therapies). These DNA and RNA methods are currently limited by administration difficulties because the vectors are either viruses or nanoparticles. No RNA-based treatment of cancer has yet reached the market;
- activating the patient's immune system so it directly destroys cancer cells (cellular immunotherapy): these methods are still in an early stage of their development. The only immunotherapy on the market is Provenge® (Dendreon): the method involves harvesting the patient's immune cells and modifying them for their activation so they can present an antigen specific to prostate cancer cells. Once re-injected into the patient, they provoke an immune response of the patient against his(her) own cancer. The theoretical advantage of this approach is that the patient is immunized against his(her) own cancer. In spite of this promise, this technique still remains highly limited by issues of stringent production requirements and treatment costs.

These approaches are all under development and could be complementary methods to chemotherapy to combat cancer.

7.4. Adocia products developed with BioChaperone® technology

7.4.1. The BioChaperone® PDGF-BB combination for the wound healing market

Adocia has perfected an existing treatment for the wound healing market, in particular diabetic foot ulcers. The treatment involves spraying with a complex composed of BioChaperone® and growth factor PDGF-BB (platelet derived growth factor-BB), authorized for this indication with the marketing of Reframe® gel. The treatment developed by Adocia could also be used to treat venous ulcers, bedsores and burns with PDGF-BB. After the phase I-II clinical trial conducted in India, Adocia is planning a phase III trial in India, then in Europe and the United States.

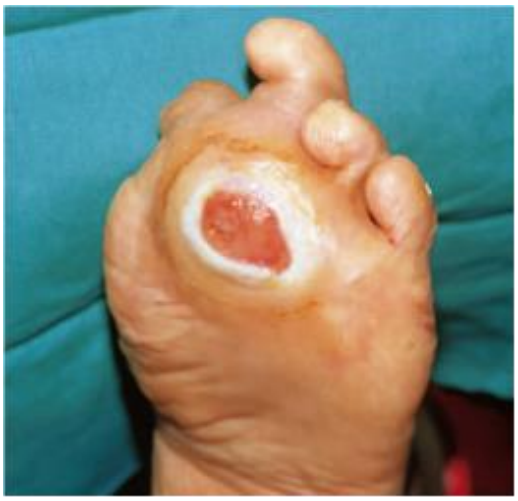
7.4.1.1 The treatment of diabetic foot ulcers

7.4.1.1.1 The pathology

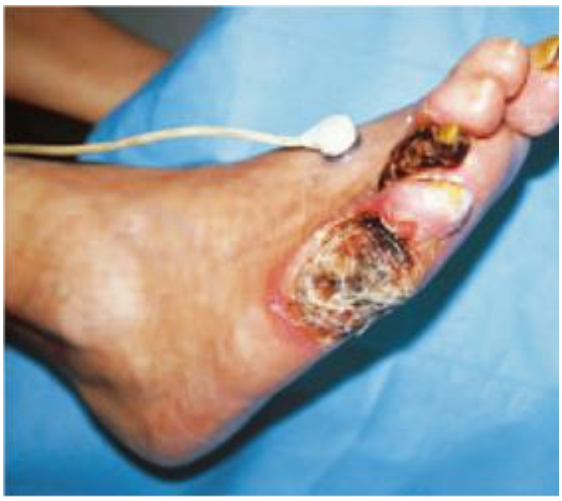
The term "diabetic foot" encompasses all pathological manifestations affecting the foot of a patient, directly related to diabetes. About 20% of hospitalizations for diabetes result from complications to the feet and there are two major causes of these pathologies:

- the involvement of nerves of the foot that can advance all the way to destruction of the nerve fiber*, a condition called neuropathy*; and
- the obstruction of arteries of the leg, called arteriopathy*.

The major risk of this pathology, dominated by the occurrence of an ulceration, is amputation.



Diabetic foot resulting from neuropathy



Diabetic foot resulting from arteriopathy

Figure 7: Photographs of neuropathic and neuroischemic diabetic feet. Source: L'Observatoire du mouvement - Le pied diabetique

Neuropathy

Neuropathy is a term that includes all disorders of the peripheral nervous system (motor and sensory nerves and nerves of the extremities) and of the autonomic nervous system that controls organs.

The origin of a neuropathy is primarily metabolic. The accumulation of the sugar sorbitol* in nerves creates an edema, in turn causing destruction of nerve fibers. These fibers, whether sensory, motor or vegetative, can be damaged by diabetic neuropathy. Sensory nerve involvement predominates and sensitivity to pain gradually disappears. In the most extreme cases, patients continue walking without being aware that the lesion on the bottom of their feet continues to exacerbate.

Figure 8: Role of different involvements of the peripheral nervous system in the appearance of diabetic foot ulcers. Source: The Diabetic Foot (in French) - The situation in 2005, Dr. J-L. Richard (Nutritional Diseases and Diabetes Department, Nîmes University Hospital)

Arteriopathy

There are two possible forms of arteriopathy, an obstruction of blood vessels of the lower extremities:

- microangiopathy, the involvement of capillaries, the tiniest blood vessels, with a functional impact on the feet[1] and a negative effect of its wound healing[1];
- macroangiopathy, the involvement of arteries causing a narrowing of their diameter (stenosis) resulting from the deposit of cholesterol on their inner wall (atheroma).

A reduced blood supply or ischemia* becomes chronic and renders the foot vulnerable to the extent that a slight trauma can lead to the formation of a wound. This ischemic state also limits the capacity of blood to circulate, rapidly becoming insufficient to the point of being unable to cope with an infectious phenomenon or to heal wounds. Ischemia is therefore the cause of diabetic foot ulcers and their exacerbation.

Diabetic foot ulcers appear in only about 15% of cases by arteriopathy, whereas 90% of diabetics with an ulceration are also affected by a neuropathy[1].

Clinical characteristics of diabetic foot ulcers

Neuropathic ulcers	Ischemic ulcers

Foot arm, pulse intact	No pulse/foot not warm
Reduced sensations/calluses	Reduced sensations
Sites of ulcers: top and extremity of toes/ head of metatarsals on plantar surface	Sites of ulcers: foot contour, extremity of toes, heels
Septicemia	Septicemia
Local necrosis	Necrosis and gangrene
Charcot's arthropathy	Critical ischemia: pallor, pain, absence of pulse, foot cold

Table 5: Clinical characteristics of diabetic foot ulcers. Source: Wesam al Arayedh and Alain Brassard, Mc Gill University Health Center, Montreal - Diabetic foot ulcers

Infection

The development of an infection of diabetic foot ulcers is the aggravating factor of the above-mentioned pathologies and can lead to amputation of the patient's foot and even mortality. The risk of gangrene to a diabetic is 17-fold higher than normal[1].

Epidemiological data

The worldwide prevalence of diabetics who develop a foot ulcer during their lifetimes has been estimated at 15%[1]; there are 10 million[1] diabetics throughout the world with a foot ulcer. In the United States, the number of diabetics has been estimated at 25.8 million[1] and the prevalence of ulcers among these patients has been estimated at 5% every year[1], i.e. more than 1 million ulcers in the United States. This number should be practically the same in Europe because the number of diabetics and the prevalence of diabetic foot ulcers are comparable. The number of amputations every year resulting from diabetes has been estimated to be more than one million[1] and so diabetes is the leading cause of non-traumatic amputation of feet in developed nations.

In metropolitan France, the number of diabetic patients (type 2 diabetes) with foot ulcers has been estimated at 218,000 for a diabetic population of about 2.2 million according to the ENTRED 2007-2010 study[1], i.e. close to 10% of the total number of diabetics. The same study estimated the number of diabetics undergoing amputation of the foot in 2007 in metropolitan France to be 33,000; this number is 80,000 more in the United States[2]. After an initial ulcer, the 5-year risk of recurrence is estimated at 70%[2].

Furthermore, the fact of being diabetic multiplies the risk of amputation by a factor of 10 to 40[2] and a second amputation is required in almost 50% of cases; in the latter situation, the survival rate is only 58%[2]. The consequences of diabetic foot ulcers multiply the risk of patient death by a factor of 2.4[2].

7.4.1.1.2 The market

The global diabetic foot ulcers market has recently been evaluated at $3 billion[2]. This figure was released by the British pharmaceutical company Shire, in its May 17, 2011 announcement of the acquisition of Advanced BioHealing for $750 million. This company owns the rights to DERMAGRAFT®, authorized to treat this pathology.

The goal of all concerned in the treatment of diabetic foot ulcers is evidently to maximally limit amputations.

The three major types of treatment are:

- removing all load to the foot by orthopedic shoes or a plaster cast;
- local treatments (antiseptics, petroleum jelly gauze, etc.); and
- the use of antibiotics in case of infection.

In this context, manufacturers of orthopedic devices are the first concerned by reducing loads on the foot in order to eliminate all physical stress to the wound.

In parallel to reducing load on the foot, local treatments are possible after debridement (excision) of the wound to dry and limit the spread of the necrosis. This local treatment requires not less than primary dressings* even though they have shown no benefit for wound healing[2]. Another treatment that has been developed involves using negative pressure, called vacuum-assisted closure (VAC), continuous aspiration of the wound to facilitate wound healing[2].

Finally, the wound can be treated with Regranex®, a gel whose drug substance, becaplermin, is a genetic recombination of growth factor PDGF-BB (platelet derived growth factor-BB). This gel stimulates granulation* and wound healing of deep, chronic, pathological diabetic ulcers. Regranex® was granted a Marketing Authorization (refer to section 6.4.2.5 "The Competition") in 1997 in the United States and in 1999 in Europe.

An alternative to these treatments could arise from cell therapy by the use of skin replacements composed of human fibroblasts. Adocia believes that these products, some of which are already on the market, remain expensive to produce and so will be used only in the most severe cases. They will therefore account for only a small market share.

A major socio-economic problem

Diabetic foot ulcers are a major socio-economic problem. According to work by a task force led by diabetic foot ulcer specialists[2], the average cost of primary health care for the treatment of this pathology in the United States is between $7,000 and $10.000; the direct cost of amputation caused by a diabetic foot is estimated at between 30 and 60.000 dollars; the cost of three years of post-operative care has been estimated to be between 43 and 63 thousand dollars. The latter, elevated figure is the result of increased home care and social services needs following the amputation. For diabetic patients presenting this complication, the cost of primary care could be estimated to be between 16 and 27 thousand dollars per patient. It is also relevant to take into account indirect costs, those due to productivity losses by these patients. If we therefore take into account reduced quality of life and lost productivity, it has been estimated that the annual costs of diabetic feet is about $4 billion in the United States.

7.4.1.1.3 The first phase II clinical trial in India

Adocia has sponsored a preclinical study using the diabetic rat model with the goal of comparing the effects of Regranex® (1 dose per day for 7 days) and BioChaperone® PDGF-BB complex (1 dose every 2 days for 7 days). The results showed comparable efficacy between the products in terms of wound healing and the quality of granulation tissues.

A phase I/II trial was started in June 2010 in India that included 192 patients in 11 investigation centers. The aim of the trial was to compare the efficacy of the Adocia formulation of PDGF-BB (Platelet Derived Growth factor) combined with BioChaperone® and delivered as a spray, to Regranex® (HealthPoint), a gel containing PDGF-BB that is currently the only available treatment for diabetic foot ulcers.

The 192 patients included were divided into four groups: three received PDGF-BB doses of 14.5, 43.75 and 87.5 µg per cm² and per week and the fourth received Regranex® at 43.5 µg par cm² and per week. BioChaperone® PDGF-BB treatments were administered every other day, while Regranex® was applied daily according to treatment protocols authorized by American and European agencies. The study was not blinded because of obvious physical differences between the two preparations, i.e. BioChaperone® PDGF-BB is a spray and Regranex® is a gel. The planned treatment period was 20 weeks or until total wound healing. The aim of the trial was to establish the non-inferiority of BioChaperone® PDGF-BB compared to Regranex® for each dose of the former.

The principal criterion of the trial was the percentage of total wound healing (closure of the lesion) after 20 weeks. The rates of total wound healing were all equal to or greater than that of Regranex®, i.e. 66% after 20 weeks. Criteria of non-inferiority were therefore fulfilled for the three doses of PDGF-BB tested.

One of the outstanding results of this trial is the 80°% rate of wound healing after 20 weeks obtained with the formulation containing only one third of the Regranex® dose, even though the product was applied only once every other day.

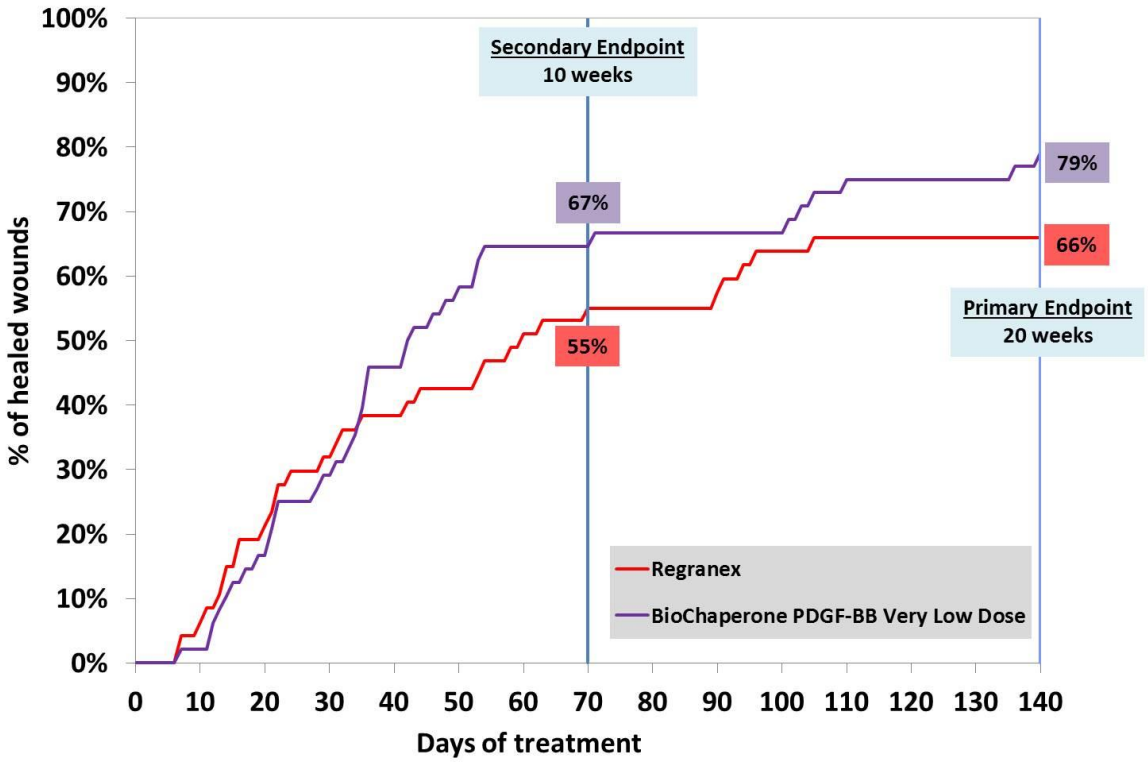


Figure 9: Incidence of total wound healing of diabetic foot ulcers (final results) in the phase II clinical trial of the treatment of diabetic foot ulcers by BioChaperone® PDGF-BB. Source: Adocia

	Principal criterion Incidence of total closure at 20 weeks	Secondary criterion Incidence of total closure at 10 weeks
Very low dose of BioChaperone® PDGF-BB	79% (38/48)	67% (32/48)

Regranex®	66% (31/47)	55% (26/47)

Table 6: Results of the phase II clinical trial of treatment of diabetic foot ulcers by BioChaperone® PDGF-BB. Source: Adocia

These positive clinical results incited the company to continue development of its project and to prepare a phase II clinical trial in India, using the lowest dose of the BioChaperone® PDGF-BB complex, equivalent to one application of 4.2 µg/cm^2 every other day for 20 weeks.

7.4.1.1.4 Future clinical trials

In September 2012, Adocia deposited an authorization application with Indian regulatory authorities in order to continue the clinical development of its product and start a phase II clinical trial. The regulatory authority in question underwent a reorganization and the examination of clinical trial applications was suspended for more than 6 months in 2013. At the time of publication of this reference document, Adocia had not yet received a response from Indian authorities.

The purpose of this trial is to demonstrate the efficacy of the BioChaperone® PDGF-BB complex vs. placebo in 252 patients divided into two groups.

Figure 10: Design of the phase III clinical trial of BioChaperone® PDGF-BB vs. standard of care

The key elements examined involved two levels:

- Primary efficacy of the treatment measured as the percentage of patients for whom total wound healing of the ulcer was obtained after 20 weeks.
- Secondary efficacy of the treatment measured by (i) the percentage of patients for whom total wound healing of the ulcer was obtained after 10 weeks, (ii) the time required for total wound healing of the ulcer, (iii) the extent of reduction of the surface of the ulcer during treatment and (iv) the rate of recurrence of the ulcer after surveillance of 3 months post-wound healing.

The results of this trial will be the basis of the Marketing Authorization (MA) application with local authorities, currently planned for the end of 2015. The trial will be subcontracted to a contract research organization (CRO) working in accordance with Good Clinical Practices (GCP) (refer to section 6.6.3.2 “Controlling subcontracted clinical trials”) to be provided as information for Marketing Authorization applications in Europe and in the United States.

Adocia then plans to start a phase III clinical trial in Europe at the end of 2015. This trial will concentrate on foot ulcers of neuro-vascular origin and for which wound healing is more difficult. As announced in the press release of March 18, 2013 (see chapter 12), the EMA confirmed than only one phase III trial conducted in Europe will be required for the MA, and that clinical data from the phase III trial conducted in India will be admissible for the MA application.

At the date this reference document was registered, Regranex® had not yet been granted an MA for this indication.

7.4.1.1.5 Progress provided by BioChaperone® technology

Adocia has developed a new pharmaceutical product by combining a growth factor, PDGF-BB, authorized since 1997 by the FDA and 1999 by the EMA with one of its BioChaperone® polymers. This new formulation resulted in an increased solubility of PDGF-BB, its protection against enzymatic breakdown and a prolongation of its duration of action.

As a result, for an efficacy at least equivalent, the new product is applied every other day while Regranex® is applied daily; in addition, the dose of PDGF-BB required for wound healing was divided

by 3 in comparison to Regranex®. BioChaperone® also led to a change in the method of administration of the growth factor: it is not a non-sterile gel, but a multi-use sterile spray to monitor the dose administered and easier application on the zone to treat.

Another major contribution of the BioChaperone® PDGF-BB complex compared to Regranex®, resulting from the reduction of the growth factor dose required, is a better safety profile for the patient, there have been concerns over a potential increased risk of cancer associated with growth factors therapies.

Finally, the considerable economic advantage of the BioChaperone® PDGF-BB complex involves reduced production costs and the final cost of the product because of the reduced quantity of drug substance used. This assumes more importance since the cost of Regranex® treatment is relatively high, limiting its prescription frequency. Lower cost could lead to widespread use of the treatment and prescription earlier in the course of patient management, which would reduce treatment duration, increase the rate of total wound healing and therefore lower the risk of amputation.

7.4.1.2 Future treatments

7.4.1.2.1 Treatment of venous ulcers

An ulcer of the leg is characterized by a chronic skin lesion that does not heal unassisted. This type of lesion can have several causes, including vascular disorders (venous, arterial or both), infections, blood diseases, cancers or inflammatory diseases. In 80% of cases[30.] ulcers of the leg result from vascular disorders (venous blood reflux, obstruction creating a venous stasis*); in these cases we speak of venous ulcers.

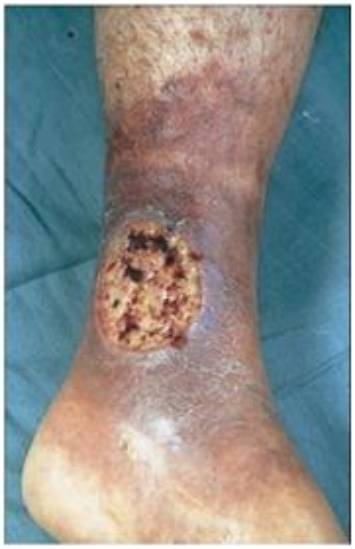


Figure 11: Internal, sub-malleolar venous ulcers on a fibrous substratum. Source: National College of Dermatology Professors

Venous ulcers are generally characterized by their isolated presence on the patient's leg at the level of the internal malleolus, in other words the inner side of the ankle at the lower extremity of the tibia, or above it. Venous ulcers are usually very large but with little or no pain, and their shape may be round, oval of polylobate.

The appearance of the bottom of the ulcer is also variable:

- a bedsore or an adhering fibrinous layer, with a sanious* and purulent bottom if the ulcer is infected;
- red, clean and smooth granulation tissue for ulcers in the course of healing.

The zones around the ulcer are characterized by inflammation of the dermis, the epidermis and/or the hypoderm.

Depending on the study, the prevalence of venous ulcers varies from 0.1% to 0.2%[3]. The percentage of the population having had at least one venous ulcer in a lifetime has been estimated at 1%[32 33]. Venous ulcers are a pathology that primarily affects the elderly: in a study on this pathology[34], prevalence reached 1.69% in a British sample of 50,000 subjects.

Venous ulcers are predominantly a feminine pathology, with a 1/3 ratio between men and women[35,36].

The rate of relapse is high, sometimes reaching 69%[37] after 12 months.

The basic treatment of venous ulcers involves local care with the goal of drying and delimiting the lesion in order to accelerate wound healing. This is done before treating the causes of venous ulcers,

generally involving vascular surgery, occasionally major operations, and before recourse to other surgical treatments such as a skin graft. The initial basic treatment involves different types of wound protection and/or care, such as polyurethane films, hydrocolloids, absorbent polymers, aqueous gels and collagen dressings.

The similarities in the mechanisms of wound healing between diabetic foot ulcers and venous ulcers explain why Adocia is considering the start of a phase III clinical trial in India on the treatment of venous ulcers with the BioChaperone® PDGF-BB complex.

7.4.1.2.2 Bedsores

Similarities also exist between bedsores (eschars), diabetic foot ulcers and venous ulcers (localization in the lower part of the body, ulceration from a vascular cause, role of diabetes as aggravating factor, a lack of novel treatment with growth factors, serious consequences that could lead to amputation, etc). This explains why Adocia considers that wound healing of bedsores with the BioChaperone® PDGF-BB complex could be an interesting axis of development.

A bedsore is the more or less restricted destruction of a tissue resulting from its reduced vascularization. Bedsores are most often seen in bedridden and hospitalized patients, facilitated by the overall lower health status of these subjects (malnutrition, dehydration, etc.) or in a situation of prolonged compression on a limited skin surface, in particular on protrusions, i.e. the heel, sacrum, elbow, shoulder blade, etc.

The prevalence of bedsores in a French population of hospitalized patients has been estimated at 8.9%[38].

The severity of lesions involves simple skin redness, edema of varying hardness, all the way to necrosis of the skin, followed by that of underlying fat (adipose tissue) and muscles. Lesions may progress to the point of bone involvement, sometimes causing osteitis (bone inflammation). In the absence of treatment, the main risk aside from spread of the edema is superinfection that in the most extreme cases could require amputation. Treatment varies with the stage of bedsores, primarily involving local treatment and the use of dressings such as hydrocolloids to facilitate skin regeneration. In the most extreme cases a skin graft may be necessary. The parallel use of pain killers, even morphine-based products, is generally indispensable.

7.4.1.2.3 Burns

A burn is defined as the partial or total destruction of the skin, of tissues and even of bone. Severity depends on several parameters, in particular localization, depth, extent of the body surface, as well as the cause (heat, caustic substance or product, combustion, radiation, electrocution, extreme cold, etc.). Burns are categorized in four degrees:

- first degree burn: only the epidermis is affected;
- second degree burn: the dermis is affected and in the case of deep burns, regeneration of the dermis may not be possible because of vascular damage or the destruction of stem cells;
- third degree burn: if the burned surface is too large to heal, a skin graft becomes indispensable in light of the destruction of all skin cells; and
- fourth degree burn: muscles and/or bones are also damaged. The treatment of the most severe burns is obligatorily surgical (excision, skin graft).

Superficial (first degree) burns can be treated locally with ointments. In this context of local treatment, many growth factors are used in order to promote all aspects of wound healing.

In 2007 in France, 400.000 burns were reported, of which 10,000 required hospitalization. The number of third and fourth degree victims was estimated at 3,700 among whom about a thousand succumbed to their injuries[3].

7.4.1.3 The competition

7.4.1.3.1 Regranex®

Regranex® is a non-sterile aqueous gel supplied in multi-dose tubes containing 100 µg of rhPDGF-BB per gram (0.01%) marketed (only in the United States at the time of this reference document) by Healthpoint Biotherapeutics that purchased Systagenix in June 2011. Healthpoint Biotherapeutics was acquired by Smith & Nephew in November 2012.

Its Marketing Authorization indication in Europe (1999) and in the United States (1997) is limited to the treatment, combined with suitable care of the lesion, of deep, chronic diabetic ulcers of exclusively neuropathic origin, non-ischemic, and whose surface is smaller than or equal to 5 cm^2. Regranex® is formulated at an acid pH and contains methyl paraben, propyl paraben and m-cresol; the presence of non-resorbable materials such as carboxymethyl cellulose may cause inflammations.

Dosage is one application per day for local treatment of the ulcer. Application and dressing are conducted by a healthcare professional. The maximum treatment period is 20 weeks and requires 3 tubes of Regranex® whose unit cost is about €350 in France. The total cost of treatment is very high in light of the cost of Regranex® and nursing costs.

On June 9, 2008, the FDA required a black box warning concerning the elevated risk of mortality from cancer if more than 3 tubes of Regranex® are used. The FDA nevertheless indicated that Regranex® did not increase the risk of cancer. The European Medicines Agency (EMA) concluded that the data did not demonstrate an effect (positive or negative) of Regranex® on the incidence of cancer or mortality from cancer. Johnson & Johnson, the proprietor of Regranex® at the time, withdrew the product from the European market in 2010. Regranex® then underwent several transfers and acquisitions and has not re-entered the European market since.

7.4.1.3.2 Skin replacements

Skin replacements are competitors of the BioChaperone® complex, even if Adocia believes that they should account for only a limited market share as a result of their high costs.

The Dermagraft® technology, authorized by the FDA, seems to be the most advanced treatment. The product is marketed by Advanced Biohealing, acquired in May 2011 by Shire, which estimated the market share at 5% with annual sales of $146 million[2] in the United States in 2010. Other products have also been granted a Marketing Authorization by the FDA, such as Apligraf® (Organogenesis), GraftJacket® (Wright) or Oasis Wound Matrix® (Cook Biotech).

Product (company):	**Dermagraft® (Shire)**	**Apligraf® (Organogenesis)**	**GraftJacket@ (Wright)**	**Oasis Wound Matrix (Smith&Nephew)**
Authorized indications:	Diabetic foot ulcer (>6 weeks)	Diabetic foot ulcer and venous ulcers (>3 weeks)	Diabetic foot ulcer (>3 weeks)	Diabetic foot ulcer and venous ulcers (>4 weeks)
Types of cells:	Dermis	Epidermis and dermis	Dermis	Dermis
Origin of cells:	Human cells	Human cells	Cadaver cell s	Porcine cells

Shelf life:	6 months	2 weeks	2 years	2 years

Table 7: Skin replacements on the market. Source: Reports of the companies mentioned

7.4.1.3.3 Other products under development

The first spray product, Fiblast® is marketed in Japan. Its active substance is fibroblast growth factor 2 (FGF-2) developed by the Japanese company Kaken, a partner of Olympus in the area of wound healing. Fibroblasts produce large quantities of collagen and elastin, proteins located between cells and are the major constituents of connective tissue. The most important role of fibroblasts is to repair traumatic lesions. Fibroblasts can alternatively contract or relax according to a dynamic process mediated by a variety of chemical messengers. In the case of inflammation or any degenerative process, fibroblasts contribute to repair by their contraction capacities and promote wound healing. FGF-2 is authorized and marketed in Japan for several indications such as bedsores, burns and leg ulcers. A phase III clinical trial is under way in Europe for diabetic foot ulcers. The proposed treatment regimen is one application per day for 12 weeks.

Another product under development by Derma Sciences uses an angiotensin analog peptide; angiotensin regulates blood pressure. A phase II clinical trial involving 75 patients showed that the results were comparable to Regranex® in terms of wound healing. The planned treatment regimen is one application per day for 4 weeks. Derma Sciences has started two phase III trials in the United States for the treatment of diabetic foot ulcers. These clinical trials are under way.

Finally, Healor has designed a treatment using a protein kinase-C precursor peptide. A clinical trial involving 22 subjects has terminated. The planned treatment regimen is one application per day for 4 weeks.

7.4.2. BioChaperone® insulins for the treatment of diabetes

Adocia decided to profit from its BioChaperone® technological platform to enter the insulin therapy diabetes treatment market with new innovative insulin formulations. This market accounted for $22.9 billion in 2013[40].

7.4.2.1 The pathology

Diabetes is defined as an increase in the levels of blood glucose. The two major causes of diabetes are the absence of insulin secretion by pancreatic cells (type 1 diabetes) or reduced secretion of insulin in the pancreas and/or poor use of insulin by the body (type 2 diabetes). In addition, type 2 diabetes is often associated with other pathologies such as obesity, cardiovascular diseases and hypertension.

Diabetes is a chronic pathology involving close to 382 million people throughout the world in 2013, according to the International Diabetes Federation (IDF).[4] The IDF also reported that the number of deaths from this pathology was 5.1 million in 2013 and could double by 2030.

The types of diabetes

Type 1 diabetes appears in young subjects and among all diabetics, type 1 has been estimated to affect 10% of this population[4]. The symptoms of this disease are excessive urination (polyuria) occasionally with acetone in the urine, intense thirst (polydipsia), excessive appetite (polyphagia), although the subjects lose weight, their blood glucose levels are high, greater than 1.4 g/L fasting (hyperglycemia) and excessive levels of sugar in the urine (glycosuria). Type 1 diabetes is an autoimmune disease: type 1 diabetics manufacture antibodies that attack the person's own pancreatic cells, in particular those synthesizing insulin in the islets of Langerhans*. Type 1 diabetes becomes unavoidable after the vast majority of these islets are destroyed (about 90%). The link

between this autoimmune disease and a hereditary predisposition is not sufficient to explain the occurrence of type 1 diabetes: in 90% of new cases, there was no family history of type 1 diabetes and the risk of developing type 1 diabetes when one of the two parents is afflicted is less than 2 or 3%[4].

Type 2 diabetes is characterized primarily by the resistance of cells to insulin, called insulin resistance, even if the synthesis of this hormone tends to decrease in the elderly. Type 2 diabetes has been estimated to affect 90% of the diabetic population[4]. This metabolic disease prevents what is called glycoregulation (control of blood sugar levels), thereby causing diabetes. The abnormally high production of insulin by the pancreas ultimately damages the islets of Langerhans, leading to an insulin deficiency. Type 2 diabetes is considered to be asymptomatic and is often discovered after blood tests that reveal elevated blood glucose levels, i.e. hyperglycemia. Genetic predisposition is a predominant factor and overweight is an aggravating cause of type 2 diabetes.

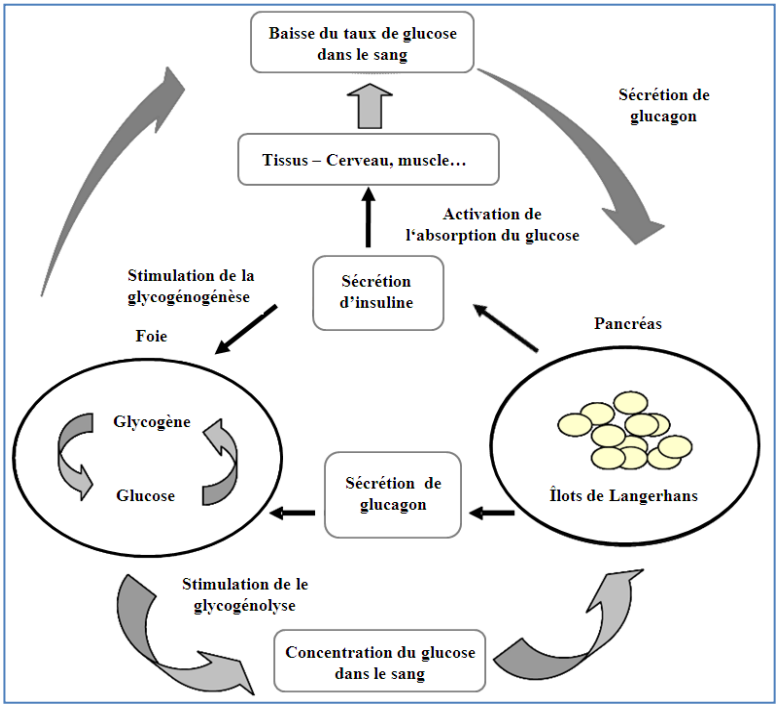


Figure 12: Production and action of insulin. Source: Business Insights/International Diabetes Federation

Other forms of diabetes, called secondary because they are the result of other dysfunctions or pathologies, exist but their prevalence is marginal: genetic defects involving insulin secretion, genetic defects involving insulin sensitivity, diabetes from pancreatitis or pancreatic cancer, diabetes caused by a drug or toxic substance, etc. Pregnancy may also cause diabetes, which could be a type 2 diabetes precursor if is disappears after birth.

Complications of diabetes

Cardiovascular complications are the principal cause of death of type 2 diabetes patients: cardiovascular morbidity and mortality are increased by a factor of 2 to 3 in men and by 4 to 5 in women. About 20% of cerebrovascular accidents (stroke) occur in diabetics. In the long term, diabetes can cause lesions to the heart, blood vessels, eyes, kidneys and nerves, such as [4]:

- diabetic retinopathy, an important cause of blindness resulting from the accumulation of damage to the small vessels of the retina; after 15 years, about 2% of diabetic lose their sight and about 10 % have a severe visual handicap;
- diabetic neuropathies, damage to nerves caused by diabetes; up to 50% of diabetics are afflicted. Diabetic neuropathies can cause a wide variety of problems but usual symptoms are tingling, pain, numbness or weakness of the feet and hands;
- the neuropathy, combined with poor blood flow, can increase the risk of foot ulcer that could require amputation;
- diabetes is among the principal causes of kidney failure and between 10 and 20% of diabetics die from this cause;
- diabetes increases the risk of cardiopathy and cerebrovascular accident and 50% of diabetics die from a cardiovascular disease; and
- the overall risk of death is at least twice as high in diabetics.

Treatment of diabetes with insulin

The treatment of diabetes by insulin therapy is broken down into two parts. Initially, prandial treatment (at mealtimes) of diabetes is implemented to control blood glucose after a meal, and secondly the basal treatment of diabetes in order to control continuous blood glucose due to hepatic glucogenesis. Prandial treatment involves so-called fast insulins and basal treatment is with so-called slow insulins.

Prandial treatment

In healthy subjects, a sudden increase in blood glucose is compensated by an equally abrupt increase in the endogenous insulin concentration in the blood. This maintains the blood glucose concentration between 4.4 mmol/L (0.80 g/L) and 7 mmol/L (1.4 g/L). Blood glucose control is considered ideal when the blood glucose concentration remains between these two limits.

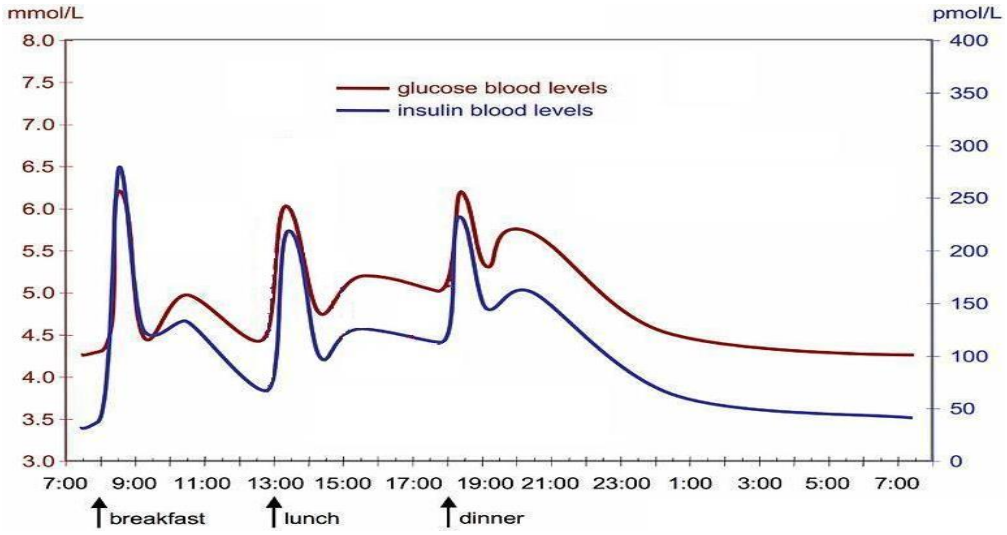


Figure 13: Blood glucose and insulin in healthy subjects. Source: Adocia

If the glucose concentration decreases below 0.80 g/L, the subject is hypoglycemic (exposing the patient to a risk of mortality) and when it rises above 1.4 g/L, the subject is hyperglycemic.

Glucose regulation is defective in diabetic patients, so that the patient is hyperglycemic, in particular after meals. It is therefore of utmost importance to start insulin treatment in order to control blood glucose at levels as close as possible to those of healthy subjects. There are two major types of

treatment available that have resulted from recombinant insulin production technology: those using human insulin and those using an analog of human insulin.

Three human insulin products are on the market: Actrapid® (Novo Nordisk), Insuman® (Sanofi-Aventis) and Humulin® (Eli Lilly). The disadvantage of human insulin treatments is that they are relatively slow acting. After the subcutaneous injection of these products, the profile of insulinmia (insulin levels in the blood) is delayed by about 30 minutes compared to healthy subjects. Diabetics therefore have to plan meals and take their injection about 30 minutes before starting the meal. In addition, human insulin treatments do not prevent hyperglycemia and hypoglycemia. These products also tend to make patients overweight and augment cardiovascular risks.

The primary sequence of insulin analogs is modified in comparison to that of human insulin. There are three fast acting insulin analogs currently on the market: NovoLog® (Novo Nordisk), Humalog® (Eli Lilly), and Apidra® (Sanofi-Aventis). Fast acting insulin analogs have the following advantages: improved post-prandial blood glucose regulation, with a reduced risk of hypoglycemia and hyperglycemia, less weight gain and enhanced patient comfort because insulin injection times and dosages are more flexible. Research on new treatments with an even shorter response time is continuing with the goal of reaching normal post-prandial blood glucose control in healthy volunteers. These new insulin treatments are called "ultra fast". The objective in terms of the pharmacokinetic profiles of insulins is shown in the following diagram.

Figure 14: Objectives in terms of pharmacokinetic profile of ultra fast insulin analogs, for better post-prandial blood glucose control. Source: Adocia

The advantage of an ultra fast insulin for patients is that is can be administered at mealtimes, rather than before. In addition, the medical advantages of analogs compared to human insulin could be increased, for example by reducing the number of hypoglycemic episodes and weight gain.

Basal treatment

It is also necessary to use treatments with slow acting insulin (called basal insulin) in addition to prandial treatment of diabetes. This regimen closely reproduces the cycle of endogenous insulin secretion between meals or overnight in patients who no longer produce the hormone or in whom production is abnormal. This insulin class enables sustained release of insulin between meals and therefore maintains an insulin level in the blood sufficient to control blood glucose[4]. There are currently two types of treatment to cover daily basal insulin needs: sustained acting insulins and a fast insulin/crystallized insulin premix.

There are currently two sustained acting insulins on the market to fulfill this need for insulin release over 24 hours: Lantus® (Sanofi Aventis) and Levemir® (Novo Nordisk). One to two injections per day are required to cover patient needs as a complement to insulin taken with meals.

The premixes on the market (Novo Nordisk and Eli Lilly) are a mixture of an insulin and protamine (highly cationic protein) in different proportions. Protamine causes the coacervation* of a portion of the insulin molecules, resulting in the formation of microcrystals that can still be injected. After injection, the free fraction of insulin (not crystallized) retains a rapid profile while the fraction of insulin immobilized as microcrystals dissolves slowly in the subcutaneous environment and so its profile is one of delayed action. In addition, depending on the proportion of protamine, the action profiles of each fraction can be modulated. Nevertheless, all premix treatments on the market containing NPH (Neutral Protamine Hagedorn) do not enable 24-hour basal insulin needs to be covered with the crystallized delayed acting fraction, or sometimes even 12-hour needs. This is why even two daily injections are sometimes insufficient to cover needs until the next morning. Finally, it is to be noted that this approach involving partial coacervation of human insulin or of a fast insulin analog is associated with a major disadvantage in terms of patient safety. The formation of microcrystals of insulin and protamine may result in partial sedimentation that may be responsible for incorrect injection dosages (risk of hyper- or hypoglycemia accidents) and in some cases can clog the small gauge needles used to inject insulin.

In addition, premixes are not a good medical solution because of the pharmacokinetic profile of insulin (top profile in the following diagram). A patient treated with a premix will be exposed to high levels of insulin over long periods, leading to an extended period of hypoglycemia and considerable weight gain.

Figure 15: Objectives in terms of pharmacokinetic profiles of insulin Combos. Source: Adocia

This explains the need for a treatment combining a prandial insulin and a basal insulin whose pharmacokinetic profile would be close to that of the lower figure in the above diagram. This combination of insulins called "Combo" would reduce the number of injections and also provide an optimal insulin therapy treatment. This approach of combining two insulins having a basal and prandial action has been validated in a clinical trial comparing the double injection of Lantus® (basal insulin) and Apidra® (prandial insulin).

This double injection leads to better regulation of blood glucose compared to the injection of a premix[4].

Epidemiology

Diabetes is a chronic disease affecting millions of people all over the world that will increase in emerging nations in the years to come. The International Diabetes Federation[4] has estimated that between 2013 and 2035, the number of diabetics in the world will increase by almost 55% (in the 20 to 79 year-old population), from 382 million people today to 592 million. The increases in Europe (22.4%) and North America (37.3%) are predicted to be lower than the global mean, but emerging nations will without doubt have to face an explosion in the prevalence of diabetes: 109.1% in Africa, 70.6% in Southeast Asia and 69.2% in the Eastern Mediterranean and Middle East.

Geographic zones	Prevalence in 2013	Prevalence in 2035	Rate of increase
Africa	20 million	41.4 million	109%
Eastern Mediterranean and Middle East	35 million	67.9 million	96%
Europe	56 million	68.9 million	22%
North America	37 million	50.4 million	37%
Central and South America	24 million	38.5 million	60%
Southeast Asia	72 million	123.0 million	71%
Asia-Pacific	138 million	201.8 million	46%

Table 8: Estimations of increases in the number of diabetics in the 20 to 79 year-old population in the world. Source: International Diabetes Federation, 2013

This phenomenon will increase the number of diabetics in the same population. By 2035, the percentage of the diabetic population in all regions except Europe and Africa is expected to exceed 8% (Source: International Diabetes Federation, 2013).

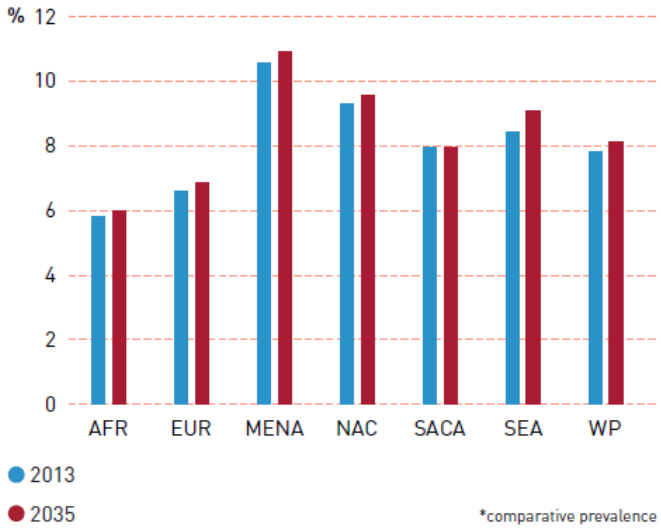


Figure 16: Prevalence of diabetes (in percentage) per region, in the 20 to 79 year-old population in 2013 and predictions for 2035. Source: International Diabetes Federation. AFR: Africa, EUR: Europe, MENA: Middle East

and North Africa; NAC: North America and the Caribbean; SACA: South America/Central America; SEA: Southeast Asia, AP: Asia-Pacific

The 2007-2010 ENTRED study[4] provided a qualitative picture of the diabetic population in metropolitan France. The most common form of diabetes is type 2 and concerns 2.2 million patients, i.e. 92% of the total number of diabetics estimated at 2.4 million. The treatment of type 2 diabetes is of long duration because the average time a patient has had the pathology is 11 years. This duration of treatment is even longer, 17 years, for type 1 diabetes patients. Type 2 diabetes is a pathology of the elderly with a mean age of 66 years and one quarter of the diabetic population (type 2) is older than 75. Type 1 diabetes affects a younger population whose men age is 42 years. The sex distribution of diabetes is practically equal for men (54%) and women (46%).

7.4.2.2 The market

According to Novo Nordisk, the world market for the insulin treatment of diabetes increased by 13.9% between 2003 and 2013, accounting for more than $2.1 billion, i.e. close to 50% of the total market for antidiabetic drugs. The domination of insulin over other drug classes is explained simply by the fact that insulin is the only way to control blood glucose in type 1 diabetic patients and that the use of insulin will ultimately become as unavoidable as for type 2 diabetic patients.

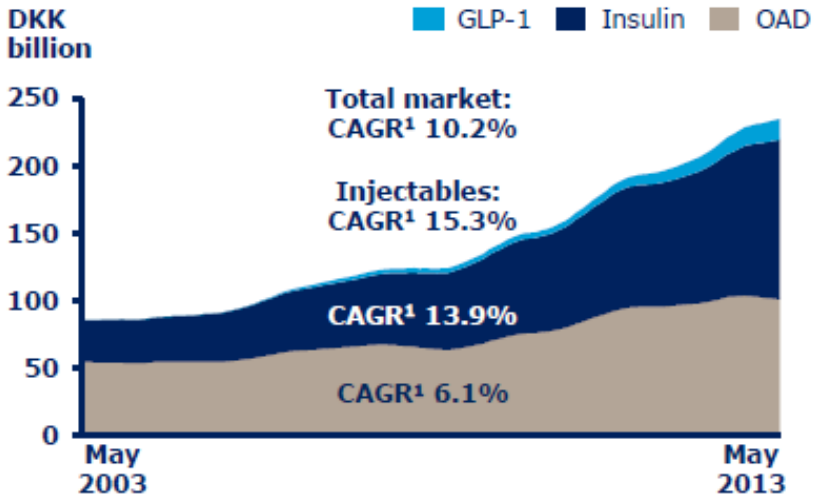


Figure 17: Global diabetes market per therapeutic class and changes between 2003 and 2013 (Source: Novo Nordisk)

Segmentation of the insulin market is conditioned by the time before onset, and duration of action of insulin. In this context, the appearance of human insulin analogs for basal treatment of the disease has transformed the insulin market that is now dominated by Lantus® (Sanofi Aventis), on the market since the early 2000s. This product alone accounts for 30% of the market with sales of more than $6.5 billion in 2012. The sales of its competitor Levemir® (Novo Nordisk) were more than $1.8 billion in 2012.

The segment of fast acting insulins (prandial treatment) is dominated by human insulin analogs, in spite of the higher cost compared to human insulin, whose post-injection time of action is between 20 and 30 minutes. The two flagship products are NovoLog® (Novo Nordisk) with sales of $2.8 billion in 2012) and Humalog® (Eli Lilly) with sales of $2.4 billion. Eli Lilly with Humulin® dominates the medium term action insulins segment with sales of more than $1.2 billion in 2012. Finally, sales in the premix segment were more than $2.3 billion in 2012 and close to $1.7 billion for NovoMix® from Nordisk.

	Prandial treatment (Fast Acting) Regulate blood glucose after a meal	**Basal treatment (Long Acting)** Regulate blood glucose continuously	**Prandial-basal treatment (Medium term action and/or premix)** Single injection for prandial and basal action
Novo Nordisk	NovoLog® ($2.8 billion/ patent expiration in 2014) Novolin N&R® ($1.5 billion)	Levemir® ($1.8 billion) Tresiba® (authorized in 2012 in Europe and Japan. Patent expiration in 2024	NovoMix® ($1.7 billion)
Eli Lilly	Humalog® ($1.8 billion/ patent expiration in 2013) Humulin® ($1.2 billion)	/	Humalog Mix® ($0.6 billion) Humulin® NPH
Sanofi	Apidra® ($0.3 billion/ patent expiration in 2017) Insuman® ($0.2 billion)	Lantus® ($6.5 billion/patent expiration in 2015)	Insuman® NPH

Table 9: Summary of the insulin market in 2013. Source: Annual corporate reports, Adocia.

During the next five years, the insulin market should be relatively stable (+2.5% anticipated annual growth rate between 2010 and 2016) during which sales of certain flagship products are predicted to decline (-0.7% for Lantus® and -5.8% for Levemir®, as annual growth in the basal treatment segment). Other products, however, should have a rate of annual growth higher than that of the market: +6.8% for NovoRapid® and +3% for NovoMix®.[5]

Anticipated 2010-2016 sales on the market of human insulin and human insulin analogs, in millions of dollars

2010	2011	2012	2013	2014	2015	2016
17,262	18,486	19,425	20,026	20,451	20,017	19,964

Source: Business Insights

In spite of this market size stability, Datamonitor[5] has predicted the emergence of medium-size pharmaceutical companies working to improve the pharmacokinetic profile* or formulation of existing insulins, in contrast to large pharmaceutical companies that will continue their research on new molecules. Research efforts by many companies will probably focus on reducing the adverse effects of insulins, for example hypoglycemia and weight gain. The same study predicted that prandial insulins will be the insulin involved in the largest number of ongoing clinical trials, with 14 trials among a total of 26, of which 6 are phase I, 4 are phase II, 2 are phase III and 2 are post-phase III trials. There are 7 trials on basal insulins (3 are phase I and 3 are phase II, as well as one phase III trial). The other trials involve primarily premixes.

7.4.2.3 Clinical trials conducted by Adocia

7.4.2.3.1 HinsBet human insulin ® (acronym for Human insulin is Better)

A pre-clinical study on pigs (the most widely used animal model for studies of insulin pharmacokinetics and pharmacodynamics*) sponsored by Adocia showed that HinsBet® reduces the time to onset of action of human insulin.

A phase I trial also sponsored by Adocia was carried out by the German contract research organization (CRO) I.K.F.E (refer to section 6.4.3.2 Controlling subcontracted clinical trials) in November and December 2010; the final trial report was published in April 2011. The double-blind randomized crossover study included 12 healthy male volunteers (mean age 27.2 ± 6.6 years) and its general objectives were to establish treatment safety because this was the first exposure of humans

to this formulation, and to determine the pharmacodynamic and pharmacokinetic profiles of HinsBet® in comparison to NovoLog® (fast insulin analog produced by Novo Nordisk) and to Actrapid® (human fast insulin produced by Novo Nordisk).

Three consecutive glucose clamp technique cycles* were run: this method involves the injection of glucose via infusion to maintain the patient's blood glucose constant to compensate the hypoglycemia caused by an insulin injection. Each subject received the equivalent of 12 IU* of insulin and was monitored for 6 hours during which the glucose level was held constant by the infusion of glucose to compensate for the drop in levels of insulin injected.

The principal objective of the trial was determining the time required to reach the maximum of infused glucose, called glucose infusion rate (GIR-Tmax). The secondary objectives of the trial were to determine the maximum infused glucose (GIRmax), the time to reach half-GIRmax (GIR-T50), the maximum blood insulin concentration (INSmax), the time required to reach the maximum and half-maximum of the plasma insulin concentration (INS-Tmax and INS-T50) and finally the number and type of adverse effects.

The results were very promising. First, all HinsBet® injections were well accepted and no adverse effect was reported. In addition, changes in the GIR showed that the response time of HinsBet® was similar to that of NovoLog® (insulin analog) and that HinsBet® produced its effect (decreased blood glucose) 20 minutes earlier than Actrapid® (human insulin).

Results of the phase IIa trial on 20 type 1 diabetics (Germany): HinsBet® (BioChaperone® human insulin) compared to a fast acting analog, NovoLog®

After the phase I results were obtained, Adocia decided to continue the clinical development of HinsBet® by conducting a phase II clinical trial in type 1 diabetics.

The double blind, randomized, cross-over trial was conducted in one center on 20 type 1 diabetics using the glucose clamp technique. The aim of the trial was to compare the pharmacokinetic profiles, pharmacodynamic profiles and safety of HinsBet® compared to NovoRapid®, a fast insulin analog, after three consecutive injections of each product to each patient.

The results showed the hypoglycemiant effect of the optimized HinsBet® formulation is just as rapid as that of NovoRapid® (insulin aspart, one of the modern fast insulins). In addition, in the course of the trial no adverse effect and no modification of clinical parameters were found. The local safety of HinsBet® was judged to be very good and comparable to that of NovoRapid®. Finally, repeated administration as three consecutive injections of HinsBet® revealed intra- and inter-individual variabilities of pharmacological parameters similar to those of NovoRapid®.

New optimized formulation of HinsBet®: preclinical results

Adocia decided to rapidly advance the clinical status of HinsBet® in order to obtain proof of concept of the product in humans and validate the use of BioChaperone® as excipient for an insulin formulation. In parallel, the company is continuing to study different BioChaperone® candidates and has developed an optimized HinsBet® formulation, whose preclinical pharmacodynamic profile (pig model) was shown to be better than that of the first HinsBet® formulation, with activity very close to that of NovoLog® (see Figure 18).

Figure 18 Pharmacodynamic profiles of the new HinsBet® formulation (green), NovoLog® (insulin aspart, red) and recombinant human insulin (RHI, black) in pigs, a preclinical model having good correlations with humans.

Based on phase I results with the first formulation and the very promising results obtained with the new formulation, Adocia plans on continuing development of the second generation of HinsBet® and is preparing a submission for a phase II clinical trial planned to start in 2014.

7.4.2.3.2 Ultra fast insulin analog

A preclinical study in an animal model (pigs) showed the shortened response time of BioChaperone®-Humalog® compared to Humalog® alone, as well as a shorter duration of action of the hypoglycemiant effect, resulting from the more rapid absorption of Humalog® by the body related to the presence of BioChaperone®, and its more rapid elimination.

This preclinical study also showed a reduction in the heterogeneity of action of Humalog® observed in guinea pigs because of the presence of BioChaperone®. The same performance was obtained by applying BioChaperone® to NovoLog®, a fast insulin from Novo Nordisk.

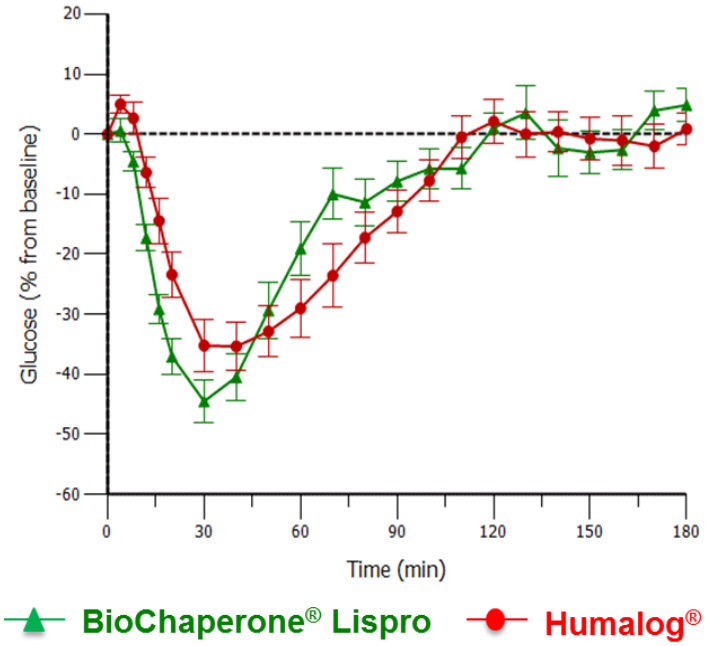


Figure 19: Pharmacodynamic profile of BioChaperone®-lispro vs. Humalog® (insulin lispro, Eli Lilly) in dogs. Source: Adocia

Based on these results, Adocia signed a licensing and joint work contract with the American pharmaceutical group Eli Lilly in 2011. According to the contract, Adocia granted exclusive worldwide rights to Eli Lilly for a BioChaperone® polymer for the development, manufacture and marketing of BioChaperone®-Humalog® and the contract covered all potential indications of BioChaperone®-Humalog®. Eli Lilly financed development of BioChaperone®-Humalog® including clinical trials, and Adocia and Eli Lilly managed joint work by a management committee composed of members of both companies.

In July 2012, Eli Lilly referenced the preparation of a phase I trial of BioChaperone®-lispro (commercial name of Humalog®) on the American website dedicated to clinical trials (clinicaltrials.gov). The trial was a success in that the results fulfilled all the clinical objectives set down. In July 2013, Adocia issued a press release announcing the end of its contract with Eli Lilly.

The results of this clinical trial cannot be presented because it continues to be the subject of certain confidentiality clauses involved in the partnership with Eli Lilly (even though it ended in July 2013).

7.4.2.4 Future clinical trials

7.4.2.4.1 HinsBet®

In parallel to the clinical development of HinsBet®, a version of BioChaperone® optimized for HinsBet® was developed. This optimized formulation of HinsBet® will be tested against NovoLog® in a phase IIa clinical trial on 12 type 1 diabetics in 2014. The clinical trial application was submitted to German regulatory authorities at the end of 2013. The Company has received approval to begin the trial in February 2014. However, and based on recent results on ultra-fast insulin analogue, the Company should review the protocol and submit an amendment to the regulatory authorities. The launch of the study is now scheduled for September 2014

The objective of this clinical trial will be to validate the superior efficacy of this new human insulin formulation in order to continue the clinical development of HinsBet®.

The success of this clinical trial should add value to HinsBet® and open the door to a partnership with a large pharmaceutical group capable of conducting additional clinical trials to obtain a Marketing Authorization for the product.

7.4.2.4.2 Ultra fast insulin analog

Based on the promising results of the phase I trial conducted in partnership with Eli Lilly, Adocia started a phase IIa trial on 36 type 1 diabetics in January 2014. The purpose of this trial is to compare the pharmacokinetic and pharmacodynamic profiles of BioChaperone®-Humalog® complex to those of Humalog® alone. Dated April 9, 2014, Adocia announced the results of this study: BioChaperone Lispro Humalog is significantly faster in patients with type 1 diabetes (onset 30% faster and 69% early metabolic effect higher).

7.4.2.4.3 Combination of prandial insulin and basal insulin

Tests *in vitro* have shown the possibility of using BioChaperone® technology to solubilize insulin glargine (Lantus®) at neutral pH and mix it with any prandial insulin including fast acting insulin analogs (Apidra®, Humalog® and NovoLog®). Adocia combined these two products and established proof of concept in the preclinical dog model that complies with numerous research criteria for the premix: total solubility of both proteins at the same pH, with good stability, with pharmacokinetic and pharmacodynamic profiles showing that the response times of the fast analog (Humalog® in the following figures) were not substantially changed by the presence of Lantus® and a BioChaperone® polymer in the formulation, and that the duration of action of Lantus® was also preserved to a substantial extent.

As shown in the figure below, BioChaperone® provides the same performance as that obtained with the double control injection (Lantus® and Humalog® injected separately).

Figure 20: Comparison of the pharmacodynamic profiles of Adocia BioChaperone® glargine-lispro Combo and the double injection of insulin glargine and insulin lispro: preclinical results in dogs (model correlated with humans). Source: Adocia

In this preclinical dog model, which is correlated with humans, it was also shown that the combination of the two insulins using BioChaperone® technology led to an optimized activity profile compared to that obtained with the Premix (Humalog Mix® here), as shown in figure 21.

Concerning the BioChaperone®-Lantus®-Humalog® Combo, the response time of the fast analog (Humalog®) was no longer correlated with that of basal insulin (good transition between the two distinct actions of the two insulins). The premix, however, was characterized by an action of the fast fraction of the premix that acts with a lag time and that risks producing post-prandial hypoglycemias, and also by a duration of action of the slow fraction that does not last long enough and that risks producing hyperglycemia (in particular nocturnal).

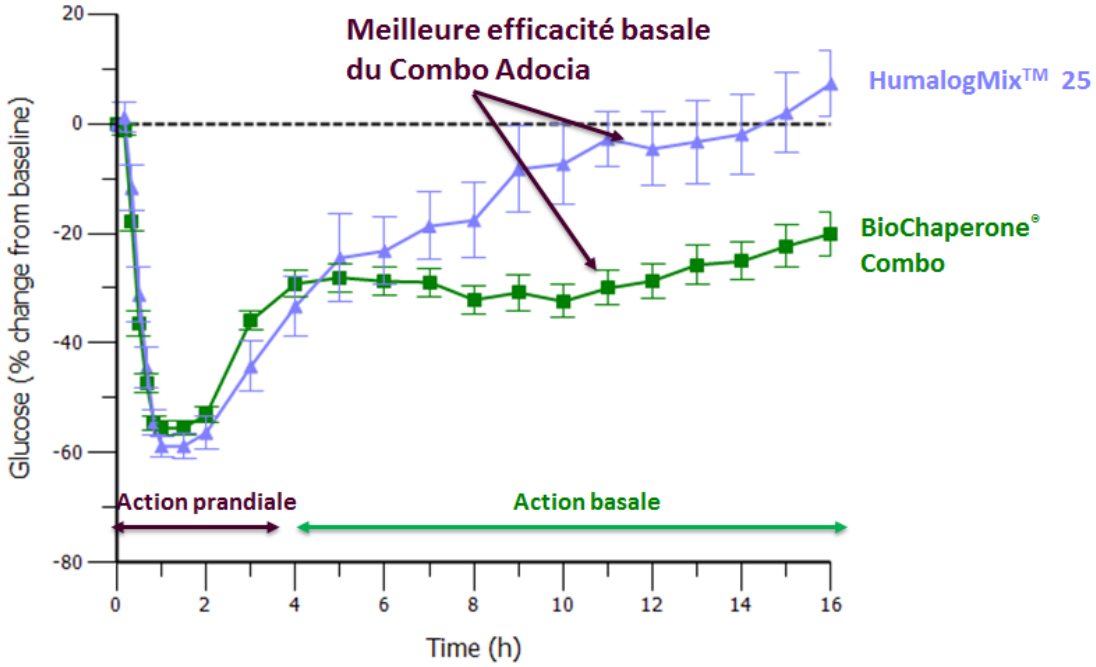


Figure 21: Comparison of the pharmacodynamic profiles of Adocia BioChaperone®-glargine-lispro Combo and of the Humalog Mix®25 premix (insulin-lispro and insulin-lispro-NPH): preclinical results in dogs (model correlated with humans)

Based on these positive results, Adocia started a phase I/II clinical trial in November 2013 on 20 type 1 diabetics. The purpose of the trial was to show that this combination provided diabetic patients with better blood glucose control than that obtained with an insulin analog premix such as Humalog Mix® formulated with insulin lispro (Eli Lilly) or NovoMix® formulated with insulin aspart (Novo Nordisk). The pharmacodynamic and pharmacokinetic profiles of the BioChaperone®-glargine-lispro combination have been compared to those of Humalog Mix® in a crossover trial in 20 type 1 diabetics using the glucose clamp technique.

The preliminary results of this trial were announced on February 27, 2013 and the final results have been published on March 20,2014:
- the onset of action of BioChaperone® Combo is at least 30% more rapid than that of Humalog Mix®,
- the duration of action is more than 30 hours in most patients,
- the BioChaperone® Combo formulation is safe and well accepted.

7.4.2.5 The competition

7.4.2.5.1 The competition for the prandial treatment of diabetes

Novo Nordisk

Novo Nordisk is developing a new formulation of its fast insulin analog (insulin aspart) whose action is believed to be more rapid than that of NovoLog® (FiAsp, ultra fast acting analog). Novo Nordisk started a phase III trial in late 2013 and initial publications on pharmacokinetic and pharmacodynamic profiles have shown a fast-in effect (more rapid onset of action).

Biodel

The American company Biodel, as Adocia, has recognized the value of a human insulin product with an action as rapid as that of analogs. Biodel has developed a formulation of fast acting human insulin called VIAject™ (BIOD-090) whose performance seems to be comparable to that of analogs.

VIAject™ is a formulation of human insulin with ethylenediaminetetraacetic acid (EDTA) and citric acid whose pH is around 4.5. The insulin concentration of VIAject™ is 4 times lower than that of products on the market. VIAject™ has been tested in many phase I, II, and III trials. Phase I results had shown that the BIODEL technology enabled the absorption of human insulin (insulinmia) and regulation of glycemia (blood glucose) that was as rapid as the insulin analog lispro and more rapid than Humulin® human insulin at the same doses[54]. In phase III, VIAject™ had shown its non-inferiority to a commercial human insulin, Humulin® (Eli Lilly)[55]. The administration of VIAject™, however, caused pain at the injection site. Biodel applied for a Marketing Authorization of this formulation (VIAject™) in the United States in October 2010, but the FDA rejected the application. The FDA requested Biodel to conduct a new phase II clinical trial on type 1 and 2 diabetics, based on the judgment that the initial data were insufficient and did not clearly demonstrate superiority of this product.

Biodel conducted new preclinical studies of performance and prepared a new formulation of human insulin, BIOD-123 whose pharmacokinetic and pharmacodynamic profiles were equivalent to VIAject™ but with attenuated reactions at the injection site. BIOD-123 has been tested in phase I and II trials. In September 2013, Biodel announced positive phase II results showing the non-inferiority of BIOD-123 compared to Humalog® in terms of control of prandial blood glucose (level of HbA1C).

BIODEL used the same type of formulation (citrate-EDTA) and also commenced the development of ultra fast insulin lispro formulations (prandial insulin analog, Humalog®, Eli Lilly), BIOD-250 and BIOD-238. BIOD-250 was tested in phase II and showed a more rapid prandial action compared to Humalog®, as well as good acceptability. The stability of this formulation, however, is insufficient for commercial development. In early 2014 BIODEL announced the continuation of development of a new formulation that would comply with stability criteria.

Halozyme Therapeutics

Halozyme Therapeutics recently conducted a clinical trial to demonstrate the increased rate of absorption of human insulin or insulin analogs. Halozyme Therapeutics is developing a recombinant human enzyme, hyaluronidase PH20 that depolymerizes hyaluronic acid in physiological conditions. This polysaccharide is a constituent of the extracellular matrix and is found in a large number of tissues: connective, epithelial and nerve. It is also present in the subcutaneous compartment where the injection of hyaluronidase degrades the matrix. The diffusion of proteins injected with this enzyme is improved, leading to more rapid diffusion of the drug substance from the injection site to the capillary network[5]. This technology is used for monoclonal antibodies to enable their subcutaneous rather than intravenous administration (products authorized in Europe in 2013 and 2014, in partnership with Roche: Herceptin SC® and MabThera SC®).

In a phase I clinical trial[5], the effect of hyaluronidase on the rate of absorption by the blood compartment was demonstrated: there was an increased rate of absorption of human insulin by the

combined administration of PH20 with Humulin® and the accelerated absorption of an insulin analog by the combined administration of PH20 with Humalog®.

A phase II clinical trial involving type 1 diabetics also showed the positive effect of PH20 on the pharmacokinetics of human insulin by the combined administration of Humulin® with hyaluronidase. The results also showed a reduction of post-prandial blood glucose and attenuated hypoglycemia in comparison to Humulin® alone.

A phase II clinical trial conducted in 2012 on type 1 diabetics showed the effect of PH20 on the increased absorption rates of two insulin analogs: insulin lispro and insulin aspart. For both insulins, there was improved control of post-prandial blood glucose for analogs formulated with PH20 compared to insulin lispro.

At the present time, however, this enzyme cannot be formulated with insulin because of insulin stability issues. The treatment therefore still involves combined administration, but insulin and hyaluronidase are mixed just before injection. Halozyme is planning to deliver its ultra fast analogs with pumps to resolve this problem, at the same time as taking a position on the future artificial pancreas market.

Mannkind

The company Mannkind was created in 1991 by Alfred Mann. Mannkind acquired Technosphere technology and the Medtone inhaler by purchasing Pharmaceutical Discovery. The acquisition of these technologies resulted in the product Afrezza, a human insulin administered by inhalation. It is an ultra fast human insulin whose concentration peak occurs 12 to 15 minutes after inhalation. Insulin delivered *via* this route has a shorter time of onset of action and the curve lacks a tail, or trailing edge, in contrast to human insulin administered subcutaneously. Its pharmacokinetic profile is very close to that of insulin secreted by the pancreas in healthy subjects. This results in better control of blood glucose after meals and a reduced proportion of glycated hemoglobin, HbA1c.

Based on these results, Mannkind submitted an initial Marketing Authorization application in 2009. The FDA issued an initial response in March 2010, requiring additional information. Following a meeting with the FDA, Mannkind re-submitted its application that the FDA again rejected in January 2011. In a second response, the FDA did not accept the use of Afrezza in type 1 and type 2 diabetic adults, requiring two additional phase III clinical trials with the new inhaler, called Dreamboat.

In August 2013, the company announced the results of these two phase III clinical trials. They established the product's non-inferiority compared to NovoLog® (insulin aspart, Novo Nordisk) in type 1 diabetics and a superiority over oral antidiabetics in type 2 diabetics; there was no negative change in the results concerning safety, the reduction of the number of hypoglycemia episodes and reduction of weight gain. The company resubmitted its MA application based on these results.

On January 10, 2014, Mannkind announced that the Endocrinology and Metabolic Drugs Advisory Committee of the FDA set April 1, 2014 as the date on which the Afrezza application could be reviewed. This date is to be confirmed by a memo (Federal Register notice) from the FDA.

In 2005, Pfizer received authorization for an inhaled insulin, Exubera, but the product was a commercial failure and was rapidly taken off the market.

7.4.2.5.2 The competition for treating diabetes with Combos

Novo Nordisk

Novo Nordisk is currently developing a Combo formulation of NovoLog® (fast acting analog) and degludec, a slow insulin analog, developed by Novo Nordisk.

Degludec was developed to replace detemir in the next few years to enable Novo Nordisk to have a product whose action is close to that of Lantus, and therefore longer than that of detemir.

Novo Nordisk recently published[5] the results of a 16 week clinical trial on type 2 diabetic patients in which the performance of two degludec/NovoLog® Combos (at two different proportions: 70/30 and 55/45) was compared to that of Lantus®. The results indicate that daily injections of Degludec Combo are well accepted by patients and lead to a control of blood glucose comparable to that of Lantus® with lower extents of hypoglycemia. These Combos also enable a better control of post-prandial blood glucose (after meals) because of the fast action of aspart.

In 2013 Novo Nordisk was granted a Marketing Authorization in Japan and Europe for Tresiba®, (insulin degludec) and for Ryzodeg®, the combination of degludec with NovoLog® (slow insulin-fast insulin Combo). Ryzodeg® is the first product of this type authorized for marketing, but these products have not yet been approved in the United States. The FDA requested Novo Nordisk to conduct additional trials on the potential cardiovascular adverse effects of Tresiba®, which will delay marketing of the product by several years. Adocia's insulins, based on Lantus® (insulin glargine), on the contrary have a large body of positive data available on the safety of insulin glargine.

Biodel

Biodel is currently developing a formulation of ultra concentrated human insulin (400 IU), BIOD-531. The company's desired market position is to be a competitor of premix products and also to treat patients with severe resistance to insulin. In February 2014 Biodel announced the preliminary results of its phase II trial in obese, non-diabetic patients, comparing BIOD-531 to Humulin® R U-500 (concentrated human insulin, Eli Lilly) and to Humalog Mix® 75/25 (Eli Lilly). The acceptability and safety profiles of BIOD-531 are comparable to that of Humalog Mix®. Compared to Humalog Mix®, the results show a significant acceleration of the onset of prandial action of the product, and a prolongation of basal action until about 18 hours post-injection.

7.4.2.6 Progress provided by BioChaperone® technology

The developments under way by Adocia involve all segments of insulin treatment of diabetes (human insulin, insulin analog, Combo). The total value of these markets is more than $7-8 billion and the company could enter them *via* the signature of partnerships (refer to section 6.4.1.2. The market). The company has shown (refer to section 6.4.2.3. Clinical trials conducted by Adocia), using insulins marketed by large pharmaceutical companies, that it is possible to use the BioChaperone® technological platform to eventually produce and market:

- a BioChaperone®-human insulin complex, HinsBet®, with a time to onset of action more rapid than that of a human insulin and similar to that of an insulin analog in a phase I trial and a phase IIa trial;
- a fast acting BioChaperone®-insulin complex (Humalog® or NovoLog®) with a time to onset of action more rapid than that of the insulin analog alone, currently in phase II; a complex at neutral pH of BioChaperone®-fast acting insulin (Humalog® for example) -slow acting insulin (Lantus). This forms a single Combo retaining the fast action of Humalog® at the same time as enabling the basal action of Lantus® up to 16 hours after its injection in a preclinical study, just as a double injection of Lantus® and Humalog®, currently being tested in phase I/II

Adocia has also received financial support from the OSEO and the Regional European Development Fund (FEDER) in the form of subsidies and upfront loans for a total of €1,640,000 euros (refer to section 22.2 of this reference document Contracts signed with OSEO).

7.4.3. Innovative formulation of monoclonal antibodies

In order to obtain maximal benefit from its BioChaperone® technological platform and ultimately sign license contracts, Adocia is currently working on two joint development programs with major pharma companies to design new formulations of their therapeutic proteins. The goal of these new formulations is to improve efficacy, safety and compliance of the therapeutic proteins of its partners by providing new properties to become best-in-class products. In the framework of these development contracts, Adocia's partners furnish the quantities of therapeutic proteins required for the work and Adocia is reimbursed for costs incurred for research and making BioChaperone® technology available, which have thus far reached €1.18 million.

Monoclonal antibodies were developed in 1975 by Georges Köhler and Cesar Milstein, who received the Nobel Prize in Medicine in 1984 for their work.

Monoclonal antibodies are the products with the highest growth of the pharmaceutical industry. This progress has been rapid because of the number of severe oncology pathologies involved (treatments of leukemias, lymphomas, breast cancers, colorectal cancers, etc.) and their value for the treatment of autoimmune and inflammatory diseases (rheumatoid polyarthritis, Crohn's disease, multiple sclerosis, etc.). An additional reason for rapid growth has been the development of large scale production techniques.

Several monoclonal antibodies have become blockbusters, i.e. with sales over one billion dollars, in particular Remicade® (Johnson & Johnson: $7.7 billion in 2012), Avastin® (Roche: $6.3 billion in 2013), Enbrel® (Amgen & Pfizer: $8.3 billion in 2013), Humira® (Abbott Laboratories: $9.3 billion in 2012), Rituxan®/Mabthera® (Roche, Biogen & Genentech: $6.1 billion in 2013) and Herceptin® (Roche: $6.45 billion in 2013).

These molecules operate primarily as inhibitors, by trapping active proteins or by binding to cell receptors to prevent the binding of ligands. This strategy requires a systemic concentration high enough to block targets and therefore the administration of high doses. In these conditions, stability and formulation issues may predominate and result in therapeutic consequences in terms of efficacy and immunogenicity. In most cases the method of administration involves intravenous infusion after diluting the antibodies in isotonic saline. Some antibodies administered intravenously aggregate during storage and this can cause immune reactions, even reduced antibody activity. The number of subcutaneously administered monoclonal antibodies is increasing. In September 2009, GENMAB and its partner GSK stated that they were re-directing work towards the production of a version for subcutaneous injection of their product Arzerra. This route of administration should be the preferred solution for the pharmaceutical industry but to reach this end, formulations of totally soluble antibodies at high concentrations must be developed.

Adocia is carrying out joint work with two large pharmaceutical companies in order to develop a second generation formulation with the goal of becoming best-in-class products that would improve:

- the physical stability of antibodies to prevent the formation of aggregates that could reduce efficacy and increase immunogenicity of the products;
- the solubility of antibodies to prepare formulations at high concentrations and low viscosity for subcutaneous injection when this route is compatible with the pathology and the antibody used.

The company has also received a subsidy of €63,367 from the OSEO for its research on monoclonal antibodies.

7.5. Adocia oncology products developed with DriveIn® technology

7.5.1. Pathology

Cancers are a pathological cell proliferation in a healthy tissue that threaten the survival of the tissue in question, even the organism itself. This abnormal proliferation results from mutations of cell cycle genes in cancer cells that may arise from hereditary anomalies and/or environmental factors (life style, exposure to carcinogens, infections, etc.).

Cancers are currently one of the leading causes of death in developed nations. The most frequent cancers in the global population are lung cancer, breast cancer and colorectal cancer (see Table 10).

Cancer	Worldwide incidence (number of new cases yearly, in millions)	Worldwide mortality (yearly, in millions)
Non-small cell lung cancer	1.6	1.4
Breast cancer	1.4	0.4
Colorectal cancer	1.2	0.6
Stomach cancer	0.99	0.7
Prostate cancer	0.9	0.3
Liver cancer	0.75	0.69
Cancer of the head and neck	0.74	0.4
Pancreatic cancer	0.28	0.25
Kidney cancer	0.27	0.1
Melanoma	0.2	0.05
Ovarian cancer	0.2	0.14
Multiple myeloma	0.1	0.05

Table 10: Worldwide incidence and mortality from the most frequent cancers (Source: Cancer Research UK)

Mortality rates depend on the type of cancer, its stage of advancement at the time of diagnosis and on available treatments. For example, while the 5 year survival of patients with a stage I ovarian epithelial cancer is 89%, the rate of the same cancer diagnosed at stage IV (metastatic) is only 18% (Source: National Cancer Institute). Similarly, patients with HER2-positive breast cancers (cancer resulting from the mutation of the HER2 gene) can be effectively treated, for example with Herceptin® (Roche, monoclonal antibody), while patients with so-called triple negative breast cancers (resulting from different genetic mutations) have very few therapeutic options available.

Medical needs vary considerably from one cancer to another and the disease therefore remains difficult to eradicate, explaining why oncology research is very active, with the hope of prolonging the lives of patients and improving their therapeutic management.

7.5.2. Drive*In*® oncology products

7.5.2.1 Types of treatment

The therapeutic oncology arsenal has become greatly diversified over the past several years. The first line of treatment for most solid tumors is surgery that excises accessible and delimited tumors. Surgery may be concomitant with, or followed by chemotherapy at a later time, whose purpose is to make cancer cells enter apoptosis (pre-programmed cell death). In a substantial number of cases, surgery and chemotherapy may, however, be unusable, insufficient or ineffective. Recourse to drug therapy is therefore very important and several types of treatments are available.

7.5.2.1.1 Chemotherapy

Chemotherapy is the treatment of cancer with chemical molecules and remains the lynchpin of therapeutic management in oncology; the first chemotherapy treatments were developed in the 1940s. The principal treatments currently on the market belong to several large families of molecules discovered between the 1950s and 1990s: taxans, platinum derivatives, anthracyclins, alkaloids, and nitrogen mustards in particular (see Table 11). In most cases, the drugs containing these molecules are administered intravenously. Many of them are now in the public domain (patents expired) and are still extensively used as first line treatment (in particular taxans, platinates and anthracyclins).

Molecule (public domain)	Name (company)	Market (year)	Peak of sales (year)
Docetaxel (2010)	Taxotere® (Sanofi)	$742 million (2012)	$3.1 billion (2010)
Pemetrexed (2015-2022)	Alimta® (Eli Lilly)	$2.594 billion (2013)	$2.594 billion (2013)
Temozolomide (2013)	Temodar® (Merck) (Dacarbazine pro-drug)	$2.213 billion (2013)°	2.323 billion (2011)
Oxaliplatin (2013-2016)	Eloxatine® (Sanofi)	$1.229 billion (2013)	$2.17 billion (2006)
Gemcitabin (2010)	Gemzar® (Eli Lilly)	$347 million (2013)	$1.7 billion (2008)
Paclitaxel (2000-2003)	Taxol® (BMS)	$148 million (2011)	$1.6 billion (2000)
Capecitabin (2013)	Xeloda® (Roche Genentech)	$1.435 billion (2013)	$1.624 billion (2012)
Doxorubicin (n.a.) **Liposomal doxorubicin (2009)**	Rubex®, Adriamycin®; Doxil® (J&J)	n.a. $402 million (2011)(*)	n.a. n.a.
Irinotecan	Camptosar® (Pfizer)	$130 million (2013)	$970 million (2007)

Table 11: Chemotherapy best sellers in oncology. Most of these molecules are indicated for the treatment of several types of different cancers. (Source: Datamonitor Healthcare). Sales of Doxil® reported for 2011, before the supply issues encountered by Johnson & Johnson (2012).

These treatments act on cell division, most often with the goal of stopping cell proliferation (treatments called cytostatic) or even killing cells (treatments called cytotoxic). Cancer cells divide to a greater extent and more rapidly than healthy cells and so these treatments preferentially attack rapidly dividing cancer cells. The vast majority of non-cancer cells in the body also divide regularly, however, so chemotherapies also damage healthy tissues. The elevated efficacy of chemotherapies is therefore limited by toxicity to healthy cells that is often extensive. This explains why oncology treatments have progressed to approaches called targeted.

7.5.2.1.2 Targeted therapy

In order to increase the therapeutic index (the efficacy/adverse effects ratio) of oncology treatments, research is being oriented toward development of "targeted" treatments, i.e. preferentially aimed at cancer cells and avoiding possible attack on healthy tissues as much as possible. Targeted therapies block the growth of cancer cells by acting specifically on proteins involved in carcinogenesis and tumor growth, rather than targeting all dividing cells. These therapies may be targeted inhibitors (small molecules), monoclonal antibodies or antibody-drug conjugates (ADC).

Targeted inhibitors

Most marketed targeted inhibitors interfere (by competition or inhibition) with the activity of members of the family of kinases, but their targets may differ. The first targeted inhibitors (Gleevec®, Sutent®) were marketed in the 1990s and had a significant impact on their indications, in particular for leukemia. Most of these products are administered orally. The principal targeted inhibitors on the market are listed in Table 12.

Compound	Target	Name (company)	Worldwide sales (2013)	Indications
Imatinib	Tyr-kinase	Gleevec® (Novartis)	$4.81 billion	Ph+ chronic myeloid leukemia (CML), gastrointestinal stromal tumor (GIST), acute lymphoblastic leukemia (ALL), other rare cancers
Lanalidomide	Immuno-modulator	Revlimid® (Celgene)	$3.77 billion	Myelodysplasic syndrome
Bortezomib	Proteasome	Velcade® (Millenium Pharma-Takeda)	$2.41 billion	Recurrent multiple myeloma, mantle cell lymphoma
Erlotinib	Tyr-kinase	Tarceva® (Roche)	$1.97 million	Non-small cell lung cancer (NSCLC); pancreatic cancer
Dasatinib	Tyr-kinase	Sprycel® (BMS)	$1.37 billion	CML; Ph^+ ALL
Sunitinib	Tyr-kinase	Sutent® (Pfizer)	$1.30 billion	Kidney cancer; GIST; pancreatic cancer
Nilotinib	Tyr-kinase	Tasigna® (Amgen)	$1.12 billion	Ph^+ CML (imatinib-resistant)
Gefitinib	EGFR	Iressa® (AstraZeneca)	$624 million	Breast cancer, NSCLC
Lapatinib	Tyr-kinase	Tykerb® (GSK)	$400 million	$HER2^+$ breast cancer

Table 12: Best sellers of targeted inhibitors. (Source: Datamonitor Healthcare, 2013)

7.5.2.2 Market size and pipeline

The segment of oncology is currently the largest of the pharmaceutical industry market. In 2013, it was estimated at $66 billion (Source: Datamonitor Healthcare). It is also the most active therapeutic

area in terms of products under development: in December 2013, Datamonitor inventoried 543 products tested in phase I, 894 products in phase II and 209 in phase III. The vast majority (883) of these molecules under development involves small molecules (chemotherapy and targeted inhibitors).

7.5.3. Drive*In*®, an innovative approach to targeted delivery in oncology

Chemotherapies remain one of the cornerstones of treatment in oncology because of their elevated efficacy. These molecules have harmful effects on healthy cells, however, causing toxicities that may limit the use of these treatments. In order to improve this situation, the active targeting approach is a viable option. Drive*In*® technology is promising for active targeting and cell uptake of drugs thet it transports. These properties are due to the ability of its hyaluronic acid surface to interact with the CD44 receptor, a marker of tumor stem cells.

Adocia has developed two products in-house that use Drive*In*® technology*:* Drive*In*®-doxorubicin and Drive*In*®-docetaxel. Doxorubicin (Adriamycin®, Doxil®, Myocet®, Lipodox®) and docetaxel (Taxotere®) are two of the most widely used drug substances for the treatment of solid tumors. They are now in the public domain but still generate global sales of several hundred million dollars.

<u>Preclinical results</u>

Initial work of Drive*In*® was conducted with the goal of showing:

- *In vitro*, the principle of cell targeting and increased cell uptake resulting from hyaluronic acid
- *In vivo*:
    - non-toxicity of nanoparticles
    - improved treatment safety resulting from enhanced selectivity (preferential accumulation in the tumor compared to healthy tissues) and efficacy of the treatment

Increased intracellular presence of DriveIn®-doxorubicin compared to the active molecule alone

Upadhyay and al (2010) worked *in vitro* on the MCF-7 line of cancer cells (that overexpress CD44, the hyaluronic acid ligand). They compared the cell uptake of doxorubicin and Drive*In*®-doxorubicin when the products were added to the culture medium. The authors showed that the uptake of Drive*In*®-doxorubicin was at least equivalent to that of doxorubicin alone. After 24 hours, doxorubicin levels started to decrease in cells treated with doxorubicin alone, while drug levels were maintained with Drive*In*®-doxorubicin, suggesting better retention of doxorubicin transported and/or better cell uptake of the product (see figure below).

).

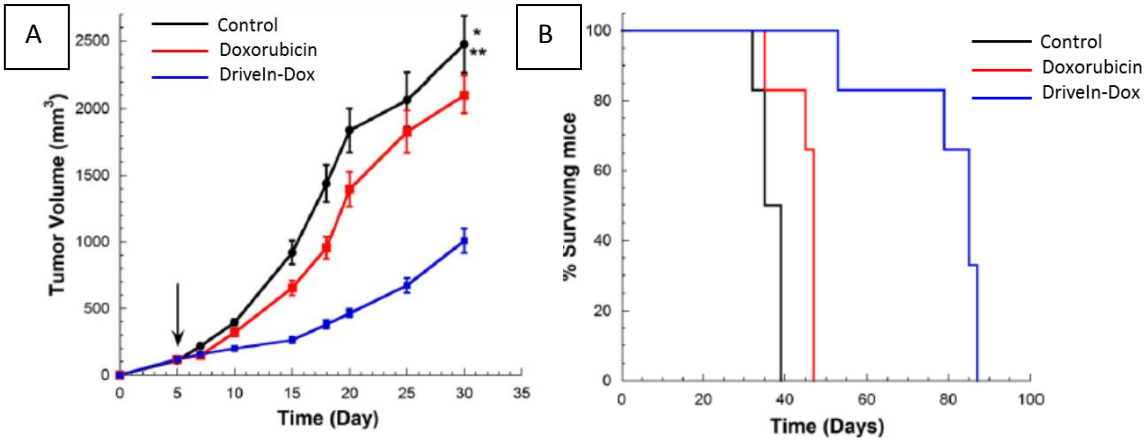


Figure 26: Changes in tumor volume (A) and survival rate (B) in EAT-Balb-C mice after an injection of doxorubicin or DriveIn®-doxorubicin at 5 mg/kg (6 animals per group).

Adocia is currently continuing the preclinical development of the Drive*In*® platform with a double strategy:

- In-house development of proprietary Drive*In*® products (Drive*In*®-doxorubicin and Drive*In*®-docetaxel): first clinical trial planned to start in late 2014/early 2015.
- Development of the platform for granting a license to a partner using Drive*In*® with its proprietary molecules

7.5.4. The competition

In order to increase the proportion of chemical molecules effectively reaching the tumor, the active targeting approach is useful. This approach was used for Drive*In*® and by a small number of competitors. The most advanced nanoparticle approaches with active targeting are:

- **BIND**: an American biotechnology company that is developing a nanoparticle platform using copolymers. Its major product, BIND-014, is a pegylated nanoparticle containing docetaxel, targeting a prostate cancer receptor (PSMA). This product is currently under phase II clinical development for the treatment of prostate cancer and lung cancer. While still under preclinical development, BIND licensed the use of its platform for the development of proprietary molecules to three partners (2013): Pfizer, Amgen and Astra Zeneca, for total potential revenues of $705 million.
- **Merrimack**: this company has developed several pegylated liposomal formulations of chemotherapeutic molecules. The most advanced formulation, MM398, is a pegylated liposomal formulation containing irinotecan. It is in phase III for the treatment of pancreatic cancer, but this is not an actively targeted approach. Merrimack is also developing a pegylated liposomal formulation of doxorubicin that uses an mAb bound to the surface of the liposome to target HER2 receptors for the treatment of breast cancer (currently in phase I). Another product of this type is under preclinical development for an application that has not yet been divulged.
- **Cristal Therapeutics** is a young Dutch company that is developing both actively and passively targeted nanoparticles. A pegylated nanoparticle formulation of doxorubicin targeting EGFR is under preclinical development.
- **NanoCarrier** is a Japanese drug delivery company that is developing nanoparticles composed of polymers.

7.6. A strategy based on several therapeutic innovations with an original and solid business model.

7.6.1. A strategy of medical innovation for the development of best-in-class products from therapeutic molecules authorized by the FDA and the EMA.

Adocia has designed a new family of polymers called BioChaperone®, whose exceptional properties improve the performance of a number of therapeutic molecules already on the market, in particular:

- by boosting their therapeutic efficacy,
- by attenuating their adverse effects (toxic effects),
- by improving their compliance (reduced administration frequency, shorter treatment regimen times , etc.),
- by making possible the combined use of products incompatible until now because of their different pH.

Adocia's strategy involves continuing the development of each of its products until proof of concept is established. It is considered that proof of concept is established when experts in the field can have the scientific and medical conviction of the efficacy of the proposed technology. Depending on the nature of the product and the therapeutic area of application, proof of concept may be obtained from animal studies, but more generally from human clinical trials. Adocia plans to license its

formulations of monoclonal antibodies based on animal studies but its PDGF-BB formulation for the treatment of diabetic foot ulcers only after having obtained probative results in a phase II clinical trial. The proof of concept for the treatment of diabetic foot ulcers cannot be established with an animal model and the large number of test on humans required to establish this proof are equivalent to a phase III trial.

In the few years, the company has developed several different, highly promising products for therapeutic applications as varied as the treatment of diabetic foot ulcers, insulin therapy, or oncology, with innovative formulations of monoclonal antibodies and the new Drive*In*® technology.

7.6.1.1 An original and solid business model

Adocia has developed a B-to-B economic model having the following advantages:

- limited needs for financing: the cost of development of a product to obtain proof of concept is much lower than the cost of bringing a product to market;
- a relatively short time to generate revenues: the company receives revenues from its partners well before the product reaches the market; and
- a risk of failure for any new formulation much lower than that of a new pharmaceutical molecule: the safety in use of the therapeutic protein used has already been established (authorized molecules).

All expenditures up to the time of establishment of this proof of concept are borne by Adocia while all costs of development will then be assumed by the partner. In the framework of the signature of a license contract, Adocia will receive an initial fee, the upfront payment, followed by payments in stages as scientific, technical or clinical milestones are reached, and finally by sharing revenues generated by the sale of products (royalties).

Adocia intends signing new joint work contracts, similar to previous joint development work with large pharmaceutical companies for the development of BioChaperone®/monoclonal antibodies complexes (refer to section 6.4.3 “Innovative formulation of monoclonal antibodies”). This enables the company to receive payments covering research and development costs. These contracts are consistent with the company's business structure, enabling it to make more profitable use of its proprietary BioChaperone® platform and to confirm the relevance of the technological choice based on the properties of BioChaperone® polymers by demonstrating the interest of major players in the sector for this technology. In addition, if joint developments generate positive results, it is probable that these contracts will be transformed into license contracts with the same revenue structure (upfront payment, milestones and royalties).

This relatively non-capitalistic development has the advantage of enabling the company to receive revenues if license contracts are signed, without waiting for products resulting from its BioChaperone® technology to reach the market.

In addition, the company can give more focus to its competitive advantages resulting from its know-how in terms of the design of innovative therapeutic and drug delivery formulations. This will be made possible by joint work with multinational partners experienced in regulatory, clinical and marketing aspects for the sales of pharmaceutical products.

7.6.1.2 Technological developments optimizing the properties of all types of therapeutic molecules (hormones, growth factors, monoclonal antibodies) and facilitating their production

Adocia is developing specific applications using its proprietary BioChaperone® technological platform for therapeutic molecules having already shown their value in the treatments of the intended or similar indications, and that in most cases have been granted international Marketing Authorizations.

These developments are built around five orientations:

- maximizing the potential of the existing BioChaperone® platform in terms of physicochemical capacities;
- extending the collection of polymers to increase the number of therapeutic molecules that could be used with BioChaperone® technology;
- reformulating existing therapeutic molecules made possible by BioChaperone® technology in order to ultimately create technological breakthroughs, for example replacing intravenous injection of monoclonal antibodies by the subcutaneous route;
- creating best-in-class products providing a real pharmaceutical-economic advantage; and
- identifying new complexes responding to public health needs not yet fulfilled.

Work on on development of the collection of BioChaperone® polymers was originally guided by requirements of the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) concerning new pharmaceutical excipients, such as the absence of biological activity, the absence of toxicity, stability of products for several months, reproducibility of the manufacturing process of the product, precise documentation on impurities of the product and conducting clinical trials in compliance with standard operating procedures (SOP*) and requirements of the International Conference on Harmonization (ICH*).

In addition to these regulatory requirements, the industrial vision of the production of best-in-class products has led Adocia to add prerequisites to enable global marketing of its BioChaperone® technology: production of BioChaperone® polymers from natural molecules complying with the requirements of the European Pharmacopoeia* and The United States Pharmacopeia - National Formulary*, rapid synthesis of BioChaperone® polymers and a manufacturing process that can scaled up to industrial production, and finally production standards compatible with Good Manufacturing Practices* of the European Commission in the context of manufacturing drug products.

7.6.2. A management team having anticipated global public health challenges

In today's context of global markets, the pharmaceutical industry has not been spared and must face a number of economic, industrial and even ethical challenges. Adocia's management has anticipated pharmaceutical-economic changes *via* a strategy combining medical benefits and cost reduction with an offer suited for both developped countries and emerging nations, the latter providing genuine opportunities because of their growth and market size.

7.6.2.1 A strategy responding to changes in the pharmaceutical industry by combining medical benefits and cost reduction

Adocia's development of BioChaperone® and Drive*In*® technological platforms was guided by the notion of proposing more effective and safer pharmaceutical products with competitive production costs and prices, using therapeutic proteins having already proven their value. In addition, most of them have been granted international Marketing Authorizations, thereby limiting the risks of failure during development.

Treatments can no longer be developed without taking their costs to consumers into account. This is because of the increased prevalence and incidence of the pathologies addressed by Adocia, as well as the growth and aging of the population in a political climate of controlling public health expenditures in developed nations and increasing demand from emerging nations. Primary health

insurance and second carriers, whether public or private, require pharmaceutical companies to consider the costs of the products they propose. The fact of simply having been granted a Marketing Authorization is no longer sufficient and the reasoning applied during research and development must take economic and therapeutic aspects into account. The entities reimbursing medical expenditures are increasing their vigorous protests of the costs of medicines and services, explaining the partial or total reduction of certain reimbursements.

These political-economic issues are dealt with by improving the efficacy of therapeutic molecules used with BioChaperone® polymers enabling treatments and dosages to be changed, in particular with substantial reductions in dosages, the number of applications and/or treatment duration, similar to the treatment of diabetic foot ulcers, as well as reduced production costs because the manufacturing process is easily scaled up to the industrial level.

The explosion of generic drugs that will increase as many patents expire in the years to come[61] and the increased use of biosimilar* products by companies in both developed nations and emerging economies also force large pharmaceutical companies to rethink the management of the life cycle of their flagship drugs, even in some cases their innovation policy in research and development, diversification and industrial partnership.

Obtaining a Marketing Authorization for a new pharmaceutical molecule is very long, requiring more than 10 years of research and development investment with a very high risk of failure related to toxicity, low or absent acceptability or adverse effects to humans not compensated by the therapeutic benefits provided. A response to issues of innovations by the pharmaceutical industry can thereby be furnished by new formulations of existing therapeutic molecules on the market and developed using BioChaperone® and Drive*In*® technological platforms based on polymers having no intrinsic biological activity and that are registered with regulatory authorities as new excipients. Pharmaceutical companies will be able to continue proposing their therapeutic molecules with new formulations that are at least as effective as before but with new properties (shorter onset to action, sustained action, new routes and/or methods of administration) with shorter lead times, with lower development costs and with a lower probability of project failure.

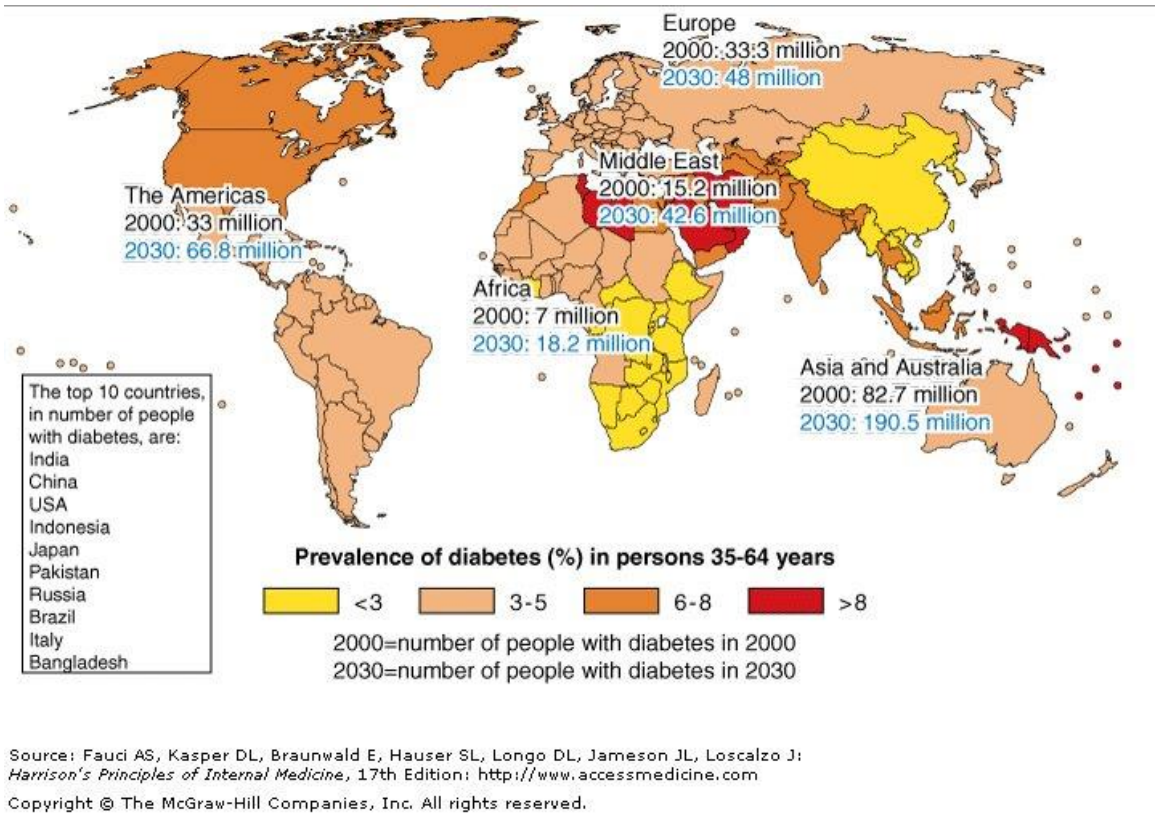
Adocia can provide credible responses in the context of political, economic and regulatory pressure, the explosion of drugs and biosimilars, and globalization of the pharmaceutical industry:

- to issues of innovations for large pharmaceutical companies that must cope with the increased use of generic drugs and the expiration of many patents protecting their flagship products, by proposing new formulations of their therapeutic proteins with new properties and with efficacy at least equivalent to that of existing treatments; and
- to issues of reducing treatment costs by enabling a reduction in dosages, the number of applications and the duration of treatment, or by new routes and/or mechanisms of administration of treatments.

[61] Biopharma prepare for first wave of biosimilars, Mary Serebov. BioWorld Today Vol. 22 (139), 21 July 2011

7.6.2.2 A strategy adapted to emerging nations

Although the demand for pharmaceutical products is increasing in emerging nations, access to healthcare and drugs on the other hand remains highly problematical, even critical in some countries. The World Health Organization has estimated[62] that more than 80% of mortalities due to chronic pathologies occur in countries with low or intermediate per capita income.



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Figure 27: Prevalence of diabetes in the world (from Fauci et al, Principles of Internal Medicine 17th Edition).

In 2011, growth of the pharmaceutical products market in emerging nations (China +20%, India +15% or Brazil +11%) was much higher than the anticipated growth rate of the entire world market (+4.8% for a market estimated at $918.6 billion)[63]. Emerging nations will therefore play an increasingly more important role in the pharmaceutical industry. As an illustration, the contribution of the United States to world growth of the pharmaceutical market was 27% between 2005 and 2010 and will be only 11% between 2010 and 2015, whereas in the same period China will increase from 12% to 26%[64].

No.	2004	2014
1	United States	United States
2	Japan	Japan
3	France	China
4	Germany	Germany
5	Italy	France
6	United Kingdom	Brazil
7	Canada	Italy

[62] Prevention of chronic diseases: a vital investment, World Health Organization
[63] IMS Health France
[64] IMS Health France

8	Spain	Canada
9	China	Spain
10	Brazil	India
11	Mexico	Russia
12	Australia	United Kingdom
13	South Korea	Venezuela
14	India	Turkey
15	Holland	South Korea
16	Belgium	Australia
17	Poland	Mexico
18	Turkey	Argentine
19	Greece	Poland
20	Russia	Greece

Table 13: Major pharmaceutical markets, listed in order of the value of the market in constant dollars. Source: IMS Health France

This strong growth in emerging nations is explained by elevated standards of living and hygiene, access to healthcare by populations and also by the creation of many local companies producing generic drugs and biosimilars, even the creation of biotechnology companies. According to a 2009 study by Ernst & Young[65], turnover by the Indian pharmaceutical industry was estimated at $22 billion in 2008 of which $2.5 billion were in biotechnologies; the domestic market was €7.7 billion with an average annual growth rate of 14.6% between 2003 and 2008. The same study stated that India was the 4th (in number) among countries producing drugs and the 13th in value.

Adocia's strategy involves proposing pharmaceutical products intended to become best-in-class products at costs lower than those of existing products to these markets. This strategy is very well suited to meet the substantial needs of these emerging nations. This strategy could also develop with the support of a growing local pharmaceutical industry and the possibility of license contracts with local companies.

This explains why Adocia is conducting clinical trials in India for its most advanced product for the treatment of diabetic foot ulcers with BioChaperone®-Growth factor PDGF-BB complex, before conducting clinical trials in Europe and the United States.

7.6.3. A model for development of pharmaceutical products with high added value

7.6.3.1 Experienced teams of scientists working on the development of innovative products

The Adocia team working on research and development of innovative pharmaceutical products developed with BioChaperone® and Drive*In*® technological platforms accounts for almost 80% of company staff. Scientific management (refer to section 17.1.1 “Main key employeed”) is assured by about 20 PhDs in the varied and complementary fields of chemistry, physical chemistry, biology, medicine and veterinary science, each having solid experience in the management of technological innovation and partnerships with large industrial groups in the field of drug delivery technologies of therapeutic proteins or in the development of medical devices.

This team of scientists was behind the in-house development of the BioChaperone® technological platform, a genuine asset for the company since they have demonstrated their capacities for the coordinated, flexible and reactive management of complex, innovative, cross-discipline research and development programs.

[65] Capitalizing on the India opportunity: Helping French companies achieve business success in India, Ernst & Young, 2009

7.6.3.2 Effective subcontracting of clinical trials

In order to maximize is economic model based on innovation and the creation of value, the company has decided to outsource preclinical and clinical trials with recognized and certified service providers after conducting quality audits. Adocia is working with:

- the International Toxicology Center for all toxicology studies on polymers in compliance with the rules defined by competent regulatory authorities (Good Laboratory Practices (GLP));
- Biomatech or the Claude Bourgelat Institute of the Lyon School of Veterinary Medicine in France, conducting preclinical studies on animals and that employ specialists in anesthesiology, surgery, endocrinology, pathology and animal breeding, with animal facilities consistent with study needs; and
- contract research organizations (CROs), companies specialized in conducting clinical trials in compliance with rules defined by competent regulatory authorities (Good Clinical Practices (GCP)).

Clinical trials of BioChaperone® insulins (refer to section 6.4.2.3. and 6.4.2.4 “Clinical trials conducted by Adocia and future clinical trials”) were conducted by PROFILE, a German CRO that provides a full range of clinical trial services in the areas of diabetes, endocrinology and cardiovascular diseases, for all phases (I to IV) in compliance with international quality standards (ICH-GCP and GLP). Adocia chose I.K.F.E. because of its experience in conducting clinical trials involving diabetes, with more than 200 trials thus far carried out.

For clinical trials on the treatment of diabetic foot ulcers with the BioChaperone®-growth factor PDGF-BB complex, the Indian partner of Adocia, Virchow Biotech that developed and markets a biosimilar of PDGF-BB, was the sponsor of the phase I trial/II in India in 11 centers specialized in treating this pathology. Future phase III clinical trials in India and phase III trials in Europe and the United States will be sponsored by Adocia who will use the services of a global CRO (refer to sections 6.4.1.1.3 and 6.4.1.4 “The first phase II clinical trial in India and Future clinical trials”).

7.6.3.3 Outsourced production

Adocia is actively participating in the organization and supervision of the production of clinical batches. Its development model, however, has resulted in subcontracting the manufacturing of its products to:

- Virchow Biotech for BioChaperone®/PDGF-BB complexes;
- The British company Aptuit, a Contract Manufacturing Organization (CMO) for BioChaperone® insulins.

In addition to regulations, authorizations and required standards, these companies also comply with Good Manufacturing Practices (GMP) validated with competent authorities and certification organizations.

For the needs of preclinical and clinical work, however, Adocia produces all BioChaperone® polymers in solution, primarily polymers of dextran manufactured by the Danish company Pharmacosmos and then transferred to the company DBI for freeze drying.

In the framework of marketing BioChaperone® polymers, they will be produced by CMOs selected by Adocia that use the same process as Adocia that was designed to comply with industrial requirements.

7.6.4. A strategy for dynamic management of intellectual property

The strategy for managing intellectual property developed by Adocia is intended to provide maximal protection of the company's innovations, in terms of both products developed and geography, in order to protect future markets in which these products could be sold.

This strategy for the protection of Adocia's innovations is a "locked door" to new players using a similar technology or to access to the company's markets. At the present time, 22 inventions have been protected by patent applications covering 22 distinct families. Adocia's portfolio is presently composed of almost 200 patents and patent applications.

7.6.4.1 Intellectual property protected at several levels

The intellectual property portfolio of Adocia has resulted from considerable in-house research and development. The company's industrial property protection policy covers the three areas of Adocia's innovation: the collection of BioChaperone® polymers, formulations of BioChaperone®/Therapeutic protein and the therapeutic applications of these formulations.

Patents protecting BioChaperone® polymers and small organic molecules

There are seven families of patents covering polymers (refer to section 11.2.2 Type and coverage of patents held by the company) and are intended to protect the entire collection of BioChaperone® polymers and small molecules, both concerning what these polymers have in common and the specific physical and chemical properties of each of them.

The proprietary BioChaperone® technological platform, the heart of Adocia's model, is intended for multiple applications and multiple indications. The therapeutic proteins selected for treatments of the pathologies targeted by Adocia, whether hormones, growth factors or monoclonal antibodies, with very different physicochemical characteristics, will be able to be combined with different specific BioChaperone® polymers.

Patents protecting BioChaperone®/therapeutic molecules complexes

There are three families of patents covering BioChaperone® polymers/therapeutic molecules complexes (refer to section 11.2.2 Type and coverage of patents held by the company) that cover the different types of therapeutic proteins that can be combined with BioChaperone® polymers: hormones, growth factors and monoclonal antibodies. These patents are intended to protect all the properties of therapeutic proteins provided by the combined use of a BioChaperone® polymer.

Patents protecting the scope of application of the BioChaperone® technological platform

There are eleven families of patents covering applications of the BioChaperone® technological platform (refer to section 11.2.2 Type and coverage of patents held by the company) and are intended to extend the company's innovations *via* the medical applications developed.

Patents protecting the scope of application of the DriveIn® technological platform

One family of patents covering applications of the DriveIn® technological platform has been deposited (refer to section 11.2.2 Type and coverage of patents held by the company) and are intended to extend the company's innovations *via* the medical applications developed.

Only these families of patents will be the subject of licensing contracts, in line with the economic model of partnerships developed by the company.

7.6.4.2 International coverage

Before the implementation on new regulations in United States on March 16, 2013, the patent application policy of Adocia involved an initial application in France, followed by patent applications in the United States as rapidly as possible. Since March 16, 2013, priority applications are only in France (it is no longer necessary to apply for an American patent in order to be recognized).

Twelve months after the French application, a demand for international extension *via* the Patent Cooperation Treaty (PCT) procedure is carried out. Among the 142 countries that can be covered by this procedure, each country is selected with respect to Adocia's commercial strategy for the patent. The three main geographical areas of patent protection defined by the company are:

- the major European countries and the United States;
- followed by Canada, China, Japan, India, Australia and Israel;
- finally countries such as Mexico, Brazil, Russia, South Africa, Singapore and South Korea.

The goal of the strategy of international patent protection (Europe/United States/emerging nations) is to obtain the first patents more rapidly in these target zones and to place each innovation in a strong position to obtain the most effective protection possible in all these countries.

8. ORGANIZATIONAL CHART

8.1. Organization of the company

As of the filing date of this reference document, the company does not have any subsidiaries.

8.2. Subsidiaries, branches and secondary establishments

None.

9. REAL ESTATE, FACTORIES AND EQUIPMENT

9.1. Description of real estate

The company uses only the following premises:

- Its headquarters in Lyon, which are located at 115 Avenue Lacassagne, 69003 Lyon. The company's headquarters, with a total floor area of about 2,032 m², are located on two floors of Building L in a real property complex used as a business enterprise zone for innovative biotechnology firms. The company occupies these premises pursuant to a lease governed by ordinary legal provisions, which initially covered 1,500 m², and which was entered into with the city of Lyon for a firm term of three years starting on October 13, 2011, which may be renewed automatically for another three years. The lease was granted in consideration for an annual rent of €249,550, not including property charges and taxes. An amendment to the lease was signed in 2012, pursuant to which the company leased additional floor area of 482.5 m² for an additional annual rent of €77,682, not including property charges and taxes, thereby bringing the total rent to €327,232 per year, not including property charges and taxes.

The "Communauté Urbaine de Lyon" (city of Lyon) which owns the business enterprise zone, has no capital ties with any of the company's managers and/or shareholders.

The company also entered into a lease for a covered parking area, which has been in effect since October 13, 2011, pursuant to which it obtained 20 reserved covered parking spaces located at 115 Avenue Lacassagne, 69003 Lyon, for a period of three years from October 13, 2011, in consideration for a payment of €9,600 per year, including taxes.

The company recognized rental expense (excluding property charges) of €346,000 for the fiscal year ended December 31, 2013.

Property charges are paid quarterly on the basis of an amount set per m² and per year. In 2013, property charges totaled €149,000.

At the end of December 2013, the company purchased 15 parking spaces for a total amount of €130,000.

9.2. Other property, plant and equipment

The principal property, plant and equipment that the company holds is described in note 3.2 to the notes to the corporate financial statements prepared in accordance with IFRS, in Chapter 20.1 of this reference document.

9.3. Environmental issues, as required by Article R. 225-105-1 of the French Commercial Code

In light of its business (drug research and development) and its geographical location (laboratories located at a single site in Lyon), the company considers that its environmental impact is low. Its activities do not include industrial production or distribution, or significant discharges of effluents or greenhouse gases into the environment. Its activities do not require the use of the ground as a resource and employ few raw materials.

The company leases the laboratories and offices it occupies. It complies with the obligations the lease imposes on it, which concern primarily (see Article 10) compliance by environmentally sensitive sites (ICPE) with the reporting thresholds for 1432a and 1432b flammable substances.

The following factors are not discussed in this report because they were deemed irrelevant or because the company does not have significant information in light of the quantities and interests at stake:

- Greenhouse gas emissions,
- Adaptation to climate change,
- Biodiversity,
- Ground use,
- Visual and noise environmental impact of the business.

Despite the company's low environmental impact, from the outset, it has focused on environmental protection and appointed two persons to manage environmental aspects, one of whom, the HSQE manager, represents senior management.

The company has made of the treatment and recycling of chemical substances one of its priorities.

Pollution and waste management

The company purchases chemicals that are used in research and development operations. However, given the company's size, only limited quantities of chemicals are handled, all of which are carefully monitored. The traceability of chemicals is strictly ensured from the time they arrive (a register kept by each department tracks raw materials), and after their use in research operations, waste is recovered and stored under specific conditions until it is collected by a specialized company.
The company has appointed a service provider that specializes in removing and recycling chemical waste. Before collection, which takes place two or three times a year, the company stores its waste in appropriate containers in dedicated premises (a storeroom).
In 2013, the quantity of hazardous laboratory waste sent to a specific center (packaging and soiled glass, chemical waste) totaled 18 tons. The company considers that the quantity of waste that it discharges into the city of Lyon's wastewater treatment system is low, as most waste is recovered during handling.

Furthermore, the company has initiated the following recycling actions:

- Sorting of plastics and caps;
- Sorting of paper and cardboard;
- Sorting of ink cartridges; and
- Sorting of batteries.

The company has installed specific containers for each type of waste, which are available in the various departments. The company uses the services of specialized firms to remove this waste.
In 2013, the quantity of paper and cardboard removed totaled approximately 5.16 tons. The Décines Sorting Center (69) sorts and processes this waste for recycling by the paper industry.

The resources devoted to waste management issues are of two types:

- external resources, comprised of purchases of specific containers and expenses associated with services subcontracted to waste specialists;

- internal resources, consisting of involving all employees in sorting waste and reducing energy consumption.
  Training is regularly provided, in particular at the time employees are hired. Each new employee receives "integration training", during which the Safety-Environment department provides information on environmental practices that have been implemented. At such time, employees are provided with a waste management procedure.

In terms of noise pollution, only the laboratories' fume chamber extractors are potential sources of noise. This equipment, which is installed on the roof, is fitted with soundproofing casing. Accordingly, the company deems that it has minimized the risk of noise pollution.

With respect to sustainable resource use, the company is concerned by the management of its water and energy consumption.
The company's consumption of municipal water is mainly for sanitary purposes, although it also uses municipal water to produce distilled water. Water discharged after use consists mainly of water from washing machines and sinks installed in the company's various laboratories and common areas.
The building that the company occupies with other companies has no individual meters that enable it to precisely know how much water it consumes. The landlord bills water costs on the basis of the floor area that each tenant occupies. Based on the amount included in its property charges, the company estimates that in 2013 its water consumption was 7,700 m^3.
In addition, the company buys bottled water for employee's personal consumption. In 2013, this totaled a volume of 3 m^3.
Lastly, certain research operations require purified water, which is supplied in water canisters. In 2013, the volume of this consumption totaled 12 m^3.

With respect to energy, the company consumes electricity only.
As is the case for water, there are no individual meters. Based on the amount invoiced as part of its property charges, the company estimates that it consumed 921,210 kWh in 2013.
The company has set up a consumption monitoring program and, at the end of each day, has a person check and turn off electrical equipment that has been left on and adjust the temperature of heating and cooling systems. In certain premises, motion detectors that automatically turn off lights have been installed. The company has also adopted and is gradually implementing a plan to replace old generation light bulbs with low consumption light bulbs.

With respect to the environment and impact on climate change, the company considers that the quantity of greenhouse gases it emits in connection with its business is very limited. Its activities do not require combustion and its emissions are associated with the use of volatile solvents, which are handled under extractors. The company is not subject to any regulatory obligations to monitor solvents used or emissions of volatile organic compounds (VOC).
In light of the above factors and the company's limited impact, no provisions or guarantees for environmental risks have been recognized to date.

9.4. Information on societal commitments to promote sustainable development, as required by Article R. 225-105-1 of the French Commercial Code

9.4.1. Territorial, economic and social impact of the company's business

Adocia has been based in Lyon since its creation, and it endeavors to be active and involved in its local area at various levels:

- In eight years, the company has hired over 70 persons, most of whom are from the Lyon area. The company's ongoing policy is to recruit and train young people. Each year, the company accepts workers under apprenticeship or work-training contracts (five at the end of December 2013) and a certain number of interns in order to train them. Furthermore, at its level, the company is attractive to and offers professional prospects for scientists, researchers and technicians in the life sciences.

-
- In 2013, the company's payroll expenses and social security contributions accounted for nearly 40% of total expenses.
    - The company appoints service providers to perform a significant share of its activities, in particular activities that require specific accreditations (good laboratory or manufacturing practices), particular facilities (animal houses) or organizations specialized in conducting clinical trials, known as contact research organizations (CROs). These external expenses account for nearly 60% of the company's total expenses.
    - In this connection, at the local level, the company has created partnerships with the Lyon veterinary school and Biomatech for conducting its preclinical trials. It also uses the services of numerous consulting firms in the area (patents, finance, lawyers). The premises that it leases are owned by the city of Lyon.
    - The process for choosing suppliers complies with pharmaceutical regulations and takes into account criteria such as proximity, excellence and research ethics. Due to its size and the social and environmental stakes noted, the company does not audit its suppliers on CSR issues.

9.4.2. Fair practices

With respect to the risk of corruption, the company considers that it has set up mechanisms, relying on effective internal controls, that enable it to prevent this occurrence. Separating tasks associated with payments is one of the means put in place for avoiding possible errors or embezzlement.

Concerning the choice of suppliers, comparative quotations are systematically requested above a certain expenditure threshold. In connection with its research and development activities, the company is obliged to comply with standards in effect (Good Laboratory Practice, Good Manufacturing Practice), as well as with the regulations adopted by public health protection agencies, such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the United States.

The company has been listed on the Euronext-Paris stock exchange since February 2012. Accordingly, purchases and sales of securities and, in particular, bonus shares and business founders' stock warrants (BSPCE), are subject to strict rules.
Adocia has adopted a corporate disclosure policy and a code of ethics, which are in compliance with AMF recommendation no. 2010-07 of November 3, 2010, as well as the MiddleNext guide, which set forth and explain the rules applicable to privileged information and the duties owed by insiders.

9.4.3. Public health issues

The health and safety of consumers is at the heart of the company's business: developing innovative medicine for everyone, everywhere.
The company develops drugs based on therapeutic molecules that have already been approved. Using its two proprietary technologies, BioChaperone® and DriveIn®, it improves the effectiveness of such molecules, thereby simplifying and expanding their therapeutic use, while improving patients' quality of life.
In a worldwide pharmacological and economic context marked by the adoption of policies designed to control health costs, the products that Adocia develops may improve the effectiveness of therapeutic molecules, while reducing the dosage, number of applications and/or duration of treatment.

Lastly, despite the fact that the demand for pharmaceutical products in emerging countries is expanding, access to healthcare and drugs remains problematic, even critical, in certain countries. The World Health Organization estimates that over 80% of the deaths due to chronic pathologies occur in low or medium income countries. By offering pharmaceutical products destined to become “best-in-class” and at lower prices than existing products, Adocia’s strategy seems particularly suited to meet the mass needs of these emerging countries.

9.4.4. Actions taken to promote human rights

The company endeavors to comply with the laws in force and is not aware of any specific issues in this regard.

The information concerning labor issues required by Article R. 225-105-1 of the French Commercial Code is provided in Chapter 17.7 of this reference document.

10. REVIEW OF THE COMPANY'S RESULTS AND FINANCIAL POSITION

Readers are invited to read this analysis of the company's financial position and results in conjunction with the financial statements prepared in accordance with IFRS for the fiscal years ended December 31, 2012 and December 31, 2013, as well as the notes to the financial statements prepared in accordance with IFRS, in Chapter 20.1 of this reference document, and all other financial information included herein. Readers may also review the description of research activities provided in Chapter 6 entitled "Overview of Activities".

10.1. Overview

Adocia, which was created in 2005, is a biotechnology company that has designed and developed a unique and versatile technological platform, called BioChaperone®. This platform enables development of innovative therapeutic protein formulations based on molecules already approved, in the fields of regenerative medicine, the treatment of certain chronic pathologies and anticancer drugs.

The outcome of this research and the commercial development of the results obtained is a long-term project. The company's financial statements show primarily research and development expenses, which, for the most part, have been financed by capital increases, OSEO reimbursable advances and grants, and the research tax credit. However, in 2009, the company recorded its first revenues when it concluded research and cooperation agreements. At the end of 2011, a major license agreement was signed with the Eli Lilly group, from which it received an up-front payment of €7.6 million in early 2012. In July 2013, the company announced the end of this cooperation agreement, thereby recovering its rights to develop ultra-fast-acting insulin analogs and giving it the possibility of conducting its own clinical trials to obtain "proof of concept".

Since the company's creation, it has raised over €27 million through capital increases subscribed, in particular, by the company's founders, Messrs. Gérard, Olivier and Rémi Soula, and institutional investors (IdInvest, Amundi, Viveris, BioAm, SHAM and InnoBio). In 2012, the company was listed on the Euronext regulated market in Paris and raised over €27.4 million (excluding transaction expenses).

The company's financial statements have been prepared in accordance with the standards and interpretations published by the International Accounting Standards Board (IASB) and adopted by the European Union as of the date the financial statements were prepared. These financial statements as of December 31, 2013 were approved by the company's board of directors at its meeting held on March 21, 2014.

10.2. Comparison of the last two fiscal years

10.2.1. Components of net income

The table below summarizes the company's income statement prepared in accordance with IFRS for the fiscal year ended December 31, 2013, and provides a comparison with fiscal year 2012:

STATEMENT OF COMPREHENSIVE INCOME (in € thousands)	12/31/2013	12/31/2012
Revenue	5 588	3 995
Other income	3 233	3 241
Total income	**8 822**	**7 236**
Operating expenses excluding additions and reversals	(12 764)	(12 887)
Additions to and reversals of depreciation,	(360)	(419)
PROFIT/LOSS FROM ORDINARY OPERATING ACTIVITIES	**(4 302)**	**(6 070)**
Other operating income and expenses		0
PROFIT/LOSS FROM ORDINARY OPERATING ACTIVITIES	**(4 302)**	**(6 070)**
Financial income	169	142
Financial expense	(160)	(66)
FINANCIAL INCOME/EXPENSE	**9**	**75**
PROFIT/LOSS BEFORE TAX	**(4 293)**	**(5 995)**
Tax expense		
NET PROFIT/LOSS	**(4 293)**	**(5 995)**
Non-controlling interests		
GROUP NET PROFIT/LOSS	**(4 293)**	**(5 995)**
Base earnings per share (€)	(0,7)	(1,0)
Diluted earnings per share (€)	(0,7)	(1,0)
GROUP NET PROFIT/LOSS	**(4 293)**	**(5 995)**
Other comprehensive income		
TOTAL PROFIT/LOSS FOR THE YEAR	**(4 293)**	**(5 995)**

Operating income

The company's operating income is derived from public financing of research expenses and from cooperation and licensing agreements. Operating income totaled €7.2 million and €8.8 million, respectively, in the fiscal years ended December 31, 2012 and December 31, 2013, as shown in the breakdown below:

(IFRS - € thousands)	FY 2013 (12 months)	FY 2012 (12 months)
Income from licenses	5 636	2 104
Research and cooperation agreements	(47)	1 892
Revenue (a)	**5 588**	**3 995**
Grants, public financing and research tax credits (b)	3 233	3 241
Operating income (a)+(b)	**8 822**	**7 236**

Revenue in 2013 totaled €5.6 million, compared to nearly €4 million in 2012, i.e., an increase of €1.6 million.

This increase is due essentially to the termination of the Eli Lilly licensing agreement in July 2013, which had two effects:

- Firstly, advanced amortization of the revenue from licenses in the third quarter of 2013, in the amount of €4.7 million, which was the unamortized balance of the up-front payment received in 2011, and which was added to the €0.9 million that had been precisely recognized in the first half;

- Secondly, a loss of revenue from that research and cooperation agreement, which in 2012 had accounted for the major share of revenue generated from such agreements.

Since the signature of the agreement for the development of an ultra-fast-acting insulin analog formulation in December 2011, the up-front payment of €7.6 million had been amortized, using the straight line method, over the expected development period specified in the contract.

In addition, public financing of research expenses is essentially comprised of the research tax credit. This credit totaled €3.2 million, which is the same amount as in 2012.

Operating expenses

The table below presents operating expenses by function for the fiscal years ended December 31, 2012 and December 31, 2013:

EXPENSES BY FUNCTION (in € thousands)	**12/31/2013**	**12/31/2012**
Research and development costs	(11 475)	(11 784)
Administrative costs	(1 649)	(1 522)
Operating expenses	**(13 124)**	**(13 306)**

Research and development expenses are comprised essentially of the expenses of personnel assigned to research and development, subcontracting costs (including preclinical and clinical trials), intellectual property costs, and purchases of materials (reagents and other consumables) and pharmaceutical products. These expenses totaled €11.8 million and €11.5 million, respectively, in the fiscal years ended December 31, 2012 and December 31, 2013. These expenses accounted for 89% and 87%, respectively, of operating expenses in these two fiscal years.

General and administrative expenses are comprised essentially of the expenses of personnel not assigned to research and development and the costs of services in connection with the management and development of the company's commercial business. These expenses totaled €1.5 million and €1.7 million, respectively, in the fiscal years ended December 31, 2012 and December 31, 2013. These expenses accounted for a total of 11% and 13% of operating expenses in these two fiscal years.

Overall, operating expenses have remained relatively stable over the last two fiscal years (€13.1 million in 2013 and €13.3 million in 2012).

The table below breaks down operating expenses by type for the fiscal years ended December 31, 2012 and December 31, 2013:

(IFRS - € thousands)	FY 2013 (12 months)	FY 2012 (12 months)
Purchases used in operations	612	834
Payroll expense	5 445	4 934
External expenses	6 614	7 050
Taxes and contributions	93	69
Depreciation, amortization and provisions	360	419
Other current operating revenue and expenses		
Operating expenses	**13 124**	**13 306**

Purchases of materials, products and supplies used in operations fell by nearly 27% between the fiscal years ended December 31, 2012 and December 31, 2013, which reflects the transfer of insulin projects to clinical development and the reduced use of purchases of commercial products necessary in the preclinical phases.

Payroll expense rose by 10% between the two periods. This increase is due in part to the loss of "innovative startup" status, under which in 2012 the company obtained a reduction in its social security contributions, and in part by an increase in the full-time equivalent workforce, which rose from 66.6 workers as of December 31, 2012 to 69.2 workers as of December 31, 2013. The total number of workers employed as of December 31 of each year was 71 persons in 2012 and 73 persons in 2013, respectively.

External expenses consist essentially of the costs of research studies, the costs of preclinical and clinical development subcontracted to third parties, and intellectual property costs. These expenses fell by 6% (€0.4 million) between the two fiscal years, which is explained by:

- A decrease of 33% (€1 million) in the "Preclinical trials" item, which was set off by an increase in the "Clinical trials" item, and which reflects the maturity of our project portfolio. A first Phase I/II trial of the combination of long-acting insulin glargine with a fast-acting insulin on type 1 diabetes patients was begun in mid-November 2013. A second Phase IIa trial of the ultra-fast-acting BioChaperone® Lispro insulin formulation on type 1 diabetes patients was begun in early 2014. The results of the first trial were published on February 27, 2014, and the results of the second trial are expected in the second half of 2014.

- A decrease of 26% (€0.4 million) in the subcontracting item, which also reflects the progress of the diabetic foot ulcer product. The application for a Phase III clinical study was prepared in 2012 and filed with the Indian drugs agency (DCGI) in September. The company is still awaiting authorization to begin this trial. In 2013, subcontracting expenses were primarily for continued development of a platelet derived growth factor-BB (PDGF-BB) that meets European standards.

- An increase of 50% (€0.2 million) in fees (not including intellectual property), which is mostly due to expenses associated with the company's February 2012 initial public offering on the Euronext regulated market in Paris.

Net financial income

Net financial income was €142,000 in 2012 and €169,000 in 2013. The company's policy favors investments with no risk to capital and that, to the extent possible, offer guaranteed performance.

Financial expenses, which are comprised of unrealized translation adjustments and interest calculated on conditional advances, rose from €66,000 in 2012 to €160,000 in 2013.

Corporate income tax

Net income was negative in the last two fiscal years and therefore the company incurred no income tax expense. As of December 31, 2013, the company had a deferrable tax loss of €50 million (of which €12.9 million was for fiscal year 2013 and €13.1 million was for fiscal year 2012). This loss can be deferred indefinitely. Because the company is unable to determine with sufficient certainty when it will be able to offset its accumulated losses, it has not recognized any deferred tax assets as a result of this loss.

Net income for fiscal years 2012 and 2013

Net losses totaled €6 million in 2012 and €4.3 million in 2013, with a net loss per share of €1 and €0.70, respectively.

10.2.2. Principal balance sheet items

The balance sheet totals as of December 31, 2012 and December 31, 2013 were €36.6 million and €24.7 million, respectively.

Non-current assets

Non-current assets totaled €1.3 million and €1.2 million on December 31, 2012 and December 31, 2013. Non-current assets include intangible assets, property, plant and equipment and financial assets. A breakdown of non-current assets is provided in notes 3.1, 3.2 and 3.3 of the notes to the financial statements prepared in accordance with IFRS for the fiscal years ended December 31, 2012 and December 31, 2013, which are presented in Chapter 20.1 of this reference document. The decrease of €87,000 in non-current assets is explained primarily by a drop in the share of the cash position due to the liquidity agreement signed in March 2012 with BIL Finance (since renamed DSF Market). This agreement was suspended on April 23, 2013, but resumed on June 25, 2013 with the commitment reduced by €0.4 million.

Current assets

Current assets totaled €35.3 million and €23.5 million on December 31, 2012 and December 31, 2013. They are comprised essentially of the "cash and cash equivalents", "research tax credit" and "VAT receivables" items.

The "cash and cash equivalents" item fell from €30.5 million as of December 31, 2012 to €19.4 million as of December 31, 2013, i.e., cash consumption of €11 million.

Because the company has not had taxable income, the research tax credits are systematically collected in the fiscal year following the fiscal year in which they are recognized:

- 2011 research tax credit: €1.8 million was reimbursed on October 1, 2012
- 2012 research tax credit: €3.1 million was reimbursed on July 9, 2013

VAT receivables were €0.8 million and €0.25 million, respectively, as of December 31, 2012 and December 31, 2013.

Non-current liabilities

Non-current liabilities are comprised of two items: "long-term financial debts" and "long-term provisions". Non-current liabilities at the end of fiscal years 2012 and 2013 totaled €2.2 million and €2 million, respectively.

The "long-term financial debts" item corresponds to reimbursable advances made by OSEO and Coface. The balance sheet value of these advances is measured at their amortized cost in accordance with IFRS at the end of fiscal years 2012 and 2013, i.e., €2 million and €1.8 million, respectively (see note 3.10 of the notes to the financial statements prepared in accordance with IFRS for the fiscal years ended December 31, 2012 and December 31, 2013, which are presented in Chapter 20.1 of this reference document). Long-term provisions consist primarily of provisions for retirement benefits, which totaled about €0.2 million in both fiscal years (see note 3.11 of the notes to the financial statements prepared in accordance with IFRS for the fiscal years ended December 31, 2012 and December 31, 2013, which are presented in Chapter 20.1 of this reference document).

Current liabilities

Current liabilities totaled €11.4 million in fiscal year 2012 and €3.5 million in fiscal year 2013. They are comprised of trade receivables (€3.8 million in 2012 and €1.8 million in 2013), and other current liabilities, comprised of taxes and social security contributions (€1.5 million in 2012 and €1.2 million in 2013) and prepaid income. This last item, which totaled €5.6 million as of December 31, 2012, and which was the unamortized balance of the up-front payment received in 2011 following the signature of the agreement with Eli Lilly, was cancelled on December 31, 2013. As a result of the termination of this license agreement in July 2013, this amount of €5.6 million was recognized as revenue in the third quarter of 2013.

11. CASH AND EQUITY

11.1. Information on the company's equity, liquidities and sources of financing

Readers are invited to review notes 3.9 and 3.10 of the notes to the financial statements prepared in accordance with IFRS for the fiscal years ended December 31, 2012 and December 31, 2013, which are presented in Chapter 20.1 of this reference document.

11.1.1. Equity financing

Net changes in equity are, to a large extent, explained by the losses recognized in fiscal years 2012 and 2013, which were offset by capital increases.

The company received a total of about €55 million in the form of capital increases between its creation and the filing date of this reference document, of which €27.4 million was received in fiscal year 2012:

- €11,999,999.97 was raised in a first round of equity financing carried out in October 2007 and supplemented in December 2007;
- €9,023,548.80 was raised in connection with a capital increase carried out on November 2, 2009;
- €4,976,665.44 was raised in connection with various exercises of stock warrants in fiscal years 2009 and 2010; and
- €27,362,288.08 was raised from the company's stock exchange listing in February 2012, which was carried out by an initial public offering in France and an institutional placement in France and certain other European countries, which, in each case, concerned new shares.

CHANGES IN EQUITY (in € thousands)	Capital	Additional paid-in capital	Reserves and profit	Group total equity
12/31/2011	**446**	**24 038**	**(20 154)**	**4 329**
Profit/loss for the period			(5 995)	(5 995)
Capital increase	172	27 190		27 362
Share-based payments	2	(2)	59	59
Other comprehensive income				
Capital increase expenses		(2 030)		(2 030)
Other		(698)		(698)
12/31/2012	**619**	**48 498**	**(26 090)**	**23 028**
Profit/loss for the period			(4 293)	(4 293)
Capital increase	(1)			
Share-based payments	1	(1)	86	86
Other comprehensive income				
Capital increase expenses				
Other		314	(5)	309
12/31/2013	**621**	**48 811**	**(30 302)**	**19 129**

11.1.2. Debt financing

As of the filing date of this reference document, the company has received non-interest bearing reimbursable assistance for its research from OSEO and Coface, for a total amount of €3.6 million.

As of December 31, 2013, the amount still owed on these advances was €2.4 million. During the 2013 exercice, the company reimbursed a total amount of € 400,000 relatinf to the second payment mentioned in the contract signed in 2077 and which was related to a new system for local controlled release of growth factors for bone regeneration.

For additional details on the reimbursable advances, readers may also review Chapter 22.1 of this reference document.

In addition, the company uses other types of financing vehicles to finance purchases of laboratory equipment. As of December 31, 2013, future obligations under these finance leases totaled €90,000.

11.1.3. Off-balance sheet commitments

The company's off-balance sheet commitments as of the filing date of this reference document are described in note 4 of the notes to the corporate financial statements prepared under French GAAP, which are presented in Chapter 20.3 of this reference document.

11.2. Cash flows

The table presented below shows changes in the net cash between the fiscal years ended December 31, 2012 and December 31, 2013:

(IFRS - € thousands)	FY 2013 (12 months)	FY 2012 (12 months)
Net cash flow generated by the business	(10 796)	919
Net cash flow in connection with investment transactions	57	(1 774)
Net cash flow in connection with financing transactions	(309)	25 413
CHANGES IN NET CASH	**(11 047)**	**24 558**
Cash and cash equivalents at the start of the year	30 462	5 905
Cash and cash equivalents at year-end	19 415	30 462

11.2.1. Cash flows from operations

In fiscal year 2013, cash consumption dedicated to operations totaled €10.8 million. In 2012, the company received payments totaling €9.4 million, essentially from the licensing agreement signed with Eli Lilly for the development of an ultra-fast-acting insulin analog formulation (up-front payment of €7.6 million received in January 2012 and payment of €1.8 million for research services).

11.2.2. Cash flows from investments

Cash consumption associated with investments fell by €1.8 million between the fiscal years ended December 31, 2012 and December 31, 2013. In 2012, the company entered into a liquidity agreement with a commitment of €1 million with BIL bank (since renamed DSF Markets), and it acquired materials and equipment to be installed in its expanded laboratories.
In 2013, investments totaled €0.4 million and, during the year, the company reduced the resources allocated to the liquidity agreement by €0.4 million.

11.2.3. Cash flows from financing transactions

Cash consumption associated with financing transactions in 2013 is explained by the repayment of the second installment of €0.4 million of a reimbursable advance of €2.25 million that enabled the company to develop its project for a new system of local and controlled release of growth factors for bone regeneration. During the year, the company also received an additional reimbursable advance of €91,000 from Coface to support its commercial activities abroad.
In 2012, this item reflected the company's listing on the Euronext regulated market in Paris, pursuant to which it raised €25.3 million.

11.3. Restrictions on the use of equity

None.

11.4. Future sources of financing required

As of December 31, 2013, the company's cash and cash equivalents totaled €19.4 million.

The company's financing requirements for future years is strongly dependent on its ability to enter into new agreements for products under development and to expand its project portfolio, which could have a material impact on its research and development expenses.

Nevertheless, the company deems that, with €16 millions in cash and cash equivalents as of March 2014, it has the resources necessary to finance its operating expenses for at least the next 14 months starting the date of filing of the reference document.
This amount of cahs doex not include the reimbursable loans received from OSEO which totaled €2.4 millions, being précised that no reimbursement is due during 2014 exercice (please refere to Chapters 22.1,22.2 and 22.3 of this reference document for details on reimbursable loans).

12. INVENTIONS, PATENTS, LICENSES, TRADEMARKS AND DOMAIN NAMES

12.1. Innovation policy

The company's mission is to create and develop inventions that are subsequently licensed.

These inventions concern innovative therapeutic treatments based on combinations of its proprietary technologies (BioChaperone® and DriveIn®) with therapeutic agents (proteins, cytotoxic agents) approved in Europe and the United States. Inventions based on combinations of therapeutic proteins with small proprietary or non-proprietary molecules have also been made. In addition, within the last few months, a new invention was developed, involving nanoparticles that comprise a cytotoxic agent and a copolymer (DriveIn® technology).

Since it was founded, Adocia has created inventions in several therapeutic domains, such as the healing of chronic wounds and the treatment of diabetes with insulin therapy. With its DriveIn® technology, Adocia is now also active in the oncology field.

The company's innovation policy consists of all measures the company takes in this area. The company's innovative mission guides the recruitment of management employees and technicians, the training of employees, and its work methods.

Furthermore, the inventions that Adocia develops are cross-disciplinary and cover various scientific, chemical, physicochemical, analytical and biological fields. To meet this challenge, teams of experts have been formed in each discipline. The various teams are coordinated during regular working meetings held for each project. In addition, every two weeks, each management-level scientist presents a briefing, in the form of a bimonthly report, on scientific advances.

Mr. Gérard Soula has significant research and innovation management experience, with over 30 years' experience in this field. Mr. Olivier Soula, Vice-President and R&D Director, has 10 years of experience in R&D management, first with Flamel Technologies and then with Adocia.

Adocia has set up an attractive compensation policy for inventions in order to promote innovation within the company. An internal memorandum explains the conditions under which employees who develop inventions are entitled to the additional compensation prescribed by the French Industrial Property Code, and provides for payment of attractive lump-sum fixed compensation when a priority patent application is extended or a patent is issued in Europe or the USA, as well as variable compensation that increases in accordance with sales generated by the relevant invention.

Furthermore, Mr. Gérard Soula has assigned to the company, without any financial consideration, all of the rights he holds to date in his inventions within the company's field of business. Assignment agreements are signed whenever required by a country's law (in particular, in the USA and Canada). Furthermore, Mr. Gérard Soula has undertaken to assign to the company, also without any financial consideration, all new intellectual property rights within the company's field of business that he may hold in the future during the time he continues to be an officer of the company.

12.2. Patents and patent applications

12.2.1. Industrial property protection policy

The success of the company depends at least in part on its capacity to protect its inventions, primarily by obtaining and renewing patents in Europe, the United States and the rest of the world. An active policy is continued to protect products under clinical development (offensive strategy) and also to protect alternative solutions (defensive strategy). Patent applications are qualified as (i) protection of core business, (ii) protection of alternative solutions and (iii) defensive applications.

Since March 16, 2013, priority applications are only in France since it is no longer necessary to apply for an American patent in order to be recognized. Before the new regulation became effective in the United States on March 16, 2013, priority applications were deposited simultaneously in France and the United States to implement protection as rapidly as possible.

The patent portfolio is analyzed periodically and applications for inventions no longer under development and that cannot be transferred are abandoned for reasons of cost control.

An invention declaration form has been created to describe the invention in question and designate the inventor(s), mentioning their respective contributions.

The company's patents deposited or in the course of being deposited are the property of the company because their inventors are employees, except for Mr. Gérard Soula for whom all rights to his inventions (i) have been ceded to the company as stipulated in the accord signed by the principal shareholders of the company on December 15, 2009, which stated that the said accord shall be null and void when stocks are traded on the Euronext in Paris on February 20, 2012 and (ii) since that date, are ceded to the company in compliance with a contract for the transfer of intellectual property rights between the company and Mr. Gérard Soula. In the case of company employees, each labor contract contains a clause covering inventions and so all inventions legally belong to the company as stipulated in article L.611-7 of the Intellectual Property Code. In addition, transfer agreements are systematically signed for each invention.

At the present time, 22 inventions have been protected by patent application deposits for 22 distinct families. Adocia's portfolio therefore contains almost 200 patents and patent applications belonging to the company, most of which are still being examined by patent authorities.

12.2.2. Type and coverage of patents and patent applications held by the company

The core of the company's patent portfolio involves patents and patent applications protecting BioChaperone® polymers and small organic molecules that can interact with therapeutic proteins/peptides to improve their properties. The following table lists the patents and patent applications in the name of Adocia that protect families of polymers or of small organic molecules (table updated at the end of January 2014)

Families protecting polymers and small organic molecules		
Family	**Priority***	**Title**
F02	04/07/2006	Bi-functional polysaccharides
F03	09/26/2006	Dextran functionalized by hydrophobic amino acids
F13	10/06/2008	Polysaccharides with functional carboxyl groups substituted with a derivative of a hydrophobic alcohol
F29	12/23/2009	Anionic polysaccharides functionalized by a derivative of a hydrophobic acid
F30	11/19/2010	Polysaccharides with functional carboxyl groups substituted with hydrophobic derivative with a spacer at least trivalent
F35	09/30/2011	Functionalized oligosaccharides
F43	11/13/2012	Substituted anionic compounds composed of a skeleton on a small number of sugar units

The second aspect of the company's portfolio concerns patents and patent applications protecting complexes formed between BioChaperone® polymers and proteins of interest. These molecular complexes can be demonstrated using a variety of methods. The formation of complexes improves the useful properties of the protein. Patents and patent applications in the name of Adocia protecting families of complexes are listed in the following table (table updated at the end of January 2014):

Families protecting complexes		
Family	**Priority***	**Title**
F01	09/26/2005	Amphiphilic-PDGF polymer complex
F05	07/27/2007	Complex between an amphiphilic polymer and an osteogenic protein belonging to the family of BMPs
F12	09/26/2008	Complex composed of a polysaccharide and an HBP

Patents and patent applications protecting formulations of BioChaperone® polymers or small molecules with therapeutic proteins or complexes are the third aspect of Adocia's portfolio. In addition, all products under clinical development are covered by patents/patent applications.

Patents and patent applications in the name of Adocia protecting formulations are listed in the following table (table updated at the end of January 2014):

* The priority date of a patent is the date of the first application in France and/or the United States (or *via* PCT for family 39). Patents are granted for 20 years from their application date (the date when national, European or international applications were deposited, with the stipulation that European and international patent applications must be deposited within 12 months of the priority patent application). Furthermore, when products are registered (a Marketing Authorization is granted) patents may receive a maximum extension of their protection of 5 years and 6 months (corresponding to being granted a Complementary Certificate of Protection and a 6 month extension for pediatric uses).

Families protecting formulations		
Family	**Priority***	**Title**
F18	07/31/2009	New form of administration of complexes of osteogenic proteins
F21	03/27/2009	Formulation of fast acting recombinant human insulin
F33	08/10/2011	Solution for injection at pH 7 comprising at least one basal insulin whose pI is between 5.8 and 8.5
F37	01/09/2012	Solution for injection at pH 7 comprising at least one basal insulin whose pI is between 5.8 and 8.5 and a substituted co-polyamino acid
F39	09/18/2012	Stable pharmaceutical composition containing an aqueous solution of an antibody derived from a therapeutically active protein
F40	08/10/2012	Process for lowering the viscosity of solutions of proteins at high concentrations
F42	09/10/2012	Aqueous solution of a protein at high concentration with reduced viscosity
F44	11/14/2012	Formulation of fast acting insulin comprising a substituted anionic compound
F45	11/02/2011	Formulation of fast acting insulin comprising an oligosaccharide
F46	02/12/2013	Solution for injection at pH 7 comprising at least one basal insulin whose pI is between 5.8 and 8.5 and a carboxylated anionic compound and hydrophobic moieties
F47	02/12/2013	Solution for injection at pH 7 comprising at least one basal insulin whose pI is between 5.8 and 8.5 and an anionic polymer rendered hydrophobic

Finally, patents and patent applications protecting nanoparticles containing a cytotoxic agent and a copolymer (Drive*In*® technology) is a fourth and new aspect of the Adocia portfolio. The patents/ patent applications in the name of Adocia protecting families of nanoparticles are found below (table updated at the end of January 2014):

Families protecting nanoparticles		
Family	**Priority***	**Title**
F48	12/24/2013	Nanoparticles containing a HA-PLA copolymer

Adocia is currently active in four therapeutic domains:

- wound healing, in particular for the treatment of diabetic foot ulcers: Adocia polymers enable a notable improvement in treatments with PDGF-BB. BioChaperone®-PDGF-BB has been the subject of a phase II clinical trial and a phase III trial will be conducted;
- treatment of diabetes with:

* The priority date of a patent is the date of the first application in France and/or the United States (or *via* PCT for family 39). Patents are granted for 20 years from their application date (the date when national, European or international applications were deposited, with the stipulation that European and international patent applications must be deposited within 12 months of the priority patent application). Furthermore, when products are registered (a Marketing Authorization is granted) patents may receive a maximum extension of their protection of 5 years and 6 months (corresponding to being granted a Complementary Certificate of Protection and a 6 month extension for pediatric uses).

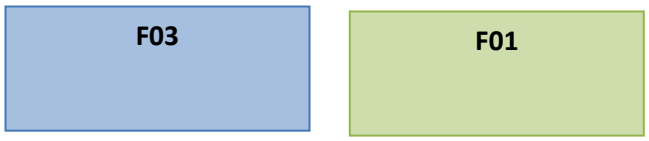
- fast acting insulins administered before each meal. BioChaperone® polymers and small organic molecules reduce the time to onset of action of these fast acting insulins, whether human insulin or fast acting insulin analogs and
- the combination of the best slow acting insulin, insulin glargine, with a fast acting insulin;

- therapeutic treatments with monoclonal antibodies;
- the treatment of cancers with nanoparticles formed by a cytotoxic agent and a copolymer.

Therapeutic agents (proteins, cytotoxic agents) used in these programs may have been the subject of patents deposited by third parties. Some of these therapeutic agents are in the public domain whereas others are still covered by valid patents. The protection status of therapeutic agents is described in the description of each program (see below). For therapeutic agents still protected by a patent, no product resulting from the company's program can be marketed by a third party other than the holder of the said patent, or without its authorization, before the therapeutic agent enters the public domain.

The following diagrams show the different levels of patent protection implemented by Adocia around each of its flagship research programs.

12.2.2.1 Program for wound healing of chronic lesions



Patent for polymers Patent for complexes

The aim of this program is to develop treatments to improve wound healing of chronic lesions such as diabetic foot ulcers. The therapeutic compositions under development include:

- a BioChaperone polymer® covered by the scope of patents and patent applications of family 03 of the company;
- a skin regeneration protein, PDGF-BB.

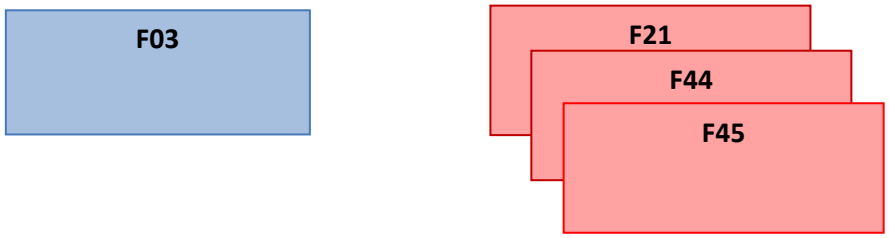
The polymer provides the protein with exceptional properties resulting from the formation of a complex: stability of the protein at room temperature for at least 3 months, resistance to enzymes in the wound and increased biological activity. The compositions resulting from this program are covered by a double patent protection, i.e. families F03 (patents for polymers) and F01 (patents for complexes).

A United States and European patent have been granted for the family F01 of complexes, in particular protecting the lead complex of the program under development. A United States patent was recently granted for family 03 of polymers whose scope covers the lead BioChaperone®.

Concerning protein PDGF-BB, a product patented by a third party, most patents involving this protein have been in the public domain since 2010.

12.2.2.2 Program of treatment of diabetes with insulin

12.2.2.2.1 Fast-acting insulin



Patents for polymers and small organic molecules

Patents for formulations

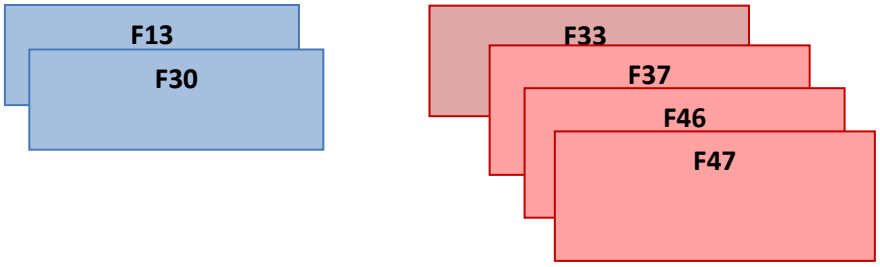
The aim of this program is to develop formulations containing fast-acting recombinant human insulin or its analogs. These formulations use special BioChaperone® polymers covered by the scope of patents and patent applications of families F03 and F35, or special small organic molecules covered by the scope of the company's patents and patent applications of family F43 that form complexes with recombinant insulin or its analogs to accelerate passage of insulin into the blood, thereby significantly reducing the time to onset of action. The formulations resulting from this program are covered by a double protection from the company's patents and patent applications for polymers (families F03 and F35), patent applications for small organic molecules (family F43) and patents and patent applications for formulations (families F21, F44 and F45).

A United States patent was recently granted for family 03 of polymers.

Human insulin is now in the public domain. There are three fast acting analogs on the market:

- Humalog® (insulin lispro), patented by Eli Lilly, that entered the public domain in 2013;
- NovoLog® (insulin aspart), patented by Novo Nordisk, that entered the public domain in December 2014;
- Apidra® (insulin glulisine), patented by Sanofi that will enter the public domain in 2017.

12.2.2.2.2 Combination of a slow acting insulin with a fast acting insulin



Patents for polymers or small organic molecules

Patents for formulations

The aim of this program is to develop insulin formulations for the combined administration of a fast acting prandial insulin and the most efficient basal insulin, insulin glargine, as a single injection of the product. Until the present, this type of combination was not possible because the products had to be formulated at different pH value. The use of the formulations proposed by Adocia resolves this issue of compatibility and thereby enables diabetic patients to reduce the number of daily insulin injections.

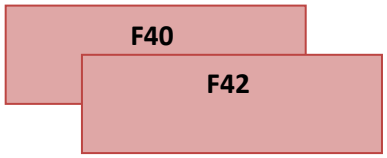
These formulations are covered by a double protection from patents and patent applications:

- for polymers (families F13, F30 and F35) and small organic molecules (family F43) of the company, that now make it possible to mix insulin glargine with commercial prandial insulins;
- for formulations (families F33, F37, F46 and F47) of the company.

A United States patent has been granted for the family of F13 products, in particular for the protection of the principal product of the program under development.

Insulin glargine is currently the subject of a patent held by Sanofi. Most patents and their extensions will expire in 2015. They are fast acting insulins and so the patent expiration dates are listed in the "fast acting insulin" part (see below).

12.2.2.3 Program of formulations of monoclonal antibodies

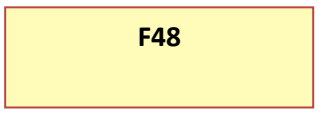


Patents for formulations

The aim of this program is to develop stable pharmaceutical compositions of monoclonal antibodies (mAb) and/or compositions with lower viscosity in solution at high concentrations. The compositions proposed by the company involve small organic molecules enabling highly concentrated solutions of monoclonal antibodies to be prepared, while maintaining physical and chemical stability and reducing their viscosity. The stable pharmaceutical compositions created with this program are protected by the family of patent applications for formulations (family F39 of the company). Pharmaceutical compositions with reduced viscosity prepared with this program are protected by the family of patent applications for formulations (families F40 and F42 of the company).

Most monoclonal antibodies are proprietary proteins still protected by third party patents.

12.2.2.4 Nanoparticles program



Patent for nanoparticles

The aim of this program is to develop nanoparticles containing a cytotoxic agent and a copolymer for the treatment of cancers. The first nanoparticles obtained with this program are protected by patent application F48 of the company. These nanoparticles contain a cytotoxic agent (doxorubicin, docetaxel) and a specific copolymer.

12.2.2.5 Bone regeneration program

Patent for polymers | Patent for complexes | Patent for formulations

The aim of this program is to develop pharmaceutical formulations containing a growth factor from the family of BMPs, in particular intended for regeneration of bone tissues *in vivo*. The formulations proposed by the company involve special BioChaperone® polymers that form complexes with the growth factor of the family of BMPs: they improve its solubility at physiological pH and its stability. The formulations resulting from this program are covered by a triple patent protection of families F13 (patent for polymers), F5 (patent for complexes) and F18 (patent for formulations) of the company.

This growth factor belonging to the family of BMPs has been patented by a third party and most of the patent protecting the product expired in 2012.

The company has abandoned this program.

12.2.3. Patents currently in use

At the present time, no patent is used to protect products.

12.2.4. Geographic coverage

Patent coverages are examined with respect to the importance of inventions and three predetermined strategies have been implemented by the company involving the choice of countries in which the national phase of PCT applications are in force (no later than 30 months after depositing the priority application).

These three predetermined strategies are:

- Strategy 1 for defensive applications: United States and Europe;
- Strategy 2 for alternative solutions: United States, Europe, Canada, China, Japan, India, Australia and Israel;
- Strategy 3 for the core of the business: United States, Europe, Canada, China, Japan, India, Australia, Israel, Mexico, Brazil, Russia, South Africa, Singapore and South Korea.

These predetermined strategies are decision-making tools enabling the company to be reactive depending on results obtained and contacts made with partners, and also enable budget control when starting the national phase. The following table lists the countries in which the company's inventions are protected by a patent/patent application. "X": patent application deposited, "D": patent delivered (obtained), "w": patent application withdrawn or abandoned and "V*": European patent delivered and validated in France, Belgium, Luxemburg, Austria, Germany, Greece, Turkey, Spain, Portugal, Switzerland, Lichtenstein, Italy, United Kingdom, Ireland, Denmark, Finland, Sweden, Iceland, Holland, Poland, Hungary, Romania and the Czech Republic.

Patents protecting polymers and small organic molecules		**Countries covered**															
Family	**Priorities***	FR	US	PCT	EP	AU	CA	CN	IL	IN	JP	BR	KR	MX	RU	SG	ZA
F02	FR06.03130 (04/07/2006)	w	w	x	x												
F03	PCT/IB2006/002666 (09/26/2006) FR07.02316 (03/29/2007)	*D*	D	x	x	D	x	D	x	x	x	x	x	x	D	x	*D*
F13	FR08.05506 (10/06/2008)	*D*	D	x	x	x	x	x	x	x	x	x	x	x	D	D	D
F29	PCT/IB2009/007899 (12/23/2009) FR10.01439 (04/07/2010)	D	x	x	x												
F30	PCT/IB2010/02970 (11/19/2010) FR10.01474 (04/08/2010)	D	x	x	x			x		x	x	x			x		
F35	FR11.58885 (09/30/2011)	x	x	x	x												
F43	FR12.60808 (11/13/2012)	x	x	x													
Patents protecting complexes		**Countries covered**															
Family	**Priority***	FR	US	PCT	EP	AU	CA	CN	IL	IN	JP	BR	KR	MX	RU	SG	ZA
F01	FR05.09803 (09/26/2005)	*D*	D	x	V	D	D	x	x	x	D	x	x	D	D	x	D
F05	FR07.05536 (07/27/2007)	D	D	x	x	w	w	w	w	w	x	w	w	w	w	w	w
F12	FR08.05321 (09/26/2008)	*r*	D	x	x	w	w	x	w	x	w	x	w	w	D	w	w
Patents protecting formulations		**Countries covered**															
Family	**Priority****	FR	US	PCT	EP	AU	CA	CN	IL	IN	JP	BR	KR	MX	RU	SG	ZA
F18	FR09.03803 (07/31/2009)	D	D	x	x	w	w	w	w	w	w	w	w	w	w	w	w
F21	FR09.01478 (03/27/2009)	*D*	D	x	x	w	w	w	w	w	w	w	w	w	w	w	w

* The priority date of a patent is the date of the first application in France and/or the United States. Patents are granted for 20 years from their application date (the date when national, European or international applications were deposited, with the stipulation that European and international patent applications must be deposited within 12 months of the priority patent application). Furthermore, when products are registered (a Marketing Authorization is granted) patents may receive a maximum extension of their protection of 5 years and 6 months (corresponding to being granted a Complementary Certificate of Protection and a 6 month extension for pediatric uses).

F33	FR11.577291 (08/10/2011)	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
F37	FR12.50224 (01/09/2012)	x	x	x													
F39	PCT/IB2012/054 950 (09/18/2012)			x													
F40	FR12.57775 (08/10/2012)	x	x	x													
F42	FR12.58494 (09/10/2012)	x	x	x													
F44	FR12.60855 (11/14/2012)	x	x	x													
F45	US13/287793 (11/02/2011)		x	x													
F46	FR13.51199 (02/12/2013)	x															
F47	FR13.51200 (02/12/2013)	x															
Patents protecting nanoparticles		**Countries covered**															
Family	**Priority****	FR	US	PCT	EP	AU	CA	CN	IL	IN	JP	BR	KR	MX	RU	SG	ZA
F48	FR13.63550 (12/24/2013)	x															

A United States patent has been delivered for the family of F13 products, in particular protecting the principal product of the program for development of the combination of a slow acting insulin with a fast acting insulin.

A United States patent and a European patent have also been granted for family F01 of complexes, in particular protecting the principal the principal complex of the program for development of wound healing of chronic lesions. A United States patent has recently been granted for family 03 of polymers whose scope covers the lead BioChaperone® polymer.

12.2.5. Litigations

No claims or litigations are declared.

12.3. Cooperation agreements and licenses granted by or to the company

12.3.1. Cooperation agreements

In November 2007, the company signed cooperation agreements with various major pharmaceutical groups.

The company did not assign the intellectual property rights in its technology pursuant to any of the agreements it signed. Furthermore, no implicit license can arise from any of the cooperation agreements that the company has concluded with its partners, as this is a prerequisite for Adocia before it signs any cooperation agreement.

Partners may hold rights only to inventions developed strictly within the scope of the cooperation that is the subject of these agreements, and to no other inventions. Depending on the partner, title may be held jointly with the company or outright by the partner.

Most of these cooperation agreements concern an assessment of the BioChaperone® technology vis-à-vis active pharmaceutical principles that are already marketed or are under pharmaceutical development.

Trials are conducted either in the company's laboratories or in the partner's laboratories, and the costs of such trials are paid by the company's partners.

Because the company's partners have demanded confidentiality about the existence itself of these agreements, neither the field of cooperation nor the identity of the partners can be disclosed in this reference document.

On December 14, 2011, the company signed a licensing and cooperation agreement with the US pharmaceutical group Eli Lilly and Company (hereinafter **"Eli Lilly"**). In July 2013, Adocia and Eli Lilly decided to terminate the licensing and cooperation agreement. This enabled Adocia to recover its rights to develop ultra-fast-acting insulin analogs.

12.3.2. Licenses granted by Adocia

On December 14, 2011, the company signed a licensing and cooperation agreement with the Eli Lilly group. This agreement concerned the development and marketing of Humalog fast-acting insulin analog in conjunction with the BioChaperone® technology (**"BioChaperone® Humalog"**). The company granted Eli Lilly exclusive worldwide rights to BioChaperone® for the purpose of developing, manufacturing and marketing BioChaperone® Humalog. This agreement covered all potential indications for BioChaperone® Humalog. The license rights granted were based on the F03 and F21 families of patent applications and patents. In July 2013, Adocia and Eli Lilly decided to terminate the licensing and cooperation agreement. This enabled Adocia to recover its rights to develop ultra-fast-acting insulin analogs.

12.3.3. Licenses granted by third parties

On December 9, 2013, the company signed an exclusive licensing agreement with the CNRS, the University of Bordeaux I, the Bordeaux Polytechnic Institute and the Aquitaine Science Transfer (SATT Aquitaine). This licensing agreement covers a family of patent applications that protects a nanoparticle drug delivery technology in the health field. The invention that is the subject of this family of patent applications was developed by Professor Sébastien Lecommandoux and his team at the Organic Polymers Chemistry Laboratory (LCPO, UMR5629 CNRS – University of Bordeaux I – Bordeaux Polytechnic Institute), and has proved particularly effective in preclinical tests/trials in carrying active principles and delivering them into solid tumors. Several articles about this work have been published in major international scientific journals.

Adocia will pursue a dual strategy to develop this technology. Firstly, Adocia plans to develop proprietary nanoparticles based on doxorubicin and docetaxel, two widely used cytotoxic anticancer agents that could benefit significantly from better penetration into the cells of solid tumors. Secondly, Adocia plans to offer its DriveIn® technology to pharmaceutical companies to optimize the effectiveness of their own proprietary molecules.

12.4. Trademarks, trademark applications and domain names

The company holds *inter alia* the following trademarks and trademark applications:

- "Adocia", which has been filed primarily in classes 1, 5 and 42, in France, the European Union, China, Japan, the Unites States, Switzerland, and India;
- "BioChaperone", which has been filed in classes 1, 5 and 42, in France, the European Union, China, Japan, and the Unites States;

- “Hinsbet”, which has been filed in classes 1 and 5, in France, the European Union, China, Japan, and the Unites States;
- “Betin”, which has been filed in classes 1 and 5, in France;
- “PPM”, which has been filed in classes 1, 5 and 42, in France;
- “Transidex”, which has been filed in classes 1, 5 and 42, in France;
- “DriveIn” and “Drive-In”, which have been filed in classes 1, 5 and 42, in France.

The company registers its trademarks by filing national, EU or international applications. In general, trademark registrations are granted for a period of 10 years and are renewable indefinitely. The laws of certain countries may impose specific requirements for the validity of trademarks, such as requiring that the trademark be actually used.

The company defends its trademark rights by filing oppositions against the registration of identical or similar trademarks by third parties. The company filed an opposition in France against an application by THL Concept SARL to register “Adoxia” as a trademark. That opposition became moot when the products and services against which the opposition had been field were withdrawn. On the other hand, the opposition that the company filed in India against the application of M/S Ajanta Pharma Limited to register “Audacia” as a trademark is still pending.

In France, Astellas Pharma Inc. filed an opposition against the company’s application to register “Betins”. The company withdrew its registration application, filed a new application to register “Betin”, and undertook not to use that trademark for products and/or services in connection with the treatment of urological diseases.

12.4.1. Domain names

The company currently holds the nine domain names listed below:

Extension	Owner	Date filed/registered
“transidex”		
.eu	Adocia	9/29/2006
.fr	Adocia	10/3/2006
“adocia”		
.com	Adocia	6/7/2006
.eu	Adocia	1/2/2007
.fr	Adocia	6/12/2006
.biz	Adocia	5/16/2008
.net		5/16/2008
“biochaperone”		
.com	Adocia	9/1/2010
.fr	Adocia	6/19/2009

In general, domain names are renewable every year or every two years, indefinitely.

13. TRENDS

See section 6.3 entitled "The markets" of this reference document, which describes the epidemiological data for the pathologies targeted by the BioChaperone® technological platform, as well as, for certain pathologies, the expected evolutions and market size.

13.1. Press release of 6 january 2014

On 6 January 2014, by press release, the company annouced the launch of a phase IIa clinical trial on its ultra-fast acting formulation of insulin lispro (Humalog®, Eli Lilly) using its proprietary technology BioChaperone®.

This clinical trial aims to demonstrate that the BioChaperone Lispro formulation acts faster than Humalog, which would allow patients to achieve a better glycemic control after a meal. During this study, pharmacodynamic and pharmacokinetic profiles of the BioChaperone Lispro formulation will be compared to those of Humalog in a cross-over design on 36 type I diabetic patients under euglycemic clamp. The first patients of this double-blind study conducted by Profil, a German CRO specialized in diabetes, have already been treated. Results from this study are expected during the second quarter of 2014.

Adocia is therefore entering the second stage of the clinical development plan of its ultra-fast acting analog insulin. During the first phase I clinical study, performed by Eli Lilly on healthy volunteers, the BioChaperone Lispro formulation reached all its predefined clinical endpoints.

"The objective of our ultra-fast analog insulin is to enhance post-prandial glycemic control in order to avoid hyperglycemia, which is responsible for long term side-effects of diabetes like retinopathy or cardiovascular issues", said Olivier Soula, VP R&D director at Adocia. "*After this second stage, we intend to follow an accelerated clinical development pathway comparable to the one taken by Novo Nordisk with its reformulation of insulin Aspart."*

"During preclinical studies, we demonstrated that BioChaperone has the same accelerating effect on all three fast-acting analog insulins on the market, namely Humalog, NovoLog® (Novo Nordisk) and Apidra® (Sanofi). This clinical trial on Humalog should establish the human proof of concept for all these insulins, which represent a USD 5 billion market," said Gerard Soula, CEO of Adocia.

The markets targeted by Adocia represent more than USD20 billion (USD17 billion for insulin therapy and USD3 billion for diabetic foot ulcer healing) (IMS Health).

13.2. Press release of 13 January 2014

On 13 January 2014, by press release, the company announced that it has been granted two patents, one in Japan for the Biochaperone PDGF composition, and the second in the United States for the Biochaperone polymers. Both patents will protect Adocia's findings in the field of chronic wound healing, especially for diabetic foot ulcers.

The BioChaperone PDGF product has been successfully tested in a phase II clinical trial in India for the treatment of diabetic foot ulcers. This product is protected by two families of patents. The first one covers the complexes between the BioChaperone polymers and PDGF; the second covers the BioChaperone polymers as such.

The patent on the complexes was granted in Europe and the United States in 2012 (cf. press release of June 13, 2012). The inclusion of Japan now extends the coverage to 29 countries. Twenty-three are in Europe and the rest are the United States, Australia, Mexico, Russia and South Africa. This patent confers a protection until September 26, 2026.

The BioChaperone polymers, a proprietary technology specifically developed by Adocia, are covered by the other patent. This patent has just been granted by the US Patent and Trademark Office (USPTO). The protection of these BioChaperone polymers is now established in the United States, Australia, China, Russia, France and South Africa. It is valid until September 26, 2027.

"We are very pleased by these positive decisions on two of our strategic patent families, especially because they have been granted by the very demanding national United States and Japanese patent offices. Our product for the treatment of diabetic foot ulcer is patent protected until at least 2026," said Remi Soula, director of business development and intellectual property at Adocia. "*The granting of these patents consolidates our 22 families strong patent portfolio. For six of these families, the US patent has already been delivered."*

"We are actively pursuing the clinical development of the BioChaperone PDGF product for the treatment of diabetic foot ulcer. These patents cover the major markets we are targeting. Moreover, we hope to receive authorization to launch the phase III clinical trial in India very soon", said Olivier Soula, delegate general director and R&D director.

13.3. Press release of 27 february 2014

On 27 February 2014, the company announced posited preliminary results for the clinical trial on an innovative formulation combining insulin analog Glargine (Lantus®, Sanofi), the gold standard basal insulin, with a rapid-acting insulin analog, Lispro (Humalog®, Eli Lilly) using Adocia's BioChaperone® technology.

BioChaperone technology enables the solubilization of insulin Glargine at physiological pH, which enables its combination with prandial insulins analogs such as insulin Lispro in solution. Eight patent applications have been filed to protect this innovation until 2032.

The objective of this trial was to show that this combination of the most widely used basal insulin (Lantus®) and one of the best commercial prandial insulins (Humalog®) formulated with the BioChaperone® technology has the potential to help patients improve their blood glucose control more effectively than with a Premix formulation of insulin analog (Humalog Mix®, Lispro and Protamine).

"The preliminary clinical efficacy results show how the BioChaperone Combo could offer patients both the long-lasting effect of Glargine, which is the gold-standard in basal insulin and the fast action of a prandial insulin analog. This confirms the product's strong market potential," said Olivier Soula, Deputy General Manager of Adocia. "From a regulatory point of view, we should benefit from a simplified clinical development path. Development could be short and less costly as Glargine and Lispro have both been on the market for many years and share a proven track record of clinical safety."

Trial Design

This clinical trial, conducted by Profil (CRO, Germany) was a double blind, two-way crossover study that enrolled 20 patients with type 1 diabetes under euglycemic clamp conditions. As part of the crossover design, all patients were treated with BioChaperone Combo and Humalog Mix 25 at the same dose of 0.8 IU/kg. The composition of BioChaperone Combo is based on 75/25 basal prandial ratio like in Humalog Mix 25. Pharmacokinetic (PK) and pharmacodynamic (PD) measurements were taken as patients were monitored for 30 hours after administration. The objective of the study was a comparison of PD and PK profiles of BioChaperone Combo to those of Humalog Mix 25. Safety and tolerability of the two products were also evaluated.

Efficacy Results Demonstrate Proof of Concept

The study demonstrated that BioChaperone Combo has the ability to deliver insulin with a faster onset and longer duration of action compared to Humalog Mix:

- BioChaperone Combo had a greater than 30% faster onset of action as compared to Humalog Mix.
- Almost all patients treated with BioChaperone Combo experienced a minimal duration of action in excess of 30 hours (end of monitoring).
- Both formulations of insulins (BioChaperone Combo and Humalog Mix) were well tolerated.

The onset of action is the time when glucose level decreases by at least 5% from the starting level and glucose infusion is started. Minimal duration of action is defined by the time when blood glucose concentration exceeds 6.5 mmol/L (118 mg/dL).

The PK profiles confirm these major conclusions based on PD profiles.

The minimal duration of action in excess of 30 hours, support the use of the BioChaperone Combo as a once-a-day insulin treatment. This may provide patients with advantages over Premix formulations that usually require injection two or three times a day. BioChaperone Combo could also be used twice-a-day to support treatment intensification.

“Our ambition is to offer diabetic patients a unique combination of insulins to simplify their lives while giving them access to the best care options. This clinical study is a key step towards this objective. BioChaperone Combo could replace Premix formulations, (which represent a market exceeding $2.4 billion). They could also capture part of the Lantus market, which is greater than $7 billion,” said Gérard Soula, CEO of Adocia. “We believe that BioChaperone Combo also represents a great commercial opportunity for potential partners.”

Adocia intends to publish a detailed analysis when the data become available in a few weeks. Adocia also intends to present the complete results at a major medical conference this year.

13.4. Press release of 20 march 2014

On 20 March 2014, by press release, the company announced positiv results for the first clinical trial on its innovative formulation combining insulin analog glargine (Lantus®, Sanofi), the gold standard basal insulin, with a rapid-acting insulin analog, lispro (Humalog®, Eli Lilly) using Adocia's BioChaperone® technology.

BioChaperone technology enables the solubilization of insulin glargine at physiological pH, which allows its combination in solution with prandial insulins analogs such as lispro. Eight patent applications have been filed to protect this innovation until 2032.

The objective of this trial was to compare the Pharmacodynamics (PD) and Pharmacokinetics (PK) of the BioChaperone Combo with a premix formulation of an insulin analog (Humalog® Mix, lispro and protamine, Eli Lilly).

Clinical results

In this double-blind crossover study, the PK/PD characteristics of BioChaperone Combo (insulin glargine 75% and insulin lispro 25%) were investigated. Twenty people with type 1 diabetes received single 0.8 U/kg doses of BioChaperone Combo and Humalog Mix25 under automated euglycemic clamp conditions (ClampArt®, target blood glucose (BG) 100 mg/dL, clamp duration 30 h post-dosing).

Both formulations were well tolerated and did not induce any local reaction.

BioChaperone Combo had a faster onset of action (25±11 vs. 40±13 min; p=0.002) and a higher early metabolic effect (AUC_GIR[0-2h] 504±210 vs. 325±183 mg/kg; p=0.001). The study also demonstrates a stronger late metabolic effect (AUC_GIR[12-30h] 1480±900 vs. 961±553 mg/kg; p=0.026) and a longer duration of action. Indeed, 30 hours after administration, 17 of the 19 patients treated with BioChaperone Combo were still under glucose control vs. only 6 of the 20 with Humalog Mix (p=0.0002). In summary, significant difference was observed for all these comparisons (p<0.05).

PK parameters are consistent with PD and will be submitted for communication to the 74th scientific sessions of the American Diabetes Association (ADA) and the 50th European Association for the Study of Diabetes (EASD) annual meeting.

In conclusion, the clinical results demonstrate faster prandial phase and longer basal action for BioChaperone Combo vs. Humalog Mix, indicating a better control of blood glucose.

“We are very pleased with the final analysis of the performance of our BioChaperone Combo. There is strong evidence of the superiority of this innovative formulation to Humalog Mix, with a statistical difference for all key parameters. What is remarkable in these results is not only that the action of our Combo lasts more than 30 hours, but also, it acts more rapidly,” says Olivier Soula, Deputy General Manager of Adocia.

“Based on these results, BioChaperone Combo could be a single daily injection treatment. This treatment simplification would be an important advantage for patients who currently require at least two injections per day of premix or one of Lantus plus at least one of a fast-acting insulin,” adds Dr Tim Heise, medical doctor, CEO of Profil.

BioChaperone Combo, combining simplicity and medical performance

Today, diabetic patients who cannot control their glycemia with basal insulin alone need to add prandial insulin to their treatment. They have two options: to use either one insulin analog premix product or two insulin products, one basal and one prandial.

Premix consists in protamine precipitated (basal fraction) and soluble (prandial fraction) insulin. It eases patient life with a single product to use but it requires two injections per day to cover the patient’s basal insulin needs. The market for insulin analog premixes was worth approximately $2.4 billion in 2013, with $1.8 billion sales of NovoLog® Mix (Novo Nordisk) and estimated $0.6 billion sales of Humalog Mix (Eli Lilly).

Nevertheless, the use of both Lantus and fast-acting insulin remains the preferred physicians’ choice because it offers a basal plateau effect and a fast prandial action. It is estimated that the market share of Lantus used in association with fast-acting insulin exceeds $2 billion.

“BioChaperone Combo combines the efficacy of both insulin glargine and insulin lispro in a single product,” says Gerard Soula, President & CEO of Adocia. “Our objective is to serve patients and BioChaperone Combo offers the simplicity of the premix treatment with the medical efficacy of insulin glargine. The potential market for this combination could be worth the $2.4 billion of the premix market plus a significant part of the $7.8 billion insulin glargine market”.

The development of BioChaperone Combo is in line with the ongoing trend of treating diabetes with combination products. Notably, 2 long-acting insulins combined with GLP-1 agonists are currently in phase 3 clinical trials: insulin glargine with lixisenatide (Lixilan®, Sanofi) and insulin degludec with liraglutide (IDegLira, Novo Nordisk). In addition, a combination of long-acting and fast-acting insulin analogs is ready for commercialization (insulin degludec and insulin aspart 70/30, Ryzodeg®, Novo Nordisk).

BioChaperone Combo is the only combination of the gold-standard basal insulin glargine with a fast-acting insulin analog with an established clinical proof-of-concept.

Clinical Development Plan

Adocia intends to launch a phase 2a clinical trial on type 1 diabetic patients in order to document the dose-response and dose-exposure of the BioChaperone Combo. This clinical trial is to be conducted by the same CRO in Germany, Profil GmbH, during the third quarter of this year. It should enroll 20 type 1 diabetic patients under automated euglycemic clamp conditions with 3 doses of BioChaperone Combo, insulin glargine (75%) and insulin lispro (25%) and one dose of Humalog Mix. Results are expected at the end of 2014.

13.5. Press release of 9 April 2014

On 9 April 2014, the company announced positive results from a Phase IIa clinical trial evaluating its innovative ultra-fast formulation of insulin lispro in comparison to Eli Lilly's Humalog® commercial insulin. Adocia's formulation incorporates proprietary BioChaperone® technology which enables accelerated absorption of prandial insulins. Humalog, which is now off-patent, has annual sales of USD 2.6B.

The present study met its primary endpoint, showing a significant increase in BioChaperone Lispro bioavailability in the first half-hour compared to Humalog. This parameter is critical as the ultimate goal for prandial insulins is an immediate absorption in the blood following subcutaneous injections. This result demonstrates that BioChaperone Lispro more closely mimics the endogenous insulin secretion observed in healthy individuals in response to a meal.

"We are excited by the performance of BioChaperone Lispro in diabetic patients, as it confirms the positive results obtained in healthy volunteers. Adocia now has three insulin products with an established proof-of-concept in diabetic patients, including BioChaperone Combo, our combination of the insulins glargine and lispro, and HinsBet, our fast-acting human insulin," said Gerard Soula, chairman and CEO of Adocia. "We think our insulin pipeline positions us to become an important player in the insulin field. Our priority is to bring, as rapidly and as efficiently as possible, these innovative treatments to patients. Adocia is now focused on finding the right partners to achieve this."

Clinical results support the ultra-fast action of BioChaperone Lispro

In this double-blind crossover study, the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of BioChaperone Lispro were compared to those of Humalog. Thirty-six patients with type I diabetes received single 0.2 U/kg doses of BioChaperone Lispro and Humalog under automated euglycemic clamp conditions (ClampArt®, target blood glucose (BG) 100 mg/dL, clamp duration six hours post-dosing).

Both formulations were well tolerated and did not induce any local reaction.

BioChaperone Lispro has a significantly faster rate of absorption than Humalog with an increase in the early insulin exposure of 170% (primary endpoint, AUClispro_0-30min 23.7 ± 11.4 vs. 9.5 ± 6.2 h*mU/L; $p<0.0001$). The time to peak insulin concentration was reduced by more than 35% (Tmax 42 ± 11 vs. 69 ± 22 min; $p<0.0001$). BioChaperone Lispro was cleared from the blood significantly earlier than Humalog, reflected in the time to half-maximum insulin levels after Tmax (late T50%max = 141 ± 43 vs. 173 ± 41 min, $p<0.0001$).

The acceleration of insulin lispro absorption translated into a significant acceleration of insulin action. The metabolic effect is triggered significantly earlier for BioChaperone Lispro than for Humalog with

30% faster onset of action (Tonset = 23.1 ± 7.0 vs. 34.4 ± 15.3 min; p<0.0001). The early metabolic effect is increased by 69% relative to Humalog during the first hour after administration (AUCGIR_0-1h = 218 ± 88 vs. 129 ± 63 mg/kg; p<0.0001). The time to reach the maximal observed hypoglycemic effect is significantly shorter relative to Humalog (TGIR_max = 99 ± 42 vs. 133 ± 45 min; p=0.0002).

Finally, the total insulin exposure and potency of insulin lispro was similar for both formulations.

“It is an outstanding result to improve by more than 35% the pharmacokinetics of insulin lispro. Strikingly, BioChaperone triggers an immediate entry of insulin lispro into the blood stream, which closely mimics the kinetics of physiological insulin release. This is particularly meaningful as this translates into a faster insulin action”, said Olivier Soula R&D director and deputy general manager. “Our last clinical results confirm the high value and versatility of the BioChaperone technology for insulin formulation to reach unique performances.”

The clinical data has been submitted for communication to the 74th scientific sessions of the American Diabetes Association (ADA) and the 50th European Association for the Study of Diabetes (EASD) annual meeting.

BioChaperone Lispro more closely mimics physiologic prandial insulin action

The main objective of prandial insulins is to control the rapid rise in glycaemia associated with digesting a meal. Ideally, the insulin release in the blood stream should begin immediately after the start of the meal as this is the case in physiological conditions. However, even with modern fast-acting insulin analogs, there is a lag time between the injection and presence of active insulin in the bloodstream. This results in the need to inject prandial insulin analogs around 15 minutes before the meal.

The ultra-fast action of insulin is key to reducing the risk of both hyper- and hypoglycemia. Hyperglycemia results from a delay in insulin response compared to glucose entry in the blood flow following a meal. Chronic hyperglycemia is correlated with cardiovascular complications in diabetic patients and represents a major health issue. The earlier onset and higher early bioavailability of BioChaperone Lispro compared to Humalog has the potential to reduce the incidence of hyperglycemic events. Conversely, hypoglycemia results from an excess of insulin relative to blood glucose concentration. The shorter exposure of BioChaperone Lispro compared to Humalog may also limit the incidence of hypoglycemic events.

“These clinical results demonstrate that BioChaperone Lispro is an ultra-fast-acting insulin that could be used at meal times or even after a meal. Moreover, as a result of its fast-in and fast-out profile, this ultra-fast-acting formulation of insulin lispro could reduce hyperglycemic and hypoglycemic events, which would be a key benefit for patients with diabetes”, said Dr. Tim Heise, medical doctor, CEO of Profil Neuss. “Ultra-fast acting insulin may also facilitate the development of an artificial pancreas, since today the ability of closed-loop algorithms to control glucose is severely limited by the slow onset of action of available prandial acting insulin analogs.” added Dr. Tim Heise.

Clinical Development Plan for Adocia’s prandial insulins

BioChaperone Lispro now has a complete clinical data package ready to support the next clinical trial, a dose-response study which will be launched this quarter. This trial will be conducted in Germany by the same CRO, Profil Neuss. According to the current design, the primary goal of the study is to examine the dose-response and dose-exposure of BioChaperone Lispro. The trial is expected to enroll 36 type I diabetic patients under automated euglycemic clamp conditions with three doses of BioChaperone Lispro and one dose of Humalog. Results are expected before the end of 2014.

Adocia plans to follow a similar development plan for HinsBet, the prandial fast-acting human insulin formulated using BioChaperone. HinsBet is on track to enter a phase IIa dose-response clinical trial expected to start in the third quarter of 2014.

13.6. Press release of 17 April 2014

On 17 April 2014, by press release, Adocia announced its firt 2014 quarter results.

Detail of revenues for the 1st quarter of 2014

In K€ - IFRS (not audited)	**03/31/2014** *(3 months)*	**03/31/2013** *(3 months)*
Licensing revenues	-	476
Research and collaborative contracts	84	-
Revenues	**84**	**476**

The revenues for the first quarter of 2014, worth EUR 0.1M, are essentially earned from research contracts on the formulation of monoclonal antibodies. For the same period last year, the revenues were EUR 0.5M, principally the result of the amortization of the upfront payment regarding the licensing contract then effective with Eli Lilly.

Cash position as of end of March 2014

On March 31, 2014, the cash and cash equivalents totaled EUR 16M, compared to EUR 19.4M on January 1, 2014. The EUR 3.5M cash consumption for this quarter is equivalent to the cash consumption over the same period in 2013. The intensification of clinical activities has been achieved while controlling expenses and in the absence of revenues and other income (the French research and development tax granted in respect to expenditure incurred in 2013 is expected to be received in the coming months).

Key events of the first quarter 2014:

These last weeks have been marked by the publication of major clinical results. Firstly, the product BioChaperone® Combo, a combination of the basal insulin glargine and the prandial insulin lispro, was successfully tested in a phase I/II clinical trial on type 1 diabetic patients and demonstrated a faster and a longer hypoglycemic action compared to HumalogMix (Premix composed of Humalog and protamine). BioChaperone® Combo thereby paves the way to a new treatment that improves patients' lives.

More recently, the phase II study on the formulation of an ultra-fast-acting insulin, BioChaperone® Lispro, carried out on type 1 diabetic patients, succeeded in demonstrating that this formulation is significantly faster than Humalog. Humalog, which is now off-patent, is a leading prandial insulin with annual sales of EUR 2.6B in 2013 . These very good results obtained on type 1 diabetic patients further confirm the ones obtained by Eli Lilly during the clinical study carried out in 2012 on healthy volunteers.

"*Today, Adocia has a portfolio of three innovative insulin formulations for which proof of concept have been established in diabetic patients: BioChaperone® Combo, BioChaperone® Lispro and BioChaperone Human Insulin, Hinsbet®. With our BioChaperone® technology, Adocia has become an important player in this vast therapeutic field,*" said Gérard Soula, chairman and CEO of Adocia. "*These important steps forward are the results of the expertise and commitment of the Adocia teams, and I am proud of the progress made. We will actively pursue these different programs for which the company has sufficient*

financial funding. Along with our project for the treatment of the diabetic foot ulcer, these recent results constitute a powerful accelerator for the development of the company."

14. PROFIT FORECASTS OR ESTIMATES

The company does not plan to make any profit forecasts or estimates.

15. ADMINISTRATIVE, MANAGEMENT, SUPERVISORY AND EXECUTIVE MANAGEMENT BODIES

15.1. Officers and directors

Until October 24, 2011, the company was incorporated as a *société par actions simplifiée* (simplified joint stock company).

The shareholders' meeting held on October 24, 2011 approved the conversion of the company into a *société anonyme* (corporation) with a board of directors, and adopted new corporate governance rules.

A summary description of the main provisions of the company's articles of incorporation and bylaws and of the internal rules and regulations of the specialized committees is provided in this reference document, in section 21.2 "Articles of incorporation and bylaws" and section 16.3 "Specialized committees – Corporate governance".

15.1.1. Members of the board of directors

As of the filing date of this reference document, the members of the company's board of directors are*:

Name	Office	Main functions within the company	Main functions outside the company	Starting and ending dates of terms of office
Mr. Gérard Soula	Chairman of the board of directors	Chairman Chief Executive Officer	None	Appointed director by the shareholders' meeting held on October 24, 2011 for a term of three years which will expire at the conclusion of the shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2013, and appointed chairman of the board of directors and chief executive officer by the board of directors' meeting held on October 24, 2011 for the duration of his term of office as director
Mr. Olivier Soula	Vice-President, Director	R&D Director VP	None	Appointed director by the shareholders' meeting held on October 24, 2011 for a term of three years which will expire at the conclusion of the shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2013, and appointed vice-president by the board of directors' meeting held on December 19, 2012 for the duration of his term of office as director

Mr. Olivier Martinez	Director	None	Investment Manager, Bpifrance Investissement (formerly CDC Entreprises)	Appointed director by the shareholders' meeting held on October 24, 2011 for a term of three years which will expire at the conclusion of the shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2013
Bpifrance Investissement (formerly CDC Entreprises), represented by Mr. Laurent Arthaud	Director	None	Vice-President, Bpifrance Investissement (formerly CDC Entreprises)	Appointed director by the shareholders' meeting held on October 24, 2011 for a term of three years which will expire at the conclusion of the shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2013
Ms. Dominique Takizawa	Director (**)	None	Secretary General, Institut Mérieux	Appointed director by the shareholders' meeting held on October 24, 2011 for a term of three years which will expire at the conclusion of the shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2013
Ms. Ekaterina Smirnyagina	Director (**)	None	Investment Manager, Capricorn Venture Partners	Appointed director by the shareholders' meeting held on June 18, 2013 for a term of three years which will expire at the conclusion of the shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2015
Viveris Management, represented by Jérôme Féraud	Board observer (*censeur*)	None	Investment Manager, Viveris Management	Appointed director by the shareholders' meeting held on October 24, 2011 for a term of three years which will expire at the conclusion of the shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2013

*Kurma Partners, represented by Mr. Thierry Laugel, resigned its position as director on February 24, 2014 in accordance with its investment policy, the majority of its investments being constitued of unlisted companies

** Independent Board members

The business address of the chairman and chief executive officer and of the vice-president is the address of company's registered office.

The business addresses of the other directors and of the board observer are shown below:

- Mr. Olivier Martinez, Bpifrance Investissement, 6-8 Boulevard Haussmann, 75009 Paris
- Mr. Laurent Arthaud, Bpifrance, 6-8 Boulevard Haussmann, 75009 Paris
- Ms. Dominique Takizawa, Institut Mérieux, 17 Rue Bourgelat, 69002 Lyon
- Ms. Ekaterina Smirnyagina, Capricorn Venture Partners, De Jonge Saint Jacob, Lei 19/1-B-3000 Leuven, Belgium
- Mr. Jérôme Féraud, Vivéris, 6 Allées Trucat-Mery, 13008 Marseille

These persons have gained expertise and management experience in the various salaried and management positions they have previously held (see section 14.1.3 “Biographies of the directors and board observer”).

There are no family ties between the persons listed above, except in the case of Messrs. Gérard Soula and Olivier Soula, who are both members of the board of directors.

Furthermore, during the five years preceding the date of this reference document, no corporate officer or board of directors member:

- has been convicted of fraud;
- has been associated in his/her capacity as corporate officer or director with any bankruptcy, receivership or liquidation;
- has been deprived of the right to hold management positions in companies; and
- has been publicly and officially accused or penalized by any statutory or regulatory authority.

15.1.2. Other corporate offices

Other corporate offices currently held by the directors and board observer

Name	Office held	Company (*)
Mr. Gérard Soula	Director	GLOWBL
Mr. Olivier Soula	Chairman of the board of directors	GLOWB
Mr. Olivier Martinez	Director Member of the supervisory board Member of the supervisory board Member of the management committee Board observer Board observer	POXEL CYTHERIS GENTICEL FAB PHARMA INNATE PHARMA CERENIS THERAPEUTICS
Mr. Laurent Arthaud	Member of the supervisory board Director Member of the supervisory board Director Director	KURMA PARTNERS TxCell EMERTEC GESTION SA SCYNEXIS INC. CELLECTIS SA
Ms. Dominique Takizawa	Permanent representative Director Director Director Director Director	TSGH chez TRANSGENE MERIEUX NUTRISCIENCES (USA) APRIL GROUP (France) ABL Inc. (USA) Lyon Place Financière Lyon Place Bourse
Ms. Ekaterina Smirnyagina	Director Director	Nexstim Oy (Finland) iSTAR Medical SA (Belgium)
Mr. Jérôme Féraud	Director Director Director Director Director Director	AXESS VISION TECHNOLOGY BIOM’UP DIEAU S.A. EGIDIUM TECHNOLOGIES EPSILINE LABORATOIRE PRECILIENS SAS

(*) *None of the companies mentioned has capital ties with Adocia*

Other corporate offices, now expired, held by the directors and board observer during the last five fiscal years

Name	Office held	Company
Mr. Gérard Soula	Chairman of the board of directors and chief executive officer Director	BIODEX LIFE CYCLE PHARMA A/S
Mr. Olivier Soula	Director	BIODEX
Mr. Olivier Martinez	Member of the supervisory board Member of the supervisory board Member of the management board	CRYOLOG MUTABILIS BIOAM GESTION
Mr. Laurent Arthaud	Director Member of the supervisory board Member of the supervisory board Chairman	OSEO GARANTIE ACE MANAGEMENT BIOAM GESTION ORGANIBIO
Ms. Dominique Takizawa	Director Director Director Director Director Director	MACSF EPARGNE RETRAITE AVESTHAGEN (India) BIOMERIEUX Benelux THERA Conseil SHANTA Biotechnics (India) SHANH
Mr. Jérôme Féraud	Member of the supervisory board Member of the supervisory board	IPSOGEN S.A. CRYOLOG S.A.
Ms. Ekaterina Smirnyagina	Director Director Director	Innate Pharma SA Cerenis Therapeutics SA Kiadis Pharma NV (Netherlands)

15.1.3. Biographies of the directors and board observer

Gérard Soula PhD, 65 years old, holds a doctorate in organic chemistry and is a graduate of IAE (Aix Marseille).

He founded Flamel Technologies (1990), a company listed on NASDAQ that specializes in drug delivery. He held the positions of chairman and chief executive officer and research director in the company until June 2005. When he left Flamel Technologies, the company employed 250 persons and a market valuation of $500 million. Flamel Technologies' success was largely due to the performances of its Micropump and Medusa platforms.

Gérard Soula has lengthy experience in negotiating licensing agreements for technological innovations with major biopharmaceutical groups (Novo Nordisk, Bristol Myers Squibb, GlaxoSmithKline, etc.).

Olivier Soula PhD, 44 years old, holds a doctorate in polymer physical chemistry, and is a graduate of ENSIC Mulhouse. He also earned an MBA from IAE in Lyon.

He began his career with Flamel Technologies, where he stayed for eight years and was *inter alia* nanotechnologies research manager. He directed the development of Medusa, a therapeutic protein sustained release platform, and successfully conducted clinical studies for three such projects. He is co-holder of nearly 40 patents.

Olivier Martinez PhD, 43 years old, holds a doctorate in cellular biology from the University of Paris XI, as well as a degree from the College of Engineers.

From 1992 to 1997, Olivier Martinez was a student researcher with Institut Pasteur, and then with Institut Curie, in the field of cellular biology. After receiving training in management, he joined the life sciences group of Gemini Consulting where, for two years, he worked on projects in the pharmaceutical and health sectors. In 2000, he joined Bioam Gestion as project manager, and was appointed investment manager and member of the management board in 2004. When Bioam Gestion was taken over by CDC Entreprises in July 2010, Olivier Martinez joined the life sciences team of CDC Entreprises, which manages the InnoBio and Bioam funds, and advises the Strategic Investment Fund (FSI) on its investments in biotechnology firms. CDC Entreprises and the FSI are now divisions of Bpifrance, the French public investment bank.
Olivier Martinez is an alumnus of the Ecole Normale Supérieure (Ulm) in Paris.

Laurent Arthaud, 51 years old, is a graduate of the Ecole Polytechnique and the National Statistics and Economic Administration School (ENSAE).

He started his career in 1986 with INSEE, and then joined the economic forecasts division of the Economy and Finance Ministry. In 1993, he was appointed technical advisor to the Labor Ministry and, in 1995, technical advisor to Prime Minister Alain Juppé, in charge of employment issues. He created the system of personal services vouchers (*chèque emploi service*). In 1997, Laurent Arthaud joined Rhône-Poulenc as secretary general of the group's scientific division, in charge *inter alia* of external collaborations. In 1999, he created Aventis Capital within the Aventis group, the group's venture capital structure, and then created the Genavent venture capital fund in partnership with Société Générale. In 2004, Laurent Arthaud became the chairman of PharmaVent Partners, a newly created venture capital fund management company. In November 2006, he joined CDC Entreprises as vice-president for new developments. In 2009, he took over all CDC Entreprises life sciences activities and the InnoBio investment fund. He is currently in charge of Bpifrance's investments in life sciences and environmentally friendly technologies.

Dominique Takizawa, 57 years old, is a graduate of the HEC Business School.

Dominique Takizawa has been secretary general of Institut Mérieux since 2001, and previously held various position within the group, both with ACCRA (since renamed Institut Mérieux) and BioMérieux. She assists executive management with the group's strategic expansion, in particular in connection with merger and acquisition transactions, relationships with other shareholders and investors, and market transactions. Previously, she held the positions of chief financial officer and controller with Institut Mérieux (since renamed Sanofi Pasteur), Mérial and Aventis CropScience, in particular during major strategic developments. She is a member of the boards of *inter alia* Mérieux NutriSciences, Transgene, Advance BioScience, and the April group.

Ekaterina Smirnyagina, 48 years old, holds a doctorate in cellular and molecular biology.

After having completed her training by obtaining a master's degree in biochemistry and attending Stanford Medical School, she began her career with the Biotechnology Business Development Council. From 2002 to 2012, she worked for Alta Partners, an investment fund company in San Francisco that specializes in the health field. Since then, she has held the position of manager with the Capricorn Partners investment fund in Belgium.

Jérôme Féraud, 38 years old**,** holds a master's degree in immunology, a post-graduate degree (DESS) with a dual specialization (scientific and technical information management) and is a graduate of ITB.

Jérome Féraud began his career in finance with Crédit du Nord in 2002 in the corporate market, after having spent one year as an independent website creator. In 2006, he joined the audit and valuation team of Viveris Management, and then the technology venture capital division in 2007. Due to his scientific and technical training, he now handles the team's flow of business, and also sits on the boards of directors of various companies in the health sector. In particular, Jérôme was appointed a director of Ipsogen when it was listed on the Alternext market in 2008.

15.2. Conflicts of interest at the level of the company's management bodies and executive management

The chairman and the directors are direct or indirect shareholders of the company (see Chapter 18 "Major Shareholders").

There are no related-party agreements.

To the company's knowledge, none of the company's directors or officers was appointed pursuant to any contract or agreement with shareholders, customers, suppliers or other parties.

To the company's knowledge, as of the filing date of this reference document, none of the persons listed in section 14.1 "Officers and directors" of this reference document has agreed to any other restriction on the sale of their equity interest in the company.

To the company's knowledge, there is no actual or potential conflict of interest between the duties to the company and the private interests and/or other duties of the persons who are members of the company's management bodies, management staff or executive management, as listed in section 14.1 "Officers and directors" above.

16. COMPENSATION AND BENEFITS

16.1. Compensation of corporate officers

The company was originally incorporated as a *société par actions simplifiée* (simplified joint stock company) which was governed by a chairman, board of directors and audit committee. It was converted into a *société anonyme* (corporation) by a resolution adopted by the general shareholders' meeting held on October 24, 2011.

The information in this chapter has been prepared with reference to the Corporate Governance Code for midcaps and small-caps published in December 2009 by MiddleNext. Tables 1, 2, 3 and 10 of the "AMF recommendation on information to be provided in prospectuses on the compensation of corporate officers, dated December 22, 2008" are presented below.

16.1.1. Table summarizing compensation, stock options and bonus shares granted to each corporate officer

(€) **Gérard Soula** - Chairman and Chief Executive Officer	**FY 2013**	**FY 2012**
Compensation owed for the fiscal year	280 000	320 500
Value of pluriannual variable compensation granted during the fiscal year	*NA*	*NA*
Value of stock options granted during the fiscal year	*NA*	*NA*
Value of bonus shares granted during the fiscal year	*NA*	*NA*
TOTAL	**280 000**	**320 500**

(€) **Olivier Soula** - Vice-President	**FY 2013**	**FY 2012**
Compensation owed for the fiscal year	191 386	210 533
Value of pluriannualvariable compensation granted during the fiscal year	*NA*	*NA*
Value of stock options granted during the fiscal year	*NA*	*NA*
Value of bonus shares granted during the fiscal year	*NA*	*NA*
TOTAL	**191 386**	**210 533**

16.1.2. Table summarizing compensation paid to each corporate officer

The tables below show the compensation owed to the corporate officers for the fiscal years ended December 31, 2012 and December 31, 2013, as well as the compensation such persons received during those same fiscal years.

(€) **Gérard Soula** - Chairman and Chief Executive Officer	FY 2013		FY 2012	
	Amounts owed (1)	**Amounts paid (2)**	**Amounts owed (1)**	**Amounts paid (2)**
Fixed compensation	230 000	230 000	220 500	220 500
Variable compensation *	50 000	50 000	50 000	70 000
Pluriannual variable compensation *	*NA*	*NA*	*NA*	*NA*
Extraordinary compensation *	*NA*	50 000	50 000	*NA*
Directors' fees	*NA*	*NA*	*NA*	*NA*
Non-cash benefits *	8 160	8 160	8 160	8 160
TOTAL	**288 160**	**338 160**	**328 660**	**298 660**

(€) **Olivier Soula** - Vice-President	FY 2013		FY 2012	
	Amounts owed (1)	**Amounts paid (2)**	**Amounts owed (1)**	**Amounts paid (2)**
Fixed compensation	151 386	151 386	130 533	130 533
Variable compensation *	40 000	30 000	30 000	50 400
Pluriannual variable compensation *	*NA*	*NA*	*NA*	*NA*
Extraordinary compensation *	*NA*	50 000	50 000	*NA*
Invension compensation	*2 800*	*2 800*	*900*	*900*
Directors' fees	*NA*	*NA*	*NA*	*NA*
Non-cash benefits *	*NA*	*NA*	*NA*	*NA*
TOTAL	**194 186**	**234 186**	**211 433**	**181 833**

(1) for the fiscal year
(2) during the fiscal year
* Bonuses set on the basis of achieving certain qualitative objectives associated with financial management controls, developing collaborations, initiating clinical trials, signing feasibility agreements, and increased expansion of the company's business.

16.1.3. History of stock subscription or purchase options granted to corporate officers

Pursuant to authorization received from the general shareholders' meeting held on June 18, 2013, the board of directors granted stock warrants ($BSA_{12\text{-}2013}$) to independent board members on December 13, 2013 (see section 15.3 for details).

16.1.4. Breakdown of compensation and other benefits granted to corporate officers

Corporate officers	**Employment contract**		**Supplemental retirement plan**		**Severance pay or benefits that will or may be due in the event the officer's position is terminated or changed**		**Payments in consideration for a covenant not to compete**	
	Yes	No	Yes	No	Yes	No	Yes	No
Gérard Soula Chairman and chief executive officer		X		X		X		X
Term of office starting date:	Board of director's meeting of October 24, 2011							
Term of office ending date:	Ordinary general shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2013							
	Yes	No	Yes	No	Yes	No	Yes	No
Olivier Soula Vice-President	X			X		X		X
Term of office starting date:	Board of director's meeting of December 19, 2012							
Term of office ending date:	Ordinary general shareholders' meeting convened to vote on the financial statements for the fiscal year ending December 31, 2013							

Directors' fees and other compensation received by non-executive corporate officers		
Non-executive corporate officers	Amounts paid in fiscal year 2013	Amounts paid in fiscal year 2012
Mr. Olivier Martinez - Director	**0**	**0**
Directors' fees (*)	0	0
Other compensation	0	0
Kurma Partners, represented by Mr. Thierry Laugel - Director**		
Directors' fees (*)	0	0
Other compensation	0	0
BPI France Investissement, represented by Mr. Laurent Arthaud - Director		
Directors' fees (*)	0	0
Other compensation	0	0
Ms. Dominique Takizawa - Director		
Directors' fees (*)	25,000	12,000
Other compensation	0	0
Ms. Ekaterina Smirnyagina - Director		
Directors' fees (*)	13,000	0
Other compensation	0	0
TOTAL	**38,000**	**12,000**

*Only Ms. Dominique Takizawa and Ms. Ekaterina Smirnyagina received directors' fees in 2013 because the company's board of directors decided to grant directors' fees to independent directors only.
**Kurma Partners, represented by Mr. Thierry Laugel, resigned its position as director on February 24, 2014.

16.2. Amounts that the company has provisioned for payment of pensions, retirement allowances and other benefits to corporate officers

As of December 31, 2013, the company recognized provisions of €32,621 for the payment of retirement benefits to Olivier Soula.

The company has not granted Mr. Soula any hiring or termination bonuses.

16.3. Bonus shares, stock warrants and stock options granted to corporate officers

Pursuant to the authority delegated by the general shareholders' meeting held on June 18, 2013, the board of directors granted 20,000 stock warrants ($BSA_{12\text{-}2013}$) to certain directors on December 13, 2013.
The $BSA_{12\text{-}2013}$ stock warrants were reserved to two independent directors, i.e., who were neither managers nor employees of the company, and who were in office at that time, as follows;

- 10,000 stock warrants to Ms. Dominique Takizawa;
- 10,000 stock warrants to Ms. Ekaterina Smirnyagina.

Each $BSA_{12\text{-}2013}$ stock warrant confers on its holder the right to subscribe for one new ordinary share of the company, with a par value of €0.10 each, in consideration for a subscription price of €5.88 per share, which is equal to the weighted average of the share price on the 20 trading days prior to the date on which the $BSA_{12\text{-}2013}$ stock warrants were granted by the board of directors on December 13, 2013, pursuant to the authority delegated by the general shareholders' meeting held on June 18, 2013.

The holders may exercise the $BSA_{12\text{-}2013}$ stock warrants, on one or more occasions, during the following periods and up to the following limits:

- Ms. Dominique Takizawa may exercise all of the $BSA_{12\text{-}2013}$ stock warrants granted to her during a period beginning on December 13, 2013 and ending on December 13, 2023.

- Ms. Ekaterina Smirnyagina may exercise all of the $BSA_{12\text{-}2013}$ stock warrants granted to her within the limits, according to the schedule, and in accordance with the conditions set out below:

    - 3,333 $BSA_{12\text{-}2013}$ stock warrants may be exercised during a period beginning on December 13, 2013 and ending on December 13, 2023;
    - 3,333 $BSA_{12\text{-}2013}$ stock warrants may be exercised during a period beginning on December 13, 2014 and ending on December 13, 2023;
    - 3,334 $BSA_{12\text{-}2013}$ stock warrants may be exercised during a period beginning on December 13, 2015 and ending on December 13, 2023.

Stock warrants not exercised by December 13, 2023 will lapse.

The characteristics of the BSA are mentioned in the template detailed in paragraph 21.1.5 of this reference document, provided that the Company has not issued any bonus shares or stock options to its executive officers as described in the tables on these two instruments in paragraph 21.1.5 of this reference document.

16.4. Summary of transactions by managers and the persons referred to in Article L. 621-18-2 of the French Monetary and Financial Code (*Code monétaire et financier*) in the company's shares during the past fiscal year

Not applicable.

17. FUNCTIONING OF SUPERVISORY AND MANAGEMENT BODIES

17.1. Management of the company

Pursuant to a resolution adopted by an extraordinary general shareholders' meeting held on October 24, 2011, the company was converted from a *société par actions simplifiée* (simplified joint stock company) into a *société anonyme* (corporation). A detailed description of the composition of the board of directors is provided in section 14.1 "Officers and directors".

During the fiscal year ended December 31, 2013, the company's board of directors met seven times. The average attendance rate for board of directors members was 94%.

Executive management of the company

Pursuant to a decision adopted on October 24, 2011, the board of directors chose to combine the functions of chairman and chief executive officer. As a result thereof, as regards third parties, the company is represented by Mr. Gérard Soula, in his capacity as chairman of the board of directors and chief executive officer.

Since December 19, 2012, he has been assisted in these duties by a vice-president, Mr. Olivier Soula.

17.2. Information on contracts between corporate officers and the company

Not applicable.

17.3. Board of administration and specialized committees – Corporate governance

17.3.1. Board of directors

17.3.1.1 Composition

The composition of the board of directors and information about its members is provided in Chapter 14 "Administrative, management, supervisory and executive management bodies" and Chapter 21.2 "Articles of incorporation and bylaws" of this reference document.

Rules of procedure were adopted on October 24, 2011, which cover *inter alia* the role and composition of the board, the rules of conduct and the obligations incumbent on the members of the company's board of directors. Each board of directors member undertakes *inter alia* to maintain his/her independence of analysis, judgment and action and to actively participate in the work of the board. Directors must inform the board of any conflicts of interests that may arise. In addition, the rules of procedure explain the laws in force concerning the disclosure and use of privileged information, and state that the directors must refrain from carrying out transactions in the company's shares if they hold privileged information. Each board of directors member is required to report to the company and to the AMF any transactions in the company's shares that they carry out directly or indirectly.

The company deems that it already has two independent directors, Ms. Dominique Takizawa and Ms. Ekaterina Smirnyagina, within the meaning of the Corporate Governance Code for midcaps and small-caps, as published in December 2009 by MiddleNext and approved as a code of reference by the AMF. Ms. Dominique Takizawa and Ms. Ekaterina Smirnyagina meet the definition of independent directors because they:

- are not employees or officers of the company, nor employees or officers of any of its subsidiaries, and have not held such position or office within the past three years;
- are not major customers, suppliers or bankers of the company, and the company does not account for a significant share of their business operations;

- are not major shareholders of the company;
- do not have close family ties with any corporate officer or major shareholder; and
- have not been auditors of the company within the past three years.

Nevertheless, recruiting one or more additional independent directors is under consideration by the company as part of its process to improve its corporate governance following the listing of the company's shares on the Euronext regulated market in Paris.

17.3.2. Specialized committees

The company has two specialized committees, the audit committee and the compensation committee.

17.3.2.1 Audit committee

17.3.2.1.1 Composition

Pursuant to a decision of the board of directors adopted on June 6, 2008, the company set up an audit committee for an indefinite period. The committee members adopted rules of procedure, as described below.

To the extent possible, the audit committee is comprised of at least two members appointed by the board of directors on the basis of a recommendation of the compensation committee. The audit committee members are chosen from among the members of the board of directors and, to the extent possible, two-thirds of its members should be independent directors, one of whom should have specific financial or accounting expertise, although all members should have a minimum understanding of financial or accounting matters.

As of the filing date of this reference document, the audit committee members are:

- Ms. Dominique Takizawa, an independent director who has financial and accounting expertise; and Mr. Olivier Martinez.
- Ms. Dominique Takizawa chairs this committee.

Ms. Takizawa is the member of the board who has "specific financial or accounting expertise" due to her experience of nearly 25 years in the pharmaceutical industry and the senior management positions she has held with Sanofi Pasteur, Biomérieux and Institut Mérieux.

17.3.2.1.2 Duties

The role of the audit committee, acting independently of the company's management, is to assist the board of directors and ensure that the financial statements are accurate, that internal controls are adequate, that information provided is pertinent, and that the statutory auditors fulfill their duties.

The audit committee's duties include:

- monitoring the process for preparing financial information;
- ensuring the effectiveness of the internal control and risk management systems;
- ensuring that the statutory auditors perform their duties with respect to the legal certification of the annual financial statements and, if applicable, the consolidated financial statements;
- making recommendations on the statutory auditors proposed for appointment to general shareholders' meetings, and reviewing the terms of their compensation;
- ensuring the independence of the statutory auditors;
- examining the conditions under which derivatives are used;
- regularly reviewing the status of major disputes; and
- in general, providing advice and making appropriate recommendations in connection with the above matters.

The audit committee's rules of procedure, which were adopted on October 24, 2011 after having been approved by the board of directors, describe the roles of the audit committee and its operating procedures, in particular the minimum number of meetings per year. These rules of procedure also state that the committee may interview any member of the company's board of directors and conduct any internal or external audits on any matter it deems to come within the scope of its duties. If it does so, the audit committee chair must give prior notice to the board of directors. In particular, the audit committee may interview any person involved in preparing or verifying the financial statements (the chief financial officer, the administrative and financial manager and the principal senior financial managers). The committee has the right to directly, independently and confidentially consult with the statutory auditors.

17.3.2.1.3 Operation

The audit committee meets at least twice a year, in accordance with a schedule set by the chair, to review the annual, semi-annual and, if applicable, quarterly financial statements, pursuant to an agenda prepared by its chair and sent to the audit committee members at least seven days before the date of the meeting. The committee may also meet at the request of its chair, two of its members, or the chairman of the company's board of directors.

The audit committee may interview any member of the company's board of directors and conduct any internal or external audits on any matter it deems to come within the scope of its duties. If it does so, the audit committee chair must give prior notice to the board of directors. In particular, the audit committee may interview any person involved in preparing or verifying the financial statements (the administrative and financial manager and the principal senior financial managers).

The audit committee is entitled to interview the statutory auditors. It may meet with them outside the presence of any company representative.

17.3.2.1.4 Reports

The audit committee chair ensures that the reports on its work that it presents to the board of directors provide complete information to the board, thus facilitating its decision-making process.

The annual report includes a presentation of the committee's work over the past fiscal year.

If in the course of its work, the audit committee becomes aware of any material risk that it does not consider is being handled appropriately, the chair must immediately inform the chairman of the board of directors.

17.3.2.2 Compensation committee

17.3.2.2.1 Composition

The compensation committee was set up on June 6, 2008. Its members adopted rules of procedure, which are described below. If possible, the committee is composed of at least two members of the board of directors appointed by the board of directors.

No board of directors member who holds a management position within the company may be a member of the compensation committee.

As of the filing date of this reference document, the compensation committee members are:

- Ms. Ekaterina Smirnyagina, independent member;
- Mr. Laurent Arthaud.

17.3.2.2.2 Duties

The compensation committee's duties include:

- reviewing the main objectives proposed by executive management with respect to compensation of company managers who are not corporate officers, including bonus share plans and stock subscription or purchase options;
- reviewing the compensation of company managers who are not corporate officers, including bonus share plans and stock subscription or purchase options, retirement and insurance plans and non-cash benefits;
- submitting recommendations and proposals to the board of directors concerning:
    - the compensation, retirement and insurance plans, non-cash benefits, and other financial rights, including severance pay, of board of directors members. The committee proposes compensation amounts and structures, in particular the rules for calculating the variable component of compensation, taking into account the company's strategies, objectives and performance, as well as market practices; and
    - bonus share plans, stock subscription or purchase options, and any other similar incentive plan, in particular benefits granted to specific members of the board of directors;
- reviewing the total amount of directors' fees and the method for distributing them among the members of the board of directors, as well as the requirements for obtaining reimbursement of expenses that board of directors members may incur;
- preparing and submitting to the board of directors any reports that may be required by the rules of procedure; and
- making any other recommendation concerning compensation that may be requested of it by the board of directors.

In general, the compensation committee provides advice and makes appropriate recommendations in connection with the above matters.

17.3.2.2.3 Operating procedures

The compensation committee meets at least twice a year, in accordance with a schedule set by the chair, pursuant to an agenda prepared by its chair and sent to the compensation committee members at least seven days before the date of the meeting. The committee may also meet at the request of its chair, two of its members, or the board of directors.

Non-executive board of directors members, who are not compensation committee members may attend the committee's meetings without restriction.

The chairman of the company's board of directors, if he is not a committee member, may be invited to attend committee meetings. The committee may request that the chairman submit proposals to it. The chairman is not entitled to vote, and may not be present during discussions concerning his personal situation.

The compensation committee may request the chairman of the board of directors to provide it with the assistance of any senior manager of the company whose expertise may facilitate dealing with a matter of business on the agenda. The compensation committee chair or the meeting chair informs all persons who attend meetings that they are bound by a duty of confidentiality.

The compensation committee met once in fiscal year 2013, in December, to assess past performances and to formulate proposals to the board of directors on the fixed and variable compensation of corporate officers, as well as on a general salary increase for company employees, and the total amount available for bonuses (excluding corporate officers).

17.3.2.2.4 Reports

The compensation committee chair ensures that the reports on its work that it presents to the board of directors provide complete information to the board, thus facilitating its decision-making process.

The annual report includes a presentation of the committee's work during the past fiscal year.

In particular, the compensation committee reviews the draft company report on executive compensation.

17.4. Statement on corporate governance

To promote transparency and public disclosure, the company has initiated a review of all of its corporate governance practices.

To comply with the requirements of Article L. 225-37 of the French Commercial Code (*Code de commerce*), the company has adopted as a code of reference the Corporate Governance Code for midcaps and small-caps published in December 2009 by MiddleNext.

The company complies with all recommendations of the Corporate Governance Code for midcaps and small-caps and, in particular, it meets the following objectives:

- the board of directors includes at least two independent members, as it has five members in total;
- the audit committee, whose current composition is in accordance with Article L.823-19 of the French Commercial Code, also complies with the recommendations of the Corporate Governance Code for midcaps and small-caps, which provide that the audit committee should have at least two independent members.

However, as of the date of this reference document, the company does not comply with:

- the 13th recommendation of the code published by MiddleNext, insofar as the number of 4 meetings per year called for specialized committees in the recommendation is not deemed necessary by the society in relation to its size and role of day each of these committees,

- the 14th recommendation of the code published by MiddleNext, which recommends that the board of directors apportion directors' fees on the basis of directors' attendance and the time they devote to their duties, as the company's board of directors has decided to grant directors' fees to independent directors only (see section 15.1.4 of this reference document).

- the 15th recommendation of the code published by MiddleNext,since the Company has not yet established procedures for assessing the work of the Board, it being specified that it intends to do so in the future.

17.5. Chairman's report on internal control

As required by Article 222-9 I of the AMF's General Regulation, and in accordance with Article L. 225-37 of the French Commercial Code, the chairman of the board of directors presents an annual report on the composition of the board, the conditions under which the board prepares and organizes its work, and the internal control and risk management procedures set up by the company. The chairman's report for 2013 can be found in Appendix I of this reference document.

In the course of its expansion, with respect to internal control, the company follows the risk management and internal control systems implementation guide for small-caps and midcaps published by the AMF on July 22, 2010.

17.6. Information required by Article L. 225-100-3 of the French Commercial Code

17.6.1. Shareholder structure of the company

See Chapter 18 of this reference document.

17.6.2. Restrictions imposed by the articles of incorporation and bylaws on exercising voting rights and share transfers or similar clauses of which the company is aware, as required by Article L. 233-11 of the French Commercial Code

Not applicable.

17.6.3. Direct or indirect equity stakes in the company of which the company is aware, as required by Articles L. 233-7 and L. 233-12 of the French Commercial Code

See Chapter 18 of this reference document.

17.6.4. List of holders of any securities with special control rights and a description of such rights

The company is not aware of the existence of any special control rights.

17.6.5. Control mechanisms included in any employee share plan in which the control rights are not exercised by the employees

The company has not set up any employee share plan that may contain control mechanisms in which the control rights are not exercised by the employees.

17.6.6. Shareholder agreements of which the company is aware that may impose restrictions on share transfers and exercising voting rights

Not applicable.

17.6.7. Rules governing the appointment and replacement of board of directors members and amendments to the articles of incorporation and bylaws

The rules governing these matters are set out in the articles of incorporation and bylaws and are in compliance with the law.

17.6.8. Powers of the board of directors, in particular the power to issue or redeem shares

The general shareholders' meeting held on June 18, 2013 renewed the authority granted to the board of directors to carry out, for a period of 18 months as of the date of the meeting, a share redemption program, in accordance with the provisions of Article L. 225-209 *et seq.* of the French Commercial Code and market practices accepted by the AMF (see section 18.1, 18.2 and 21.1.4 of this reference document).

17.6.9. Agreements entered into by the company that will be amended or terminated in the event of a change of control of the company

Not applicable.

17.6.10. Agreements that provide for compensation to board of directors members or employees if they resign or are terminated without just cause or if their employment ends due to a takeover bid

Not applicable.

18. EMPLOYEES

18.1. Human resources

18.1.1. Main key employees

The company's main managers have significant experience in managing technological innovation and partnerships with major biopharmaceutical groups, as well as in drug delivery of therapeutic proteins and in the development of medical devices.

Their experience is summarized below, with the exception of the corporate officers (Messrs. Gérard and Olivier Soula), who are discussed in section 14.1.3 "Biographies of the directors and board observer" in this reference document.

Ms. Valérie Danaguezian: Chief Financial Officer

Valérie Danaguezian is a graduate of ISC and began her career in corporate auditing and financial consulting with Calan Ramonilo et Associés, a member of Deloitte & Touche, where she stayed for four years. She then joined the Aventis Pasteur group in Lyon where, for 12 years, she was initially in charge of the group's financial consolidation, and then headed the group's research and development expenditures management control system. Thereafter, she joined Flamel Technologies as administration and financial officer. Valérie Danaguezian is specialized in the financial management of innovative research and development projects, and has acquired extensive experience in management control systems, international standards and internal controls.

Dr. José Correia: Head of the Preclinical and Clinical Department, HSQE Manager and Project Manager

José Correia holds a doctorate in biomaterials engineering from the University of Paris-Nord. He was chairman and chief executive officer of Biodex from 2002 to 2006, where he managed chemical and pharmaceutical development for nine years. He is a co-holder of four patents and has co-authored three scientific publications.

Dr. Rémi Soula: Business Development Manager and Scientific Advisor

Rémi Soula holds a doctorate in polymer chemistry from CPE Lyon. He did a post-doctorate at Max-Planck Institute in Berlin. He began his career with Flamel Technologies as a senior researcher where, over the course of three years, he acquired solid experience in the synthesis of new polymers. He is a co-holder of 30 patents and has co-authored six scientific publications.

Dr. Bertrand Alluis: Head of the Analysis Department and Project Manager

Bertrand Alluis holds a doctorate in chemistry. He did his dissertation at the CNRS polyphenols laboratory at the University of Lyon I, and studied the complex and antioxidant powers of flavonoids. He spent three years with Diatos S.A. in the field of oncology and vectorization as head of the therapeutic chemistry department. Thereafter, he joined Flamel Technologies where, for three years as senior researcher, he specialized in the development and validation of analytical methods used to characterize proteins and the formulation thereof with polymers. He is a co-holder of one patent and has co-authored four scientific publications.

Dr. David Duracher: Head of the Pharmaceutical Development and Physical Chemistry Departments

David Duracher holds a doctorate in polymer physical chemistry. His dissertation, which was financed by BioMérieux, was in the field of biomedical diagnostics, at the interface between the science of

polymers and biology. After a post-doctorate at the Key Centre for Polymer Colloids at the University of Sydney and two years' experience in the field of biochips with Apibio, he worked for Flamel Technologies on sustained release formulations for therapeutic proteins. He is a co-holder of five patents and has co-authored sixteen publications.

Dr. Martin Gaudier: Head of the Biology Department

Martin Gaudier holds an engineering degree from Ecole Polytechnique and a doctorate in structural biology and protein biochemistry. He did his dissertation in the field of structural virology, and then a four-year post-doctorate at Cancer Research UK in London on protein-DNA interactions. He has co-authored eight scientific publications and is a co-holder of two patents.

Dr. Richard Charvet: Head of the Chemistry Department

Richard Charvet earned a doctorate in organic chemistry and polymers from North Carolina State University, Raleigh, in the United States. He did a two-and-a-half year post-doctorate at Erato Nanospace Project in Tokyo, and then spent one year at the University of Wuppertal. Thereafter, he joined the National Institute for Materials Science (NIMS) in Tsukuba, Japan, as an associate researcher studying organic photoconductive nanostructures formed by supramolecular self-assembly. He is a co-holder of two patents and has co-authored fourteen scientific publications.

Dr. Violaine Desort Henin: Head of Preclinical Studies

Violaine Desort Henin is a veterinarian and toxicologist. After completing her dissertation on lasers in human medicine, focusing on transposing inter-species medical and surgical techniques to various applications (otorhinolaryngology, dermatology, spinal surgery and the lower limbs), she specialized in small animals and laboratory animals. After six years as a practitioner and surgeon in private clinics, she completed her initial training with a specialization in ophthalmology and university degrees in medicine, regulatory toxicology and clinical trials.

Dr. Joachim Garric: Head of the Analysis Department

Joachim Garric holds a doctorate in organic chemistry. He did his dissertation on the synthesis and characterization of new helicoidal capsules at the European Chemistry and Biology Institute of the University of Bordeaux I. He then did a post-doctorate on the synthesis and characterization of new HCI receptors in cancer cells at the University of Southampton. He has co-authored eight scientific publications.

Mr. Walter Roger: Head of the Industrial Property Department

Walter Roger holds a doctorate in organic chemistry and a degree from the International Intellectual Property Studies Center (CEIPI) with specialization in trademarks and designs. He is also a professional representative accredited by the European Patent Office (EPO). Walter began his career with the Regimbeau firm, and then worked for various industrial property firms. At his last position with Rhodia, he consolidated his experience in drafting patent applications, overseeing the examination procedure, providing right-of-use opinions, and studying patentability.

18.1.2. Number and breakdown of employees

At the end of the periods under review, the company's workforce experienced the following changes:

Workforce at year-end	FY 2013	FY 2012
Management	4	4
Research and development	57	56
Support functions	12	11
Total positions	**73**	**71**
Total full-time equivalent workforce	**69,2**	**66,6**

As of December 31, 2013, the company had 73 workers (both full-time and part-time), including 1 blue-collar employee, 35 technicians and 37 management-level employees. Of these employees, 25 hold a doctorate in science, medicine or pharmacy, i.e., more than one-third of the company's employees.

18.1.3. Employee representatives

The company had two employee representatives, one incumbent and one alternate, who were elected on December 15, 2011 for a four-year term. At the end of 2012, the company reached the statutory number of workers for setting up a single employee representative body (*délégation unique du personnel*) and a health, safety and working conditions committee (CHSCT), which were set up in March 2013 (see section 17.7 below).

18.2. Financial instruments conferring equity rights in the company granted to the top ten employees who are not corporate officers

Bonus shares

The table below shows the number of bonus shares that have been granted:

Name	Number of bonus shares granted	Date granted	Shares vested and available	Shares vested that are within the lock-in period	End of the lock-in period	Shares cancelled	Shares granted but not yet vested
Rosy Eloy	8 400	1/23/2008	4 200	2 100	2 100 (jan. 2014)	2100 (*)	
Valérie Danaguezian	14 000	1/23/2008	7 000	7 000	3 500 (jan. 2014) 3 500 (jan. 2015)		
Bertrand Alluis	5 600	06/06/2008	2 800	2 800	1 400 (jan. 2014) 1 400 (jan. 2015)		
José Correia	5 600	1/23/2008	2 800	2 800	1 400 (jan. 2014) 1 400 (jan. 2015)		
David Duracher	8 400	1/23/2008	4 200	4 200	2 100 (jan. 2014) 2 100 (jan. 2015)		
Martin Gaudier	5 600	1/23/2008	2 800	2 800	1 400 (jan. 2014) 1 400 (jan. 2015)		
Violaine Desort-Hénin	5 600	12/15/2009	1 400	2 800	1 400 (dec. 2014) 1 400 (dec. 2015)		1 400
Richard Charvet	5 600	03/05/2010		2 800	1 400 (march 2014) 1 400 (march 2015)		2 800
Emmanuel Dauty	2 800	12/07/2010		1 400	1 400 (dec. 2014)		1 400
Grégory Meiffren	2 800	12/07/2010		1 400	1 400 (dec. 2014)		1 400
TOTAL	**64 400**		**25 200**	**30 100**			**7 000**

(*) Ms. Rosy Eloy left the company at the end of October 2012. Therefore, the 2,100 shares of the fourth tranche were cancelled.

Business founders' stock warrants (BSPCE)

Pursuant to a delegation of authority granted by the ordinary and extraordinary general shareholders' meeting held on June 18, 2013, the board of directors, at its meeting of December 13, 2013, decided to grant, free of charge, a total of 50,400 business founders' stock warrants to certain company employees, entitling them to subscribe for 50,400 new shares with a par value of €0.10.

Pursuant to that decision, the board of directors set up:

- Business founders' stock warrants plan no. 1, which grants 28,000 business founders' stock warrants to employees whose employment contract with the company or promotion predates January 1, 2013;
- Business founders' stock warrants plan no. 2, which grants 22,400 business founders' stock warrants to employees whose employment contract with the company or promotion is subsequent to January 1, 2013, or to any other employee pursuant to a specific proposal of the company's management.

Each beneficiary may exercise, at a price of €5.76 per warrant, one-fourth of the business founders' stock warrants on January 1 of each year, with the first tranche becoming exercisable on January 1, 2014 (plan no. 1) or January 1, 2015 (plan no 2). Business founders' stock warrants must be exercised within ten years from the date they are granted, i.e., no later than December 13, 2023. At the end of the ten-year period from the date the business founders' stock warrants are issued, business founders' stock warrants that have not been exercised will lapse and cease to confer the right to subscribe for shares in the company.

As of the filing date of this reference document, the company has received all subscription forms from eligible employees.

18.3. Equity interests and stock options held by corporate officers

The direct and indirect equity interests of board of directors members and the number of securities that confer equity rights in the company that they hold as of December 31, 2013 are shown below:

Name	Number of shares held directly	Number of shares held by tied entities [1]	% of the company's capital	Securities
Mr. Gérard Soula	898 463		14,5%	None
Mr. Olivier Soula	317 490		5,1%	None
Kurma Partners, represented by Mr. Thierry Laugel [2]		683 710 [4]	11,0%	None
Bpifrance Investissement, represented by Mr. Laurent Arthaud [3]		1 041 840 [4]	16,8%	None
TOTAL	**2 941 503**		**-**	**None**

[1] "Tied entities" means entities with which the member has capital or contractual ties (such as delegated management authority) or ties pursuant to articles of incorporation provisions.
[2] Pursuant to portfolio management authority, Kurma Partners represents Fonds IdInvest, a shareholder that holds an 11.01% stake in the company. Kurma Partners, represented by Mr. Thierry Laugel, resigned from its position as director on February 24, 2014.
[3] CDC Entreprises is the management company for the Innobio fund and for sub-fund II of the Bioam 1B fund, which hold a 16.77% stake in the company (11.27% and 5.50%, respectively).

(4) Not including bearer shares, if any.

18.4. Equity interests held by employees

As of the filing date of this reference document, the company's employees held 683,980[70] shares, i.e., 11.01% of the company's capital and 13.04% of its voting rights. Of these shares, 52,500 are bonus shares, representing 0.84% of the company's capital, all of which are within the lock-in period.

On the last day of fiscal year 2013, employees' equity interest in the company, calculated in accordance with Article L. 225-102 of the French Commercial Code (i.e., shares held in a corporate savings plan provided for in Article L. 3332-1 *et seq.* of the French Labor Code or an employee shareholding fund (FCPE)) was 0%.

18.5. Discretionary profit sharing agreement (*intéressement*)

Not applicable.

18.6. Mandatory profit sharing agreement (*participation*)

In 2013, the company prepared a mandatory profit sharing agreement, which was submitted to the single representative body in December 2013. This agreement, which applies to all employees with more than six months' seniority with the company at the fiscal year-end, took effect on January 1, 2014.

The amounts granted to all beneficiaries, known as the mandatory profit sharing special reserve fund, are calculated in accordance with the statutory formula.

18.7. Employment information required by Article R. 225-105-1 of the French Commercial Code

18.7.1. Employment

The main objectives of Adocia's human resources policy are to:

- attract, retain and motivate the most competent talent necessary to enable development of the company's ambitious innovative projects;
- provide training opportunities to employees;
- promote internal mobility so as to offer employees a broader scope of activities and enable them to gain new expertise.

18.7.1.1 Workforce

At the end of December 2013, the company had 73 workers (both full-time and part-time), including 1 blue-collar employee, 35 technicians and 37 management-level employees. Of these employees, 66 are on permanent employment contracts and 7 are on fixed-term employment contracts (5 on apprenticeship contracts and 2 on fixed-term contracts entered into due to temporary increases in business).

The company's leading managers have broad experience in technological innovation management and in partnerships with major biopharmaceutical groups, as well as in drug delivery of therapeutic proteins and in the development of medical devices. All employees are based in Lyon, at the company's registered office at 115 Avenue Lacassagne.

---

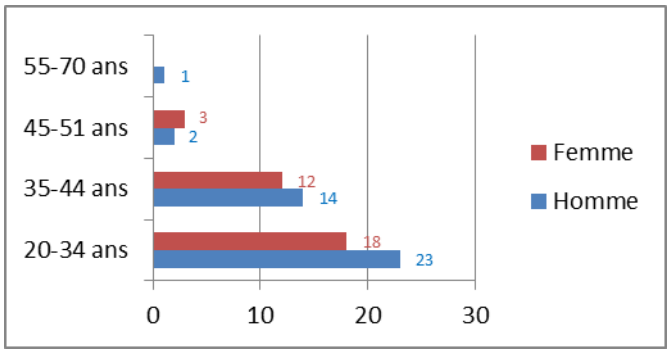
[70] Including the 634,980 shares held by Olivier and Rémi Soula, which represent 10.22% of the company's capital and 12.36% of its voting rights.

At the end of December 2013, the company employed 25 researchers who hold a doctorate in science, medicine or pharmacy, i.e., over one-third of all employees.

As of December 31, 2013, over 80% of the workforce was assigned directly to research and development, with the remaining employees performing support functions, such as accounting, administrative services, quality control, intellectual property and human resources.

As of December 31, 2013, the average age of the company's employees was 34. The staff was 55% male and 45% female.

The graph below shows the distribution of employees by age and sex:



18.7.1.2 Personnel movements in 2013

In 2013, the company signed eight permanent employment contracts and eight fixed-term employment contracts (including five apprenticeship contracts).

During the same period, eight fixed-term employment contracts expired (including four apprenticeship contracts and one work-training contract), there was one resignation by a trailing spouse, and four employment contracts were terminated during the probationary period.

The company must remain competitive and attractive in order to appeal to the best talents and retain them. To do so, it has an ambitious compensation policy, which includes significant yearly pay increases. Thus, over the last three years, average general and individual pay increases were in the range of 4% to 6%, plus bonuses on the basis of collective and individual performances.
Pay increases and/or bonuses are granted on the basis of objective criteria and individual merit. Employees are treated equally in employment matters without distinction as to race, sex, color, religion, disability, family situation, sexual orientation, age or ethnic origin.

18.7.2. Work organization

Employees' employment contracts are governed by the pharmaceutical industries collective bargaining agreement.
In 2010, the company implemented an organization of working hours agreement, the provisions of which reflect the flexibility and latitude necessary for research activities.
Pursuant to this agreement, the working time of management-level employees (groups VI to IX of the pharmaceutical industries collective bargaining agreement classification) is counted in days and the working time of technicians (employees in groups I to V) is counted in hours. The standard working time for technicians is 35 hours per week, which may be increased, in which case employees are entitled to offsetting days off.

In 2013, seven employees worked part-time. All of these employees choose to work part-time to deal with family responsibilities.
The main reasons for absences in 2013 were illness and maternity and paternity leaves.
The absenteeism rate was 2.14%. This rate is a percentage calculated by dividing the total number of workdays lost (days off due to illness, workplace accidents, sick children) by the theoretical number of work days per year. Planned absences, such as maternity and paternity leaves, are excluded from this calculation.
In 2013, absences were primarily sick leave days and “sick children days”. In 2013, the absenteeism rate was impacted by one employee who was on extended sick leave following a motorcycle accident that required a full-time leave of absence of 91 days, followed by a half-time medical leave of 100 days.

18.7.3. Labor relations

In 2012, the company reached the statutory number of workers for setting up a single employee representative body, which the company set up in 2013. This single representative body combines the powers of employee representatives and of the works council in a single elected body, and assigns the duties of the works council to the employee representatives. The single representative body is comprised of:

- 2 incumbent members and 2 alternates for the non-management group;
- 1 incumbent member and 1 alternate for the management group.

The company ensures that the rights and freedoms of the representatives of employee representative bodies are scrupulously respected, and that these representatives enjoy the same career perspectives and training opportunities as other employees.

Management and the employee representative bodies jointly and freely decide the common measures to be taken to guarantee the development of a progressive and quality industrial relations policy by maintaining an ongoing and constructive labor-management dialogue.

All Adocia employees are based in France. The company complies with the fundamental conventions of the International Labor Organization on respect for the freedom of association and the right to collective bargaining, the elimination of discrimination in respect of employment and occupation, the elimination of forced or compulsory labor, and the abolition of child labor.

18.7.4. Health and safety

The company has a two-person Health, Safety and Environment department. About a dozen persons in the company’s various departments have received first aid at work training. Individual and collective safety equipment has been installed and is inspected regularly. Evacuation drills are held according to a predetermined schedule. Fire safety equipment and electrical systems are inspected annually by certified organizations.

In March 2013, the company held an election for representatives to the health, safety and working conditions committee, which has three incumbent members.

Quarterly meetings are held, which are attended by the Health and Safety department.

In 2013, the company recorded two accidents that resulted in medical leave (one fainting spell and one motorcycle accident).

A workplace accident means any accident that is suffered due to or during work by any person who is a company employee or who is performing work for the company.

Workplace accidents also include commuting accidents that occur in the course of ordinary travel by an employee between his/her home and workplace (round trip).
The company recorded 33 minor incidents, 42% of which involved needle sticks and cuts to hands.
In 2013, the frequency and severity rates of workplace accidents were 14.95 and 0.11, respectively. These rates are calculated using the following formulas:

- Frequency rate = (number of workplace accidents and commuting accidents resulting in medical leave / hours worked) x 1,000,000
- Severity rate = (number of days lost due to temporary disabilities as a result of a workplace accident or commuting accident / hours worked) x 1,000,000

No occupational or work-related illness was reported in 2013 or during the previous two fiscal years. An occupational illness means an illness due to a person's exposure to a risk in connection with his/her employment position. The company has not been informed of any permanent disability in this fiscal year or prior fiscal years.

The company pays for a medical examination for all employees, with varying frequencies depending on the nature of employees' positions. Laboratory personnel undergo a medical examination, including a blood test, every 18 months, and administrative personnel are examined every two years.
To date, no agreement on occupational health and safety has been signed with the labor unions or employee representatives.

18.7.5. Training

Staff members have extensive training and the company places particular importance on maintaining each employee's knowledge and expertise at a high level. Continuing education focuses on the following areas: communication in English, development of cross-disciplinary skills, training in the use of new tools and materials, and regulatory watch. Each year, all employees receive general training on a theme of interest to the company as a whole. In 2013, this training day was devoted to India, its history, culture and specificities.

In 2013, the company planned to devote a significant budget to training, i.e., 1.6% of payroll for the period between March 2013 and March 2014. Ultimately, in fiscal year 2013, training expenditures were about 1% of payroll because certain training programs were cancelled or postponed until 2014.
In 2013, the company offered a total of 2,117 hours of training, and 60 persons attended at least one training program during the year.

Furthermore, in order to develop individual skills and maintain a high level of expertise, the company encourages all researchers to attend international conferences and seminars.

In 2013, no training initiatives were undertaken pursuant to individual training rights (DIF).

18.7.6. Equality in the workplace

To promote the recruitment of disabled workers, the company has taken steps to hire disabled workers, in particular holding meetings with CAP Emploi, the national placement network for disabled persons. Despite these actions and the fact that all positions are open to disabled persons, the company has received few applicants (problem of skills not matching the position profile). At the end of December 2013, the company had no employees in its workforce recognized as having disabled worker status.

The company uses a disabled workers' assistance center to provide it with various services.

18.7.7. Gender equality action plan

After having consulted the single employee representative body in December 2013, an action plan was scheduled to take effect on January 1, 2014, in accordance with Article L. 2242-5-1 of the French Labor Code and Decree no. 2011-822 of July 7, 2011 on the implementation of companies' gender equality obligations (Articles R. 2242-2 to R. 2242-8 of the French Labor Code).

This plan focuses primarily on the following three points:

- Workforce: The Company will continue to hire its employs on the basis of objective expertise criteria and individual merit. If candidates have equal qualifications, the company will opt in favor of female applicants in two fields in which women are underrepresented (analysis and chemistry).
- Training: The Company will ensure that training, whether to develop each employee's business skills or to enable them to adapt to changes in the company, is accessible to and equal for both men and women.
- Compensation: The Company will continue its policy of compensating men and women equally.

19. MAJOR SHAREHOLDERS

19.1. Change in the company's capital structure over the past two years on an undiluted basis

The following detailed table of the shareholding structure on an undiluted basis reflects the 10-for-1 stock split approved by the shareholders' meeting on October 24, 2011 and the conversion of all shares into ordinary shares on the date of admission of the company's shares to the Euronext regulated market in Paris, i.e. February 20, 2012.

	Situation at December 31, 2013			Situation at December 31, 2012			Situation au 31 décembre 2011		
	Number of shares	% of capital	% of voting rights	Number of shares	% of capital	% of voting rights	Nombre d'actions	% du capital	% des droits de vote
Soula Family	**1 550 933**	**25,0%**	**29,7%**	**1 551 720**	**25,0%**	**29,5%**	**1 551 720**	**34,8%**	**36,7%**
Gérard Soula	898 463	14,5%	16,9%	899 250	14,5%	16,9%	899 250	20,2%	21,3%
Olivier Soula	317 490	5,1%	6,2%	317 490	5,1%	6,2%	317 490	7,1%	7,5%
Rémi Soula	317 490	5,1%	6,2%	317 490	5,1%	6,2%	317 490	7,1%	7,5%
Laure Soula	17 490	0,3%	0,3%	17 490	0,3%	0,3%	17 490	0,4%	0,4%
Financial investors	**2 916 042**	**46,9%**	**53,5%**	**3 077 962**	**49,7%**	**55,8%**	**2 881 790**	**64,6%**	**63,0%**
Innobio	700 020	11,3%	13,6%	700 020	11,3%	13,6%	700 020	1,5%	0,8%
BioAM fund	341 820	5,5%	6,7%	341 820	5,5%	6,6%	341 820	15,3%	15,4%
Sub total BpiFrance Investissement	*1 041 840*	*16,8%*	*20,3%*	*1 041 840*	*16,8%*	*20,2%*	*1 041 840*	*16,9%*	*16,3%*
IdInvest fund	683 710	11,0%	13,3%	683 710	11,0%	13,3%	683 710	15,7%	13,9%
Amundi fund	179 890	2,9%	3,5%	341 810	5,5%	6,6%	341 810	7,7%	7,7%
Viveris fund	364 754	5,9%	6,9%	364 754	5,9%	6,9%	341 820	23,4%	21,6%
Oréo Finance	191 343	3,1%	2,2%	191 343	3,1%	2,2%	170 910	7,7%	8,0%
Deleage Trust	68 360	1,1%	1,3%	68 360	1,1%	0,7%	68 360	7,7%	8,2%
SHAM[(1)]	386 145	6,2%	6,0%	386 145	6,2%	6,0%	233 340	3,8%	3,4%
Key employees	**49 000**	**0,8%**	**0,7%**	**35 000**	**0,6%**	**0,4%**	**25 200**	**5,2%**	**5,6%**
warrants)							-		
Directors (stock warrants)								0,6%	0,3%
Treasury shares	**40 326**	0,6%		**62 848**	**1,0%**	-	-	-	
Other shareholders*	**1 655 575**	**26,7%**	**16,2%**	**1 470 346**	**23,7%**	**14,3%**	-		
Total	**6 211 876**	**100,0%**	**100,0%**	**6 197 876**	**100,0%**	**100,0%**	**4 458 710**	**100,0%**	**100,0%**

*Including any shares held in bearer form by the company's long-standing financial investors.

(1) SHAM: Société Hospitalière d'Assurance Mutuelles

As of the registration date of this reference document, the company had no knowledge of any significant changes in its shareholding structure after December 31, 2013.

19.2. Distribution of capital and voting rights as of December 31, 2013 on a fully diluted basis

The following detailed table of the shareholding structure reflects the 10-for-1 stock split approved by the shareholders' meeting on October 24, 2011 and the conversion of all shares into ordinary shares on the date of admission of the company's shares to the Euronext regulated market in Paris, i.e. February 20, 2012.

	Situation at December 31, 2013 on an undiluted basis			Situation at December 31, 2013 on a fully diluted basis [1]		
	Number of shares	% of capital	% of voting rights	Number of shares	% of capital	% of voting rights
Soula Family	**1 550 933**	**25,0%**	**29,7%**	**1 550 933**	**24,6%**	**29,4%**
Gérard Soula	898 463	14,5%	16,9%	898 463	14,3%	16,8%
Olivier Soula	317 490	5,1%	6,2%	317 490	5,0%	6,1%
Rémi Soula	317 490	5,1%	6,2%	317 490	5,0%	6,1%
Laure Soula	17 490	0,3%	0,3%	17 490	0,3%	0,3%
Financial investors	**2 916 042**	**46,9%**	**53,5%**	**2 916 042**	**46,3%**	**53,1%**
Innobio (Bpifrance Investissement)	700 020	11,3%	53,5%	700 020	11,1%	13,5%
BioAM fund (Bpifrance Investissement)	341 820	5,5%	53,5%	341 820	5,4%	6,6%
Sub total BpiFrance Investissement	*1 041 840*	*16,8%*	*107,0%*	*1 041 840*	*16,6%*	*20,1%*
IdInvest fund	683 710	11,0%	13,3%	683 710	10,9%	13,2%
Amundi fund	179 890	2,9%	3,5%	179 890	2,9%	3,5%
Viveris fund	364 754	5,9%	6,9%	364 754	5,8%	6,8%
Oréo Finance	191 343	3,1%	2,2%	191 343	3,0%	2,2%
Deleage Family[2]	68 360	1,1%	1,3%	68 360	1,1%	1,3%
SHAM (*)	386 145	6,2%	6,0%	386 145	6,1%	6,0%
Key employees	49 000	0,8%	0,7%	109 200	1,7%	1,3%
Scientific committee (stock warrants)				2 100	0,0%	0,0%
Directors (stock warrants)				20 000	0,3%	0,2%
Treasury shares	40 326	0,6%		40 326	0,6%	
Other shareholders [3]	1 655 575	26,7%	16,2%	1 655 575	26,3%	16,0%
TOTAL	**6 211 876**	**100,0%**	**100,0%**	**6 294 176**	**100,0%**	**100,0%**

(*) SHAM: Société Hospitalière d'Assurance Mutuelles

(1) As of the date of this reference document, the dilutive instruments issued by the company consist of (i) 64,400 shares (after taking into account the 10-for-1 stock split approved by the shareholders' meeting on October 24, 2011) granted free of charge by the company to key employees, 9,800 of which are in the vesting period as described in detail in paragraph 21.1.5 of this reference document, (ii) 2,100 stock warrants giving a right to subscribe for 2,100 shares (after taking into account the 10-for-1 stock split approved by the shareholders' meeting on October 24, 2011), (iii) 20,000 stock warrants giving a right to subscribe for 20,000 shares granted to independent directors, and (iv) 50,400 start-up company stock warrants giving a right to subscribe for 50,400 shares.

(2) With the stipulation that the 68,360 shares are owned equally by Messrs. André Jean Deleage, Michel William Deleage, Emmanuel Yves Deleage and Philippe Olivier Deleage, i.e. 17,090 shares each.

(3) Including any shares held in bearer form by the company's long-standing financial investors.

19.3. Major shareholders not represented on the board of directors

The following major shareholders of the company are represented on the board of directors as follows:

- the Innobio and Bioam funds, which own 16.77% of the company's shares, are represented by Bpifrance Investissements.
- Viveris, which owns 5.87% of the company's shares, acts as censeur (non-voting member).

Société Hospitalière d'Assurance Mutuelles (SHAM), which owns 6.22% of the company's shares, and IDInvest, which owns 11.01% of the company's shares, are not represented on the board of directors.

19.4. Voting rights of major shareholders

A voting right double that which is conferred on other shares, based on the portion of share capital they represent, is assigned to all fully paid-up shares (regardless of their class) registered in the name of the same shareholder for at least two years, it being stipulated that the conversion of preferred shares into ordinary shares has no impact on the calculation of the holding period.

This right is also conferred at the time of issue, in case of a capital increase by capitalization of reserves, earnings or issue premiums, to registered shares granted free of charge to a shareholder in exchange for old shares for which this right is already enjoyed.

19.5. Control of the company

As of the registration date of this reference document, no single shareholder owned a percentage likely to raise a presumption of control of the company within the meaning of Article L. 233-3 of the French Commercial Code (*Code de commerce*).

The company has therefore not been required to take measures to ensure that such control is not improperly exercised.

A shareholders' agreement that existed at the end of 2011 became null and void when the shares were admitted to trading on the Euronext regulated market in Paris in February 2012.

To the company's knowledge, there are no shareholders acting in concert.

19.6. Agreements that can lead to a change in control

No specific element of the issuer's instrument of incorporation, bylaws, charter or regulations could have the effect of delaying, deferring or preventing a change in its control.

19.7. Pledges of the company's shares

None.

20. RELATED-PARTY TRANSACTIONS

The regulated agreements that exist to date are mentioned in the special reports of the statutory auditors presented below.

20.1. Intra-group agreement

None

20.2. Related-party transactions

None

20.3. Statutory auditors' report on regulated agreements made for the fiscal year ended December 31, 2013

Adocia

Shareholders' meeting held to approve the financial statements for the fiscal year ended December 31, 2013

Statutory Auditors' Special Report
on Regulated Agreements and Commitments

ODICEO
115, boulevard de Stalingrad
B.P. 52038
69616 Villeurbanne Cedex
Limited liability company with €275,000 in share capital

Statutory Auditor
Member of the Compagnie
Régionale de Lyon

ERNST & YOUNG et Autres
Tour Oxygène
10-12, boulevard Marius Vivier Merle
69393 Lyon Cedex 03
Simplified joint stock company with variable capital

Statutory Auditor
Member of the Compagnie
Régionale de Versailles

Adocia

Shareholders' meeting held to approve the financial statements for the fiscal year ended December 31, 2013

Statutory Auditors' Special Report on Regulated Agreements and Commitments

Dear Shareholders,

In our capacity as your company's statutory auditors, we present to you our report on regulated agreements and commitments.

It is our responsibility to inform you, based on the information provided to us, of the characteristics and essential terms and conditions of the agreements and commitments brought to our attention or about which we may have learned during the course of our audit, without our being required to comment on their usefulness and relevance or to determine the existence of other agreements and commitments. It is your responsibility, pursuant to Article R. 225-31 of the Commercial Code, to assess the advantage of entering into these agreements and commitments with a view to their approval.

It is also our responsibility, where applicable, to provide you with the information referred to in Article R. 225-31 of the Commercial Code regarding the performance, during the previous fiscal year, of the agreements and commitments already approved by the shareholders' meeting.

We have conducted the work that we deemed necessary in accordance with the accounting standards of the *Compagnie nationale des commissaires aux comptes* that apply to this audit.

Agreements and commitments subject to the approval of the shareholders' meeting

We inform you that we have not been advised of any agreement or commitment authorized during the previous fiscal year which is subject to the approval of the shareholders' meeting pursuant to Article L. 225-38 of the Commercial Code.

Agreements and commitments already approved by the shareholders' meeting

We inform you that we have not been advised of any agreement or commitment already approved by the shareholders' meeting which remained in force during the previous fiscal year.

Villeurbanne and Lyon, March 24, 2014

The statutory auditors

ODICEO	ERNST & YOUNG et Autres
Sylvain Boccon-Gibod	Sylvain Lauria

21. FINANCIAL INFORMATION CONCERNING THE COMPANY'S ASSETS, FINANCIAL POSITION AND EARNINGS

21.1. Individual financial statements prepared under IFRS for the fiscal years ended December 31, 2012 and 2013

Balance Sheet, IFRS

STATEMENT OF FINANCIAL POSITION ASSETS - (in € thousands)	Notes	12/31/2013	12/31/2012
Goodwill			
Intangible assets		3	13
Laboratory equipment	3.2	528	555
Other property, plant and equipment	3.2	418	384
Holdings in affiliates			
Financial assets	3.3	244	329
Deferred tax assets			
NON-CURRENT ASSETS		**1 194**	**1 281**
Inventories	3.5	124	103
Other current financial assets			
Trade and similar receivables	3.6	2	316
Current tax assets			
Other current assets	3.7	3 993	4 465
Cash and cash equivalents		19 415	30 462
CURRENT ASSETS		**23 535**	**35 345**
**** GRAND TOTAL ****		**24 729**	**36 627**

STATEMENT OF FINANCIAL POSITION LIABILITIES - (in € thousands)	Notes	12/31/2013	12/31/2012
Share capital		621	620
Share premium		48 810	48 498
Group translation gains and losses			
Group reserves		(26 008)	(20 095)
Group net profit/loss		(4 293)	(5 995)
NON-CONTROLLING INTERESTS			
EQUITY	3.9	**19 130**	**23 028**
Long-term financial debt	3.10	1 814	2 046
Long-term provisions	3.11	252	198
Deferred tax liabilities			
Other non-current liabilities			
NON-CURRENT LIABILITIES		**2 066**	**2 244**
Provisions			
Short-term financial debt	3.13	420	396
Other current financial liabilities	3.13	83	23
Trade and similar payables	3.12	1 784	3 824
Other current liabilities	3.12	1 245	7 111
CURRENT LIABILITIES		**3 532**	**11 354**
**** GRAND TOTAL ****		**24 729**	**36 627**

Income Statement, IFRS

STATEMENT OF COMPREHENSIVE INCOME (in € thousands)	Notes	12/31/2013	12/31/2012
Revenue	3.15	5 588	3 995
Other income	3.16	3 233	3 241
Total income		**8 822**	**7 236**
Operating expenses excluding additions and reversals	3.14	(12 764)	(12 887)
Additions to and reversals of depreciation,	3.19	(360)	(419)
PROFIT/LOSS FROM ORDINARY OPERATING ACTIVITIES		**(4 302)**	**(6 070)**
Other operating income and expenses			0
PROFIT/LOSS FROM ORDINARY OPERATING ACTIVITIES		**(4 302)**	**(6 070)**
Financial income		169	142
Financial expense		(160)	(66)
FINANCIAL INCOME/EXPENSE	3.20	**9**	**75**
PROFIT/LOSS BEFORE TAX		**(4 293)**	**(5 995)**
Tax expense			
NET PROFIT/LOSS		**(4 293)**	**(5 995)**
Non-controlling interests			
GROUP NET PROFIT/LOSS		**(4 293)**	**(5 995)**
Base earnings per share (€)	3.22	(0,7)	(1,0)
Diluted earnings per share (€)		(0,7)	(1,0)
GROUP NET PROFIT/LOSS		**(4 293)**	**(5 995)**
Other comprehensive income			
TOTAL PROFIT/LOSS FOR THE YEAR		**(4 293)**	**(5 995)**

Cash Flow Statement, IFRS

STATEMENT OF CASH FLOWS (in € thousands)	12/31/2013	12/31/2012
Net profit/loss	**(4 293)**	**(5 995)**
Net depreciation, amortization & provisions (excl. current assets)	387	393
Capital gains and losses on non-current assets		
Calculated income and expenses	271	(9)
Cash flow from operations after cost of net financial debt and tax	**(3 635)**	**(5 611)**
Cost of net financial debt		
Tax expense (including deferred taxes)		
Cash flow from operations before cost of net financial debt and tax	**(3 635)**	**(5 611)**
Taxes paid		
Change in working capital requirement (including employee benefits)	**(7 160)**	**6 530**
NET CASH FLOW GENERATED BY OPERATING ACTIVITIES	**(10 796)**	**919**
Acquisitions of property, plant and equipment & intangible assets	(428)	(747)
Disposals of property, plant and equipment & intangible assets	85	
Acquisitions of non-current financial assets		(27)
Disposals of non-current financial assets	400	
Other cash flows related to investing activities		(1 000)
NET CASH FLOW RELATED TO INVESTING ACTIVITIES	**57**	**(1 774)**
Capital increase		25 333
New loans and reimbursable advances	91	800
Repayments of loans and reimbursable advances	(400)	(720)
Net financial interest paid		
Other cash flows related to financing activities		
NET CASH FLOW RELATED TO FINANCING ACTIVITIES	**(309)**	**25 413**
CHANGE IN NET CASH AND CASH EQUIVALENTS	**(11 047)**	**24 558**
Opening cash	30 462	5 905
Closing cash	19 415	30 462

Detailed analysis of changes in working capital requirement (WCR):

WORKING CAPITAL REQUIREMENT (in € thousands)	Change 2013/2012	Change 2012/2011
Inventories	(22)	(10)
Trade and similar receivables	313	7 724
Other receivables and advances	373	(1 376)
Pre-paid expenses / other receivables	98	(53)
Provision - employee benefits	0	0
Trade and similar payables	2 058	(2 053)
Other debt	230	(175)
Unearned income / other debt	5 636	1 982
Change in working capital requirement	**(7 160)**	**6 530**

Components of net cash and cash equivalents analyzed by type and reconciliation with the balance sheet:

NET CASH AND CASH EQUIVALENTS (in € thousands)	12/31/2013	12/31/2012
Short-term investment securities (due in < 3 months)	15 765	27 581
Cash on hand	3 650	2 881
Net cash and cash equivalents	**19 415**	**30 462**

Statement of Changes in Equity, IFRS

CHANGES IN EQUITY (in € thousands)		Number of shares	Capital	Additional paid-in capital	Reserves and profit	Group total equity
	12/31/2011	**4 458 710**	**446**	**24 038**	**(20 154)**	**4 329**
Profit/loss for the period					(5 995)	(5 995)
Capital increase		1 723 066	172	27 190		27 362
Share-based payments		16 100	2	(2)	59	59
Other comprehensive income						
Capital increase expenses				(2 030)		(2 030)
Other				(698)		(698)
	12/31/2012	**6 197 876**	**619**	**48 498**	**(26 090)**	**23 028**
Profit/loss for the period					(4 293)	(4 293)
Capital increase						
Share-based payments		14 000	1	(1)	86	86
Other comprehensive income						
Capital increase expenses						
Other				314	(5)	309
	12/31/2013	**6 211 876**	**621**	**48 811**	**(30 302)**	**19 129**

NOTES TO THE FINANCIAL STATEMENTS PREPARED UNDER IFRS

1. Presentation of business activity and major events

1.1. Information about the company and its activity

Adocia is a simplified joint stock company (*société par actions simplifiée*) formed under French law on December 22, 2005.
It specializes in the development of best-in-class medicines from already approved therapeutic protein and anti-cancer molecules.
The company owned 100% of a subsidiary (BIODEX) from March 9, 2006 to August 26, 2011, at which time all of its assets and liabilities were transferred.

Adocia's financial statements under IFRS for the fiscal year ended December 31, 2013 were approved for publication by the board of directors on March 21, 2014.

1.2. Major events of the fiscal year ended December 31, 2013

The year 2013 marked the end of the collaboration with the Eli Lilly group, with which the company had signed a licensing agreement in December 2011 for the development and marketing of a fast-acting insulin analog, Humalog, formulated with BioChaperone® technology.
Adocia subsequently reacquired the rights to its technology applied to insulin analogs and ownership of all the results generated during the agreement.
These 20 months of collaboration with a major player in the field of insulin enabled the company to take in €9.4 million (€7.6 million of which in up-front payments), develop an optimized formula, obtain initial clinical results and acquire expertise in the development of ultra-fast acting insulin.
Following the announcement on July 25, 2013 of the end of the collaboration, the company continued to actively develop this project and prepared a phase 2a clinical trial, the launch of which was announced in early January 2014. The purpose of this clinical trial is to confirm, on type I diabetes patients, the positive clinical results obtained during the phase I trial conducted by Eli Lilly in Singapore in July 2012.

In 2013, the company pursued the clinical development of its two other insulin projects: the formulation of a fast-acting human insulin (HinsBet®) and the formulation of a combination of long-acting insulin and fast-acting insulin. For this latter project, a phase I-II clinical trial was launched in mid-November 2013. Through this trial, conducted on 20 type I diabetes patients, it will be possible to compare the performance of the combo (combination of long-acting insulin glargine and a fast-acting insulin analog) with that of the HumalogMix® product marketed by Lilly.

For its wound healing project, and more specifically the project for the treatment of diabetic foot ulcers, in 2013 the company had not yet obtained authorization from the Indian authorities to launch the phase III clinical trial in India.

Finally, in 2013 the company obtained an exclusive license for a new technology that improves the efficacy of anti-cancer agents by targeting their action into tumors. This technology, developed by the CNRS and the University of Bordeaux, was particularly effective in pre-clinical studies.
This new platform allows the company to enter the field of oncology and its research will be focused primarily on the treatment of ovarian cancer.

1.3. Events subsequent to year end

None.

2. Accounting methods and principles used to draw up the financial statements

2.1. Principles used to draw up the company's financial statements

Declaration of compliance

In accordance with EU regulation 1606/2002 of July 19, 2002 on international standards, the company's year-end financial statements were prepared according to the standards and interpretations published by the International Accounting Standards Board (IASB) and adopted by the European Union as of the reporting date.

These standards, available on the website of the European Commission (http://ec.europa.eu/internal_market/accounting/ias_fr.htm), include the international accounting standards (IAS and IFRS) and the interpretations of the Standing Interpretations Committee (SIC) and the International Financial Interpretations Committee (IFRIC).

Principles used to prepare the financial statements

The company's financial statements were prepared based on the historical cost principle, with the exception of certain categories of assets and liabilities according to the rules set out in the IFRS. The relevant categories are indicated in the following notes.

Going concern

The going concern assumption was used given the company's financial ability (available cash assets) to meet its financing requirements over the next 12 months.

Accounting principles and methods

The accounting principles and methods used by the company for the year-end financial statements are the same as those used in the financial statements for the year ended December 31, 2012.

The income recognized at December 31, 2013 (€43,000) following the introduction of the tax credit for competitiveness and employment (CICE) is recorded in the financial statements in accordance with IAS 19 as a deduction from payroll expense.

In addition, the new mandatory texts applicable to fiscal years beginning on January 1, 2013 are as follows:

- Amendments to IAS 1 – Presentation of Financial Statements – presentation of other comprehensive income (applicable to fiscal years beginning on or after July 1, 2012);
- Amendments to IAS 12 – Deferred Tax: Recovery of Underlying Assets (applicable to fiscal years beginning on or after January 1, 2013);
- Amendments to IAS 19 – Employee Benefits - Accounting for defined benefit plans (applicable to fiscal years beginning on or after January 1, 2013);
- Amendments to IFRS 7 – Financial instruments: Disclosures (applicable to fiscal years beginning on or after January 1, 2013);
- IFRS 13 – Fair Value Measurement (applicable to fiscal years beginning on or after January 1, 2013);
- IAS 16 – Property, Plant and Equipment (applicable to fiscal years beginning on or after January 1, 2013).

These new standards are not being developed as part of the interim financial reporting since the impacts are considered immaterial.

Therefore, the amendment to IAS 19 did not give rise to a retroactive restatement given its immaterial impact.

New standards, amendments and interpretations applicable at a later date and adopted by the European Union:

- Amendments to IAS 32 – Financial Instruments: Presentation (applicable to fiscal years beginning on or after January 1, 2014).
- IFRS 10 – Consolidated Financial Statements (applicable to fiscal years beginning on or after January 1, 2014);
- IFRS 11 – Joint Arrangements (applicable to fiscal years beginning on or after January 1, 2014);
- IFRS 12 – Disclosure of Interests in Other Entities (applicable to fiscal years beginning on or after January 1, 2014);
- Revised IAS 28 – Investments in Associates and Joint Ventures (applicable to fiscal years beginning on or after January 1, 2014);
- Amendments to IFRS 10, 11 and 12: transitional provisions (applicable to periods beginning on or after January 1, 2013).

The company has not applied these interpretations in advance. None is expected to have a material impact on the financial statements.

2.2. Use of judgments and estimates

To prepare the financial statements in accordance with IFRS, certain estimates, judgments and assumptions have been made by the company's management, which may have affected the amounts shown for the assets, liabilities and contingent liabilities as of the date of preparation of the financial statements, and the amounts shown for income and expenses during the year.

These estimates are based on the going concern assumption and are based on the information available at the time they were made. They are assessed continuously based on past experience and various other factors deemed reasonable which form the basis of the estimates of the carrying amount of the assets and liabilities. The estimates may be revised if the circumstances on which they were based change or as a result of new information. Actual results may differ significantly from these estimates based on different assumptions or conditions.

In preparing its year-end financial statements, the main judgments made by management and the main assumptions used are the same as those used to prepare the financial statements for the fiscal year ended December 31, 2012.

2.3. Functional presentation currency

The company's financial statements are prepared in euros, which is the presentation currency and functional currency of the parent company and its subsidiary.

2.4. Current/non-current distinction

The balance sheet presentation used by the company makes a distinction between current and non-current assets and liabilities.

This distinction is made based on the following rules:

- assets and liabilities that fall within the scope of the company's operating working capital requirement are classified as "current";
- assets and liabilities that are not part of the company's normal operations are presented as "current" or "non-current" based on whether their due date is more than or less than one year.

2.5. Intangible assets

Research and development:

In accordance with IAS 38, internal research costs are recognized as expenses as soon as they are incurred.
Development costs are capitalized if and only if the following criteria are met:
- (a) technical feasibility needed to complete the development project is established,
- (b) the company intends to complete the project,
- (c) the company is able to use the intangible asset,
- (d) the company is able to demonstrate the probability that the asset will generate future economic benefits,
- (e) the company has the technical, financial and other resources to complete the project, and (f) the development costs are measured reliably.

Patents:

The costs incurred prior to filing and obtaining patents are capitalized by the company based on the same provisions as those used to capitalize development costs.

Other intangible assets:

Intangible assets acquired separately by the company are recognized at cost and those acquired through a business combination are recognized at fair value.
Concessions, licenses and software are amortized over the expected useful life (two to five years depending on the type of software).

2.6. Property, Plant and Equipment

Property, plant and equipment are recognized at their original cost. They are then measured at cost less any accumulated depreciation and impairment, with the exception of acquisitions of parking lots, which the company has chosen not to depreciate.

Depreciation is calculated on a straight-line basis according to the estimated useful life of the assets and, if applicable, the residual values:

	Life
Fixtures and facilities	1 to 6 years
Laboratory equipment	3 to 5 years
Furniture, office equipment	5 years

An item of property, plant and equipment is derecognized when it is disposed of or when no future economic benefits are expected from its use or disposal. Any gain or loss resulting from the derecognition of an asset (difference between the net proceeds and carrying amount of the asset) is included in the income statement for the year in which derecognition occurs.

The residual values, useful lives and depreciation methods of assets are reviewed and, if necessary, adjusted at each year-end closing. Such adjustments are treated as changes in estimate.

The depreciation of property, plant and equipment is recognized in profit or loss under depreciation and amortization.

2.7. Leasing (including lease financing)

Where applicable, an asset held under a finance lease (which substantially transfers all the risks and rewards of ownership of the asset to the company) is recorded as an asset and a liability (in the same amount) on the balance sheet at the lower of the fair value of the asset and the sum of the discounted payments.

These assets are depreciated according to the same methods and rules described above in note 2.6. The corresponding liabilities are recorded on the balance sheet and repaid in an amount equal to the theoretical amortization of loans whose characteristics are comparable to those of the lease agreements.

Operating lease agreements are recorded as expenses on a straight-line basis over the term of the agreement until its expiration.

2.8. Borrowing costs

Borrowing costs directly attributable to the acquisition, construction or production of an asset that takes a substantial amount of time to prepare for its intended use or sale are included in the cost of the asset. All other borrowing costs are recorded as financial expenses for the fiscal year in which they are incurred. Borrowing costs include interest and other costs that an entity incurs to borrow funds.

2.9. Recoverable amount of non-current assets

Assets with an indefinite useful life are not depreciated and are subject to an annual impairment test. Depreciated assets are subject to an impairment test whenever there is an internal or external indicator that an asset may be impaired.

Impairment testing entails comparing the net carrying amount of the tested asset to its recoverable amount. The test is performed at the cash generating unit level, which is the smallest group of assets that includes the asset and whose continuous use generates cash inflows that are largely independent of those generated by other assets or groups of assets.

Impairment is recorded in the amount by which the carrying amount of an asset exceeds its recoverable amount. The recoverable amount of an asset is the higher of its fair value less costs of disposal and its value in use.

Fair value less costs of disposal is the amount that can be obtained from the sale of an asset in an arm's length transaction between well-informed, consenting parties, less costs of disposal.

Value in use is the present value of the estimated future cash flows expected to be derived from the continuous use of an asset and from its disposal at the end of its useful life. Value in use is determined according to cash flow projections generally made on the basis of five-year budgets or forecasts. For periods after five years, cash flows are extrapolated using a steady or declining growth rate and discounted at long-term after-tax market rates that reflect market estimates of the time value of money and the risks specific to the asset. The terminal value is determined based on the discounting of the last cash flow of the test to infinity.

As of December 31, 2013, there is no internal or external impairment indicator for any non-current assets.

2.10. Basis of measurement of inventories

Inventories are recognized at the lower of cost and net realizable value. The cost of inventories is determined using the first-in first-out method.

2.11. Financial assets

Financial assets are classified into four categories based on their type and the intention to hold them:

- held-to-maturity investments,
- financial assets at fair value through profit or loss,
- loans and receivables,
- available-for-sale financial assets.

With the exception of assets at fair value through profit or loss, all financial assets are initially recognized at cost, which corresponds to the fair value of the price paid plus acquisition costs.
All regular way purchases and sales of financial assets are recognized on the settlement date.

Held-to-maturity investments:

Held-to-maturity investments are financial assets which the company intends and is able to hold to maturity. After their initial recognition, these assets are measured at amortized cost, using the effective interest method, less the amount of any impairment.

Financial assets at fair value through profit or loss:

This category represents assets held for trading, i.e. assets acquired by the company for the purpose of selling them in the short term. They are measured at fair value and changes in fair value are recorded in profit or loss. Certain assets can also be voluntarily classified in this category.

Loans and receivables:

Non-current financial assets include advances and guarantee deposits given to third parties. Advances and guarantee deposits are non-derivative financial assets with fixed or determinable payments that are not quoted in an active market. Such assets are recognized at amortized cost using the effective interest method. Gains and losses are recorded in profit or loss when the loans and receivables are derecognized or impaired.

Available-for-sale financial assets:

This category includes all other financial assets. They are measured at fair value and changes in fair value are recorded in profit or loss until the asset is sold, cashed in or disposed of in any other way or until it is shown that the asset has been impaired in a prolonged and significant manner. In such cases, the profit or loss, recognized until then in equity, is transferred to profit or loss.
Available-for-sale financial assets are tested for impairment when impairment indicators exist.
When the available-for-sale financial asset is an equity instrument, impairment is final. Subsequent increases in fair value are recognized directly in equity.
When the available-for-sale financial asset is a debt instrument, any subsequent increase is recorded in profit or loss in an amount equal to the impairment loss previously recorded in profit or loss.

Purchases and sales of financial assets are generally recognized on the trade date.

The only financial assets measured at fair value are cash and cash equivalents, which include short-term investment securities (money market mutual funds in euros) quoted in an active market. They therefore constitute level 1 financial assets at fair value.

Cash reserve of the liquidity agreement:

The cash reserve related to the liquidity agreement for the buyback of the company's own shares is recorded as non-current financial assets.

2.12. Cash and cash equivalents

Cash and short-term deposits recorded on the balance sheet include bank balances, cash on hand and short-term deposits with an initial maturity of less than three months.

Cash equivalents are held for trading purposes, readily convertible to a known cash amount and subject to an insignificant risk of changes in value. They are measured at fair value and changes in value are recorded in financial profit or loss.

For the purposes of the statement of cash flows, net cash includes cash and cash equivalents as defined above, net of bank overdraft facilities. In the balance sheet, bank overdrafts are shown in Current financial liabilities.

2.13. Reimbursable advances

The company receives a certain amount of government assistance in the form of reimbursable advances.

Government grants are recognized as assets when there is reasonable assurance that:

- the company will comply with the conditions attached to the grants; and
- the grants will be received.

Reimbursable advances are recognized as "long-term financial debt" or "short-term financial debt" depending on their due date. In case of failure to repay the grant, the debt write-off is recognized in "Grants, government financing and tax credits".
These advances were recognized in accordance with IAS 20. Since they are financial advances granted at below-market interest rates, they are measured according to IAS 39 if the impacts are material.

2.14. Equity

Classification in equity depends on the specific analysis of the characteristics of each instrument issued. Ordinary shares and preferred shares have therefore been classified as equity instruments.

The incidental costs directly attributable to the issue of shares or stock options are accounted for as a deduction from equity, net of tax.

Treasury shares held by the company under a liquidity agreement are recognized at their acquisition cost as a reduction in equity. The gain or loss on disposal of these treasury shares is also recognized directly in equity.

2.15. Share-based payments

In accordance with IFRS 2, benefits granted to certain employees in the form of share-based payments are measured at the fair value of the instruments granted.

This payment can take the form of equity-settled instruments or cash-settled instruments.

The company has introduced several equity-settled payment plans.

For example, stock options are granted to senior managers, certain company employees and other private individuals.

The company uses the Black-Sholes model to measure the fair value of these options. This model takes into account the features of the plan (strike price, exercise period), market data on the grant date (risk-free interest rate, volatility, expected dividends) and grantee behavior assumptions. Changes in value subsequent to the grant date have no impact on this initial measurement.

The value of the options is based on their expected term. This value is recorded as payroll expense or external charges as follows: the fair value of the options granted is determined on the grant date and recognized in profit or loss over the vesting period (period between the grant date and the plan maturity date).

For bonus shares, the fair value is also determined based on the features of the plan, market data on the grant date and an assumption of continued employment at the end of the vesting period. If the plan does not specify vesting conditions, the expense is recognized in full when the plan is granted; otherwise, the expense is recorded over the vesting period based on the conditions being met.

2.16. Provisions

Provisions are recorded when the company has a present obligation (legal or constructive) resulting from a past event, it is probable that an outflow of resources representing economic benefits will be needed to settle the obligation, and the amount of the obligation can be measured reliably. If the company expects the full or partial reimbursement of the provision (for example under an insurance policy), the reimbursement is recognized as a separate asset, but only if the reimbursement is virtually certain. The expense related to the provision is shown in the income statement net of any reimbursement. If the effect of the time value of money is material, provisions are discounted using a pre-tax rate that reflects, where appropriate, the risks specific to the liability. When discounting is used, the increase in the provision related to the passage of time is recognized as a borrowing cost.

Provisions correspond to risks and charges that are specifically identified. They are classified as non-current or current liabilities based on their nature, purpose and duration.

2.17. Corporate commitments

In accordance with IAS 19, retirement plans, similar payments and other employee benefits that are considered defined benefit plans (plan in which the company agrees to guarantee a defined amount or benefit level) are recorded in the balance sheet based on an actuarial assessment of the obligations on the closing date, reduced by the fair value of the plan assets. These calculations mainly include:

- an assumption related to the benefit payment date;
- a financial discount rate;
- an inflation rate;
- assumptions related to salary increases, employee turnover rate and mortality rate.

The main actuarial assumptions made at December 31, 2013 are described in note 3.11.

Actuarial gains and losses include the effects on the obligation of changes in the calculation assumptions and experience adjustments to the obligation. These gains and losses are recognized in other comprehensive income for post-employment benefits.

The provision shown on a specific line of the balance sheet represents the total obligation on the closing date, adjusted, where appropriate, for past service costs. Past service costs related to a plan

change are recognized immediately in the income statement for the portion of rights already acquired, and are spread out over the average period remaining until the corresponding benefits are vested.

The expense for the year consists of the cost of services rendered, which represents an operating expense, and the accretion expense, which represents a financial expense.

2.18. Financial liabilities

Financial liabilities are classified into two categories and include:

- financial liabilities recognized at amortized cost, and
- financial liabilities recognized at fair value through profit or loss.

Financial liabilities recognized at amortized cost:

Loans and other financial liabilities, such as conditional advances, are generally recognized at amortized cost calculated using the effective interest rate.
Loans and conditional advances are initially recorded at the fair value of the amount received, less directly attributable transaction costs. After the initial recognition, interest-bearing loans are measured at amortized cost using the effective interest method.
The portion of debt due in less than one year is presented as a current liability.

Financial liabilities at fair value through profit or loss:

This category represents liabilities held for trading, i.e. liabilities that are intended to be sold in the short term. They are measured at fair value and changes in fair value are recorded in the income statement.

2.19. Receivables and liabilities denominated in foreign currencies

Receivables and liabilities denominated in foreign currencies are recognized at the exchange rate at the time of the initial transaction. At the end of the fiscal year, the items corresponding to assets and liabilities are measured at the closing rate or at the hedging rate, where appropriate.

2.20. Current and deferred tax

Current tax assets and liabilities for the fiscal year and previous fiscal years are measured at the amount expected to be collected from or paid to the tax authorities. The tax rates and tax laws used to determine these amounts are those enacted or substantively enacted as of the closing date.
Deferred taxes are recognized using the liability method of tax allocation for all temporary differences existing as of the closing date between the tax base of the assets and liabilities and their carrying amount on the balance sheet, as well as for tax loss carryforwards.
A deferred tax asset, generated by tax losses, is recognized when there is persuasive evidence that a sufficient taxable profit will be available.

2.21. Revenue

Revenue corresponds to the fair value of the consideration received or receivable for goods and services sold in the normal course of the company's business. Revenue is shown net of value-added tax, returns of merchandise, rebates and discounts.

In the normal course of its business, the company may enter into commercial agreements with pharmaceutical groups. Payment under these agreements is generally based on:

- The payment of a signing bonus (access fees or up-front payment),
- Payment for specific developments based on the attainment of technical milestones (milestone payments),

- Payment for research and development efforts (collaborative agreements),
- Future sales of products (royalties).

The company recognizes revenue when the amount can be measured reliably, it is probable that future economic benefits will flow to the company, and specific criteria are met for each of the company's activities.

With regard to licenses, an initial payment (up-front fee) may be stipulated in the agreement. If the company has fulfilled all its obligations at closing, the amount has been definitively received and the company is not obligated to provide additional services over the term of the agreement, this initial payment is recognized immediately in the income statement for the fiscal year. Adocia considers the circumstances and facts to determine whether such payments received should be spread out over the entire payment period of the agreement or recognized immediately.

To date, the company's revenue corresponds primarily to revenue generated for research and development services which are assessed based either on the attainment of technical milestones or on the accrued cost method. Where appropriate, impairment may be recorded when the collectibility of the invoiced amounts is uncertain.

2.22. Other income

Grants:

Due to its innovative nature, since its creation the company has received a certain amount of assistance and grants from the French government and public authorities to help finance its operation or recruit specific individuals.

These grants are recognized as income over the fiscal year in which the corresponding costs or expenses are recorded.

Research tax credit:

The French government grants research tax credits to companies to encourage them to conduct technical and scientific research. Companies that can substantiate expenditures meeting the required criteria (research costs in France or, since January 1, 2005, within the European Community or in another State that is part of the Agreement on the European Economic Area and has signed a tax treaty with France containing an administrative assistance clause) are eligible for a tax credit that can be used to pay the corporation tax due for the fiscal year in which the expenses are incurred and the following three fiscal years or, where appropriate, be reimbursed for the excess share of such tax.

Innovative startup:

Since the beginning of 2013, the company is no longer eligible as an innovative startup that carries out research and development projects.

2.23. Segment information

To date, the company has not identified distinct operating segments. For the most part, the company's operations involve regenerative medicine for the treatment of chronic diseases. All the assets and operating income presented are located in France.

2.24. Presentation of the income statement

The company presents its income statement by nature.
The purpose of the expenses is provided in note 3.14.

Research and development costs:

Internal and external costs related to the research and development of new products.

Administrative expenses:

Total costs of the support and central management functions.

Other operating income and expenses:

Information appears in this item when a significant event occurring during the accounting period could give a distorted view of the company's performance.
Other operating income and expenses include income and expenses that are very limited in number and unusual given their frequency, nature or amount.

Operating profit/loss:

Operating profit/loss includes all income and expenses directly related to the company's activities, whether such income and expenses are recurrent or result from one-time decisions or operations.

Financial income/expense:

Financial income/expense includes all:

- Expenses related to financing the company: interest paid and accretion expense on reimbursable advances
- Income related to interest received.

Foreign-exchange gains and losses are also recognized in financial income/expense.

2.25. Earnings per share

Basic earnings per share is calculated by dividing the profit or loss attributable to holders of the company's shares by the weighted average number of ordinary shares outstanding during the period.

Diluted earnings per share is determined by adjusting the profit or loss attributable to holders of ordinary shares and the weighted average number of ordinary shares outstanding for the effects of all dilutive potential ordinary shares.

2.26. Fair value of financial instruments

Fair value measurements are detailed by level according to the following fair value hierarchy:

- the instrument is quoted in an active market (level 1);
- measurement uses valuation techniques based on observable inputs, either directly (price) or indirectly (price derivatives) (level 2);
- at least one material component of fair value is based on unobservable inputs (level 3).

Fair value of financial instruments traded in active markets is based on quoted prices on the balance sheet date. A market is considered active if quoted prices are easily and regularly available from an exchange, trading officers, brokers, an appraiser or a regulatory agency and such prices are based on regular trades. These instruments are classified as level 1.

Fair value of financial instruments that are not quoted in an active market (for example, over-the-counter derivatives) is determined based on valuation techniques. These methods maximize the use of observable market inputs, if available, and, for the most part, are not based on the company's own estimates. If all the elements required to calculate the fair value of the instrument are observable, this instrument is classified as level 2.

If one or more of the main calculation elements are not based on observable market inputs, the instrument is classified as level 3.

3. Additional information regarding certain balance sheet and income statement items

3.1. Intangible assets

INTANGIBLE ASSETS (in € thousands)	GROSS AMOUNT	AMORTIZATION AND IMPAIRMENT	NET AMOUNT
Value at December 31, 2012	**63**	**50**	**13**
Acquisitions/(Additions)	11	20	(9)
(Disposals)/reversals	(1)	(0)	(1)
Value at December 31, 2013	**73**	**70**	**3**

Intangible assets consist of software.

Given the risks and uncertainties related to regulatory authorizations and the R&D process, the six criteria for recognition of intangible assets are not considered as being met for any of the pending development projects. As a result, all costs incurred by the company are recognized as expenses. The same is true for costs related to patents.

The amounts recognized as expenses are provided in note 3.14.

3.2. Property, plant and equipment

GROSS AMOUNT (in € thousands)	Laboratory equipment	Fixtures and facilities	Furniture, office equipment	Total
Total value at December 31, 2012	**1 439**	**530**	**533**	**2 502**
Acquisitions	268	140	26	434
Disposals	(85)			(85)
Total value at December 31, 2013	**1 623**	**670**	**558**	**2 852**

DEPRECIATION AND IMPAIRMENT (in € thousands)	Laboratory equipment	Fixtures and facilities	Furniture, office equipment	Total
Total value at December 31, 2012	**885**	**323**	**356**	**1 564**
Additions	209	45	87	341
Reversals/Disposals				0
Total value at December 31, 2013	**1 094**	**368**	**443**	**1 905**

NET AMOUNT (in € thousands)	Laboratory equipment	Fixtures and facilities	Furniture, office equipment	Total
Total value at December 31, 2012	**554**	**207**	**177**	**938**
Total value at December 31, 2013	**529**	**302**	**116**	**947**

The company owns several assets financed through leasing. It holds two agreements. The first concerns an asset with an acquisition cost of €68,000 financed for three years and the second concerns equipment with a total acquisition cost of €85,000 financed for four years. The first agreement will expire in January 2014.

3.3. Non-current financial assets

The company's non-current financial assets are as follows:

NON-CURRENT INVESTMENTS (in € thousands)	GROSS AMOUNT	AMORTIZATION AND IMPAIRMENT	NET AMOUNT
Value at December 31, 2012	**330**		**330**
Acquisitions/(Additions) (Disposals)/reversals	(86)		(86)
Value at December 31, 2013	**244**		**244**

Non-current financial assets consist mainly of guarantee deposits paid under operating lease agreements and the cash reserve related to the liquidity agreement (refer to paragraph entitled "Capital management" in note 3.10.).

3.4. Additional information regarding deferred taxes

The company cannot determine with sufficient reliability when it will be able to reduce its accumulated losses. Therefore, the company has not recognized deferred tax assets related to these losses.

The amount of deferred tax assets not recognized for prior carry-over losses was €11.7 million at December 31, 2012 and €7.7 million at December 31, 2013.

3.5. Inventories

The net value of inventories was €103,000 at December 31, 2012 and €124,000 at December 31, 2013.

There is no impairment of inventories.

3.6. Receivables

TRADE RECEIVABLES (in € thousands)	12/31/2013	12/31/2012
Gross amount	**2**	**316**
Impairment		
Total net value	**2**	**316**

All receivables are not yet due.

3.7. Other current assets

OTHER CURRENT ASSETS (in € thousands)	12/31/2013	12/31/2012
Research tax credit	3 214	3 061
VAT claims	244	822
Receivables from suppliers	269	219
Pre-paid expenses	250	348
Miscellaneous	17	15
Total other current assets	**3 993**	**4 465**

All other current assets are due in less than one year.

The company has benefited from a research tax credit since its creation. It requests and obtains reimbursement of the declared research tax credit in the year following the end of the relevant fiscal year.

Pre-paid expenses relate to current expenses.

In addition to social security claims and other sundry creditors, the miscellaneous item includes grants receivable.

3.8. Classification and fair value of financial assets

FINANCIAL ASSETS (in € thousands)	2013	Value on the balance sheet under IAS 39				2013
	Value on the balance sheet	Assets at fair value through profit or loss	Held-to-maturity investments	Loans and receivables	Available-for-sale financial assets	Fair value
Non-current financial assets						
Trade receivables	2			2		2
Other current financial assets	3 993			3 993		3 993
Cash on hand	3 650	3 650				3 650
Cash equivalents (UCITS)	15 765	15 765				15 765
Total assets	**23 410**	**19 415**		**3 996**		**23 410**

FINANCIAL ASSETS (in € thousands)	2012	Value on the balance sheet under IAS 39				2012
	Value on the balance sheet	Assets at fair value through profit or loss	Held-to-maturity investments	Loans and receivables	Available-for-sale financial assets	Fair value
Non-current financial assets						
Trade receivables	316			316		316
Other current financial assets	4 465			4 465		4 465
Cash on hand	2 881	2 881				2 881
Cash equivalents (UCITS)	27 581	27 581				27 581
Total assets	**35 243**	**30 462**		**4 781**		**35 243**

The only financial assets measured at fair value are cash and cash equivalents, which include money market mutual funds in euros, time accounts quoted in an active market and interest-bearing accounts. They therefore constitute level 1 financial assets at fair value.

3.9. Equity

For easier cross-reference between the two periods, the number of shares in fiscal year 2011 has been restated to reflect the decision by the shareholders' meeting on October 24, 2011 to approve a 10-for-1 stock split and to grant 10 shares, each with a par value of €0.10, for a previously held share with a par value of €1.

Share capital

The company was created on December 22, 2005. All the shares issued are fully paid-up.
The company owns treasury shares under its liquidity agreement.
Following the initial public offering, preferred shares were converted into ordinary shares and the Ratchet stock warrants became null and void.

	Number of shares (*)	Ordinary shares	Preferred shares - category A	Preferred shares - category B	Nominal amount (euros)
At January 1, 2007	**140 000**			**140 000**	**1 400 000**
10/19/2007 - Capital increase	93 339		93 339		933 390
12/20/2007 - Capital increase	46 668		46 668		466 680
10/22/2009 - Reduction of par value					-2 520 063
10/22/2009 - Capital increase	119 007		119 007		119 007
01/20/2010 - Grant of bonus shares	1 050	1 050			1 050
04/06/2010 - Capital increase	5 424		5 424		5 424
06/06/2010 - Grant of bonus shares	140	140			140
06/18/2010 - Capital increase	1 283		1 283		1 283
12/10/2010 - Capital increase	37 630		37 630		37 630
03/04/2011 - Grant of bonus shares	1 050	1 050			1 050
06/17/2011 - Grant of bonus shares	140	140			140
10/24/2011 - Reduction of par value	4 011 579	21 420	2 730 159	1 260 000	0
12/15/2011 - Grant of bonus shares	1 400	1 400			140
02/14/2012 - Issue of IPO shares	1 592 798	1 592 798			159 280
02/14/2012 - Conversion of preferred shares to ordinary shares		4 433 510	-3 033 510	-1 400 000	0
03/07/2012 - Grant of bonus shares	10 500	10 500			1 050
03/17/2012 - Issue of IPO shares	130 268	130 268			13 027
06/15/2012 - Grant of bonus shares	2 800	2 800			280
12/19/2012 - Grant of bonus shares	2 800	2 800			280
03/26/2013 - Grant of bonus shares	8 400	8 400			840
06/18/2013 - Grant of bonus shares	2 800	2 800			280
12/13/2013 - Grant of bonus shares	2 800	2 800			280
At December 31, 2013	**6 211 876**	**6 211 876**	**0**	**0**	**621 188**

Stock warrants

Stock options were granted (i) to certain employees in the form of start-up company stock purchase warrants ("BSPCE") and (ii) to two independent directors on the board of directors in the form of stock purchase warrants ("BSA").

The main characteristics of the stock purchase warrants and the principal assumptions used to measure the fair value of the options based on the Black-Sholes model are as follows:

situation at 12/31/2013	**$BSPCE_{12\text{-}2013}$ Plan No. 1**	**$BSPCE_{12\text{-}2013}$ Plan No. 2**	**$BSA_{12\text{-}2013}$**
Recipients	employees	employees	independent directors
Number of warrants issued	28 000	22 400	20 000
Number of warrants granted	28 000	22 400	20 000
Number of warrants subscribed	28 000	22 400	20 000
Date of shareholders' meeting	06/18/2013		
Date of Board of Directors' meeting	12/13/2013		
Issue price	free		0,588 €
Strike price	5,76 €		5,88 €
Deadline to exercise warrants	12/13/2023		
Start date to exercise options	1/4: Jan. 1, 2014 1/4: Jan. 1, 2015 1/4: Jan. 1, 2016 1/4: Jan. 1, 2017	1/4: Jan. 1, 2015 1/4: Jan. 1, 2016 1/4: Jan. 1, 2017 1/4: Jan. 1, 2018	13,333 on Jan. 1, 2014 3,333 on Jan. 1, 2015 3,333 on Jan. 1, 2016
Parity	One warrant for one share		
Dividend yield	none		
Volatility	67%		
Risk-free rate of return	2% (iBoxx Sovereign AA 7-10)		

	Number of shares
Options granted in 2013	70 400
Options exercised in 2013	-
Canceled or expired options	-
Outstanding options at 12/31/2013	**70 400**
Exercisable options at closing	-

The cost of services rendered is recognized as a payroll expense and external charge over the vesting period. The total expense was €81,000 as of December 31, 2013.

Bonus shares

Bonus shares have been granted to certain employees of the company since 2008.
Movements in bonus shares are as follows:

Date of shareholders' meeting / Type	**No. of rights granted**	**No. of shares issued**	**No. of rights canceled**	**Maximum number of shares to be issued**
01/20/2008 - Bonus shares	42 000	(39 900)	(2 100)	
06/06/2008 - Bonus shares	11 200	(5 600)	(5 600)	
12/15/2009 - Bonus shares	5 600	(4 200)		1 400
03/05/2010 - Bonus shares	5 600	(2 800)		2 800
12/07/2010 - Bonus shares	5 600	(2 800)		2 800
At December 31, 2013	**70 000**	**(55 300)**	**(7 700)**	**7 000**

BONUS SHARES - Date of ESM decision	20/12/2007				20/12/2007				20/12/2007			
Date of grant by the Board of Directors	01/23/2008				06/06/2008				12/15/2009			
Number of vesting years	2	3	4	5	2	3	4	5	2	3	4	5
Performance condition	No	No	No	No	No	No	No	No	No	No	No	No
Total number of bonus shares granted	10 500	10 500	10 500	10 500	1 400	1 400	1 400	1 400	1 400	1 400	1 400	1 400
Share value on grant date (euros)	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57
Fair value of a bonus share (euros)	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57
Initial valuation (€ thousands)	90	90	90	90	12	12	12	12	12	12	12	12
Number of bonus shares to be issued at 12/31/2012	-	-	-	**10 500**	-	-	-	**1 400**	-	-	**1 400**	**1 400**
Number of bonus shares granted												
Number of bonus shares canceled				(2 100)								
Number of bonus shares definitively granted				(8 400)				(1 400)			(1 400)	
Number of bonus shares to be issued at 12/31/2013	-	-	-	-	-	-	-		-	-		**1 400**
2012 accounting expenses (€ thousands)		19				4				9		
2013 accounting expenses (€ thousands)		-17				1				5		

BONUS SHARES - Date of ESM decision	20/12/2007				20/12/2007				Total
Date of grant by the Board of Directors	03/05/2010				12/07/2010				
Number of vesting years	2	3	4	5	2	3	4	5	
Performance condition	No	No	No	No	No	No	No	No	
Total number of bonus shares granted	1 400	1 400	1 400	1 400	1 400	1 400	1 400	1 400	64 400
Share value on grant date (euros)	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	
Fair value of a bonus share (euros)	8,57	8,57	8,57	8,57	8,57	8,57	8,57	8,57	
Initial valuation (€ thousands)	12	12	12	12	12	12	12	12	552
Number of bonus shares to be issued at 12/31/2012	-	**1 400**	**1 400**	**1 400**	-	**1 400**	**1 400**	**1 400**	**23 100**
Number of bonus shares granted									0
Number of bonus shares canceled									-2 100
Number of bonus shares definitively granted		-1 400				-1 400			-14 000
Number of bonus shares to be issued at 12/31/2013	-	-	**1 400**	**1 400**	-		**1 400**	**1 400**	**7 000**
2012 accounting expenses (€ thousands)		10				15			58
2013 accounting expenses (€ thousands)		6				9			5

The cost of services rendered is recognized as a payroll expense over the vesting period. The total expense was €59,000 at December 31, 2012 and €4,500 at December 31, 2013.

Dividends

The company has not paid out any dividends over the last three years.

Capital management

The group's policy is to maintain a solid capital base in order to safeguard investor and creditor confidence and support future business development.

To this end, a liquidity agreement was signed in March 2012 with Banque BIL (now called DSF Market). This agreement was suspended on April 23, 2013 and reactivated on June 25, 2013 with a €0.4 million decrease in the amount of resources allocated. As of December 31, 2013, under this agreement 40,326 treasury shares were recognized as a deduction from equity and cash in the amount of €215,000 was recorded as long-term financial assets.

3.10. Long-term financial debt

As of December 31, 2012 and 2013, reimbursable advances accounted for most of the long-term financial debt. Details about these advances and repayment terms are available in note 3.1 to the individual financial statements prepared under French GAAP for the fiscal years ended December 31, 2012 and 2013 provided in Chapter 20.3 of this reference document.

At the end of 2013, the classification as current and non-current was as follows:

FINANCIAL DEBT (in € thousands)	**Current**	**Non-current**	**Total**	**Bank overdrafts**
Reimbursable advances	396	2 046	2 441	
Other financial debt	23		23	0
Total financial debt	**419**	**2 045**	**2 464**	**0**

Details about advances granted and repayment in fiscal year 2013:

REIMBURSABLE ADVANCES	**(in € thousands)**	**Historical cost**	
Value at December 31, 2012	**2 441**	**2 750**	(A)
Long-term portion	*2 046*		
Short-term portion	*396*		
Grant during the year	91	91	
Repayment during the year	(400)	(400)	
Discount on grant during the year	(5)		
Financial expenses	106		
Value at December 31, 2013	**2 234**	**2 441**	(B)
Long-term portion	*1 814*		
Short-term portion	*420*		
	-0		

The fair value of the new advance received in 2013 was determined based on a 3% interest rate.

(A) in € thousands	**12/31/2012**	**Less than 1 year**	**1 to 5 years**	**More than 5 years**
Osteoporosis advance	1 950	400	1 550	
Insulin advance (2012)	800	0	130	670

(B) in € thousands	**12/31/2013**	**Less than 1 year**	**1 to 5 years**	**More than 5 years**
Osteoporosis advance	1 550	450	1 100	
Insulin advance (2012)	800	0	280	520
Coface advance (2013)	91		91	

3.11. Provisions

PROVISIONS (in € thousands)	Employee benefits	Other long-term provisions	Provisions for risks and charges - less than one year	Total
Value at December 31, 2011	**117**	**16**		**133**
Additions	81			81
Reversal of used provisions		(16)		(16)
Reversal of unused provisions				
Value at December 31, 2012	**198**			**198**
Additions	54			54
Reversal of used provisions				
Reversal of unused provisions				
Value at December 31, 2013	**252**			**252**

The reversals in fiscal year 2012 mainly concern revaluations of the company's potential commitments to third parties with which it is in litigation.

Retirement indemnities:

The provision for retirement indemnities was measured based on the terms of the applicable collective agreement, i.e. collective agreement 176.

The main actuarial assumptions used to value retirement benefits are as follows:

Retirement indemnities (in € thousands)	12/31/2013	12/31/2012
Economic assumptions		
Discount rate	3,0%	3,0%
Rate of annual salary increase	3.1% to 3.5%	3.5% to 4%
Demographic assumptions		
Retirement age	67	67
Type of retirement	Initiated by employee	Initiated by employee
Mortality table	INSEE 07-09	INSEE 07-09
Rate of tax and social security charges	45%	45%
Annual mobility	Average or High depending on category	Average or High depending on category
Provision		
Present value of obligations	252	198
Payments to a fund		
Provision recorded on the balance sheet	**252**	**198**
Past service costs for the period	42	81
Financial expense	7	
Actuarial gains and losses	5	
Annual expense	**49**	**81**

3.12. Trade payables and other current liabilities

The company's current liabilities are as follows:

(in € thousands)	12/31/2013	12/31/2012
Subsidiary accounts	1 105	2 076
Notes payable		
Invoices pending	678	1 748
Trade payables	**1 784**	**3 825**
Customer credit balances		
Tax and social security liabilities	1 245	1 463
Other debt	0	12
Unearned income	0	5 636
Other current liabilities	**1 245**	**7 111**
TOTAL CURRENT OPERATING LIABILITIES	**3 029**	**10 936**

The unearned income recorded at December 31, 2012 (€5.6 million) pertained mainly to the restatement of the up-front payment of €7.6 million received from the partner following the signing of the license agreement and initially spread out over the term of the agreement (see notes 1.2 and 3.15). Following the termination of the agreement with Eli Lilly announced on July 25, 2013, Adocia recognized the entire balance not yet amortized as revenue, i.e. €4.7 million during the third quarter of 2013.

All trade payables and other current liabilities are payable within less than one year.

Tax and social security liabilities are as follows:

TAX AND SOCIAL SECURITY LIABILITIES (in € thousands)	12/31/2013	12/31/2012
Compensation owed	493	684
Debt owed to social welfare agencies	670	709
Value added tax		2
Other tax and social security liabilities	83	68
Tax and social security liabilities	**1 245**	**1 463**

3.13. Financial liabilities

(in € thousands)	Value on the balance sheet	Fair value	12/31/2013	Breakdown by instrument category
			Fair value through profit or loss	Debt at amortized cost
Reimbursable advances	1 814	1 814		1 814
Financial debt				
Total non-current financial liabilities	**1 814**	**1 814**		**1 814**
Short-term reimbursable advances	420	420		420
Short-term financial debt	83	83		83
Trade and similar payables	1 784	1 784		1 784
Other debt	1 245	1 245		1 245
Unearned income	0	0		0
Total current financial liabilities	**3 532**	**3 532**		**3 532**
TOTAL FINANCIAL LIABILITIES	**5 346**	**5 346**		**5 346**

(in € thousands)	Value on the balance sheet	Fair value	12/31/2012	Breakdown by instrument category
			Fair value through profit or loss	Debt at amortized cost
Reimbursable advances	2 046	2 046		2 046
Financial debt				
Total non-current financial liabilities	**2 046**	**2 046**		**2 046**
Short-term reimbursable advances	396	396		396
Short-term financial debt	23	23		23
Trade and similar payables	3 824	3 824		3 824
Other debt	1 475	1 475		1 475
Unearned income	5 636	5 636		5 636
Total current financial liabilities	**11 354**	**11 354**		**11 354**
TOTAL FINANCIAL LIABILITIES	**13 400**	**13 400**		**13 400**

3.14. Operating profit/loss

INCOME STATEMENT (in € thousands)	Notes	12/31/2013	12/31/2012
Research agreements and license revenue	3.15	5 588	3 995
Grants, public financing and research tax	3.16	3 233	3 241
Income		**8 822**	**7 236**
Cost of goods sold		(612)	(834)
Payroll expense	3.18	(5 445)	(4 934)
External charges	3.17	(6 614)	(7 050)
Taxes		(93)	(69)
Depreciation, amortization & provisions	3.19	(360)	(419)
Other current operating income and			
Operating expenses		**(13 124)**	**(13 306)**
PROFIT/LOSS FROM ORDINARY OPERATING		**(4 302)**	**(6 070)**
Non-recurring operating income and expenses			
PROFIT/LOSS FROM OPERATING ACTIVITIES		**(4 302)**	**(6 070)**

Breakdown of expenses by function:

EXPENSES BY FUNCTION (in € thousands)	12/31/2013	12/31/2012
Research and development costs	(11 475)	(11 784)
Administrative costs	(1 649)	(1 522)
Operating expenses	**(13 124)**	**(13 306)**

Research and development costs are as follows:

RESEARCH AND DEVELOPMENT COSTS (in € thousands)	12/31/2013	12/31/2012
Cost of goods sold	(611)	(826)
Payroll expense	(4 411)	(4 080)
External charges	(6 087)	(6 474)
Taxes	(75)	(57)
Depreciation, amortization & provisions	(291)	(347)
Total research and development costs	**(11 475)**	**(11 784)**

3.15. Revenue

REVENUE (in € thousands)	12/31/2013	12/31/2012
Research agreements	(47)	1 892
License revenue	5 636	2 104
Other		
Total	**5 588**	**3 995**

Revenue consists of:

- Under research agreements: revenue generated by research services carried out for partners,
- Under licenses: revenue generated pursuant to licensing agreements, particularly the agreement signed in 2012 with Eli Lilly, which resulted in the collection of an up-front payment. This amount was initially amortized over the planned development period. After the partnership ended in July 2013, the balance not yet amortized was recognized during the third quarter of 2013.

3.16. Other income

OTHER INCOME (in € thousands)	12/31/2013	12/31/2012
Project financing	5	167
Research tax credit	3 215	3 061
Other	14,3	13
Total	**3 234**	**3 241**

3.17. Other purchases and external charges

These are mainly in-vivo studies, clinical trials, lease payments and all the company's operating expenses.

3.18. Payroll expense

Payroll expense is as follows:

PAYROLL EXPENSE (in € thousands)	12/31/2013	12/31/2012
Wages and salaries	3 789	3 554
Social contributions	1 656	1 380
Total payroll expense	**5 445**	**4 934**

STAFF	12/31/2013	12/31/2012
Technicians	36	37
Management personnel	37	34
Total employees	**73**	**71**

At December 31, 2013, the company had 25 postdoctoral researchers.

Over 80% of employees are assigned directly to research and development activities.

The number of training hours acquired at the end of December 2013 under employees' individual right to training was 4,395. As this number was considered immaterial, no provision was set up.

3.19. Depreciation, amortization and impairment losses

Net depreciation, amortization and provisions are as follows:

DEPRECIATION, AMORTIZATION AND IMPAIRMENT (in € thousands)	12/31/2013	12/31/2012
Depreciation of property, plant and equipment	336	332
Amortization of intangible assets		
Depreciation of leased assets	24	23
Depreciation, amortization and provisions for fixed assets	**360**	**355**
Provisions for risks and charges (additions)		81
Provisions for current assets (additions)		
Reversals		(16)
Additions to/Reversals of Depreciation, Amortization and Provisions	**360**	**419**

3.20. Financial income/expense

The cost of net financial debt is as follows:

FINANCIAL INCOME/EXPENSE (in € thousands)	12/31/2013	12/31/2012
Cash and cash equivalents income	169	142
Interest on conditional advances	(107)	(99)
Cost of net financial debt	**62**	**43**
Foreign exchange gains and losses		
Other financial income and expenses	(53)	33
FINANCIAL INCOME/EXPENSE	**9**	**76**

3.21. Corporation tax

Given its taxable income and the regulations limiting the use of tax losses, the company did not owe any tax in 2013.

The difference between pre-tax profit/loss and the actual tax expense is shown below:

(in € thousands)	12/31/2013	12/31/2012
Profit/loss before tax	(4 293)	(5 995)
Notional tax of 34.43%	1 478	2 064
Permanent differences	1 078	1 725
Uncapitalized tax loss adjusted for deferred tax	(2 556)	(3 789)
Actual tax expense	**0**	**(0)**
Actual tax rate	*0%*	*0%*

No tax asset was recognized since the company cannot determine with sufficient reliability when it will be able to reduce its losses.

3.22. Earnings per share

	12/31/2013	12/31/2012
Consolidated net profit/loss (in € thousands)	**(4 293)**	**(5 995)**
Average number of shares	6 205 961	5 985 079
Net earnings per share (in euros)	**(0,7)**	**(1,0)**

Equity instruments outstanding are not included in the calculation of earnings per share since they are considered anti-dilutive given the company's losses over previous fiscal years.

4. Related parties and compensation of the corporate officers

Compensation paid to the management and supervisory bodies is described in the table below.

(in € thousands)	12/31/2013	12/31/2012
Fixed gross compensation (*)	381	351
Variable gross compensation (*)	90	80
Exceptional gross compensation (*)		100
Benefits in kind	8	8
Directors' fees	38	12
TOTAL	**518**	**551**

Stock warrants were granted in 2013 to two independent members (see note 3.9 to the individual financial statements prepared under IFRS for the fiscal years ended December 31, 2012 and 2013 provided in Chapter 20.1 of this reference document).

5. Financial risk management objectives and policies

Foreign exchange risk

Foreign exchange risk is the risk that the fair value or future cash flows of a financial instrument will fluctuate due to changes in foreign exchange rates. The company's strategy is to enter into agreements denominated in euros. Until 2012, the company had little exposure to changes in the euro/US dollar exchange rate. As a result of the licensing and collaboration agreement signed with the American Eli Lilly pharmaceutical group at the end of 2011, the company may have occasion to carry out euro/US dollar foreign currency hedging transactions and forward sale transactions.

The company cannot rule out the possibility that a significant increase in its activity may result in greater exposure to foreign exchange risk. The company will therefore again consider developing an appropriate policy to hedge these risks.

Credit risk

The debt related to the government grants and research tax credit poses a credit risk that is considered immaterial in light of the company's history (see note 3.8).

Credit risk related to cash, cash equivalents and current financial instruments is immaterial given the quality of the contracting financial institutions.

With regard to clients, the company has no significant credit risk concentration. It has developed policies to ensure that its clients have an appropriate credit risk history.

Liquidity risk

The company obtains financing under a policy implemented by the Finance Department.

The structure of the company's financing is based primarily on equity, the use of public financing (OSEO) and an initial public offering.

Interest rate risk

The company has no debt with financial institutions and therefore no interest rate risk.

Equity risk

The company has no non-consolidated holdings or investment securities tradable on a regulated market.

6. Off-balance sheet commitments

Stock warrants were granted in 2013 to two independent members (see note 3.9 to the individual financial statements prepared under IFRS for the fiscal years ended December 31, 2012 and 2013 provided in Chapter 20.1 of this reference document).

21.2. Statutory auditors' reports on the individual financial statements prepared under IFRS for the fiscal year ended December 31, 2013

Adocia

Fiscal year ended December 31, 2013

Statutory auditors' audit report on the year-end financial statements prepared under IFRS as adopted in the European Union

ODICEO
115, boulevard Stalingrad
B.P. 52038
69616 Villeurbanne Cedex
Corporation with €275,000 in share capital

Statutory Auditor
Member of the Compagnie
Régionale de Lyon

ERNST & YOUNG et Autres
Tour Oxygène
10-12, boulevard Marius Vivier Merle
69393 Lyon Cedex 03
Simplified joint stock company with variable capital

Statutory Auditor
Member of the Compagnie
Régionale de Versailles

Adocia

Fiscal year ended December 31, 2013

Statutory auditors' audit report on the year-end financial statements prepared under IFRS as adopted in the European Union

To the chairman of the board of directors:

In our capacity as statutory auditors of Adocia and in response to your request, we have audited the company's year-end financial statements, prepared under IFRS as adopted in the European Union, for the fiscal year ended December 31, 2013, as attached to this report.

These year-end financial statements prepared under IFRS as adopted in the European Union were approved by the board of directors. It is our task, on the basis of our audit, to express an opinion on these financial statements.

We have conducted our audit in accordance with the accounting standards applicable in France. These standards require the use of due diligence to provide reasonable assurance that the year-end financial statements prepared under IFRS as adopted in the European Union do not contain any significant misstatements. An audit entails verifying, on a test basis or through other selection methods, evidence supporting the amounts and information contained in the financial statements. It also entails assessing the accounting principles applied, the significant estimates used and the overall presentation of the financial statements. We believe that the information we have collected is sufficient and appropriate to provide a basis for our opinion.

In our opinion, the year-end financial statements prepared under IFRS as adopted in the European Union fairly present, in all material respects and in accordance with IFRS as adopted in the European Union, the assets and financial position of the company at December 31, 2013, as well as the results of its operations for the year under review.

Villeurbanne and Lyon, March 24, 2014

The Statutory Auditors

ODICEO — ERNST & YOUNG et Autres

Sylvain Boccon-Gibod — Sylvain Lauria

21.3. Individual financial statements prepared under French GAAP for the fiscal years ended December 31, 2012 and 2013

Balance sheet (French GAAP)

ASSETS - (in € thousands)	12/31/2013			12/31/2012
	Gross Amount	*Depr./Amort. and Prov.*	*Net Amount*	*Net Amount*
Intangible assets				
* Start-up costs	11	11	0	0
* Concessions, patents and similar rights	73	70	3	13
TOTAL Intangible assets	**84**	**81**	**3**	**13**
Tangible fixed assets				
* Land	127		127	
* Fixtures & fittings, industrial equipment	1 531	1 094	437	555
* Other tangible fixed assets	1 034	743	291	360
* Construction work in progress	8		8	
* Advances and payments on account			0	
TOTAL Tangible fixed assets	**2 699**	**1 837**	**862**	**915**
Financial assets:				
* Other financial assets	628	151	478	940
TOTAL Financial assets	**628**	**151**	**478**	**940**
LONG-TERM ASSETS	**3 412**	**2 069**	**1 343**	**1 868**
Inventory and work in progress	**124**		**124**	**103**
Receivables				
* Advance payments made on orders	27		27	12
* Trade and similar receivables	2		2	316
* Other receivables	3 724		3 724	4 109
* Subscribed capital called but not paid			0	
TOTAL Receivables	**3 753**		**3 753**	**4 437**
Cash assets and Misc.				
* Short-term investment securities	15 764		15 764	11 512
* Cash assets	3 650		3 650	18 928
* Pre-paid expenses	250		250	348
TOTAL Cash assets and Misc.	**19 663**		**19 663**	**30 788**
CURRENT ASSETS	**23 541**	**0**	**23 541**	**35 327**
Translation losses				5
TOTAL ASSETS	**26 953**	**2 069**	**24 884**	**37 201**

LIABILITIES - (in € thousands)	12/31/2013	12/31/2012
	Net Amount	*Net Amount*
Net position		
Paid-up capital	621	620
Additional paid-in capital	49 791	49 793
Balance brought forward	(21 317)	(13 288)
Profit/loss for the year	(9 689)	(8 029)
TOTAL Net position	19 406	29 096
EQUITY	**19 406**	**29 096**
Conditional advances	2 441	2 750
OTHER EQUITY	**2 441**	**2 750**
Provisions for risks		5
PROVISIONS FOR RISKS AND CHARGES	**0**	**5**
Misc. debt		
Trade and similar payables	1 791	3 828
Tax and social security liabilities	1 245	1 463
Debt on fixed assets and similar accounts		
Other debt		12
TOTAL Misc. debt	3 036	5 304
Unearned income		
DEBT	**3 036**	**5 304**
Translation gains		46
TOTAL LIABILITIES	**24 884**	**37 201**

Income statement (French GAAP)

INCOME STATEMENT - (in € thousands)	12/31/2013			12/31/2012
	France	*Export*	*Net Amount*	*Net Amount*
Sales of goods				
Sales of services	1	(27)	(26)	2 025
TOTAL Net revenue	1	(27)	(26)	2 025
Operating subsidies			11	5
Reversals of depr./amort. and prov., transfers of charges			33	50
Other income			23	0
OPERATING INCOME	**1**	**(27)**	**41**	**2 081**
External charges				
Purchases of raw materials and other supplies			634	844
Change in inventory of raw mat. and supplies			(22)	(10)
Other purchases and external charges			6 596	7 060
TOTAL External charges			7 208	7 894
Taxes and similar payments			93	69
Wages and salaries			3 745	3 531
Social contributions			1 656	1 380
TOTAL Payroll expense			5 400	4 911
TOTAL Operating allowances			338	328
Other operating expenses			38	24
OPERATING EXPENSES			**13 077**	**13 226**
OPERATING PROFIT/LOSS			**(13 036)**	**(11 145)**
Financial income on investments				48
Income from other securities and receivables on long-term assets			131	47
Other interest and similar income			3	1
Reversals of provisions and transfers of charges			88	
Foreign exchange gains			31	21
Net income on sales of short-term investment securities			28	35
TOTAL Financial income			281	153
Depreciation allowance and provisions			151	88
Interest and similar expenses			(3)	6
Foreign exchange losses			4	12
TOTAL Financial expenses			152	106
FINANCIAL INCOME/EXPENSE			**129**	**47**
PROFIT/LOSS FROM ORDINARY ACTIVITIES BEFORE TAX			**(12 907)**	**(11 098)**
Extraordinary income from capital transactions			85	
Reversals of provisions and transfers of charges				16
TOTAL Extraordinary income			85	16
Extraordinary expenses on capital transactions			85	16
TOTAL Extraordinary expenses			85	16
EXTRAORDINARY PROFIT/LOSS			**0**	**0**
Income tax			3 218	3 069
PROFIT OR LOSS			**(9 689)**	**(8 029)**

Assets (French GAAP)

ASSETS - (in € thousands)	Period from 01/01/2013 to 12/31/2013			Period from 01/01/2013 to 12/31/2013			
	Gross amount at start of fiscal year	*Increases by revaluation*	*Acquisitions, contributions, creation, transfers*	*Decreases by transfer*	*Decreases by disposals and removals from service*	*Gross amount at end of fiscal year*	*Statutory revaluations*
Start-up and development costs	11					11	
Other intangible assets	63		11		(1)	73	
TOTAL Intangible assets	**74**		**11**		**(1)**	**84**	
Fixtures & fittings and industrial equipment	1 440		133		(42)	1 531	
General facilities, fixtures and misc.	531		13			544	
Office, computer equipment and furniture	464		26			490	
Tangible fixed assets in progress			51		(43)	8	
TOTAL Tangible fixed assets	**2 435**		**349**		**(85)**	**2 699**	
Loans and other financial assets	1 028		1		(400)	628	
Total Financial assets	**1 028**		**1**		**(400)**	**628**	
GRAND TOTAL	**3 537**		**361**		**(485)**	**3 412**	

ASSETS - (in € thousands)	Period from 01/01/2012 to 12/31/2012			Period from 01/01/2012 to 12/31/2012			
	Gross amount at start of fiscal year	*Increases by revaluation*	*Acquisitions, contributions, creation, transfers*	*Decreases by transfer*	*Decreases by disposals and removals from service*	*Gross amount at end of fiscal year*	*Statutory revaluations*
Start-up and development costs	11					11	
Other intangible assets	47		16			63	
TOTAL Intangible assets	**58**		**16**			**74**	
Fixtures & fittings and industrial equipment	1 074		365			1 440	
General facilities, fixtures and misc.	295		235			531	
Office, computer equipment and furniture	348		121		5	464	
Tangible fixed assets in progress	146			146			
TOTAL Tangible fixed assets	**1 863**		**722**		**5**	**2 435**	
Loans and other financial assets	0		1 027		0	1 028	
Total Financial assets	**0**		**1 027**		**0**	**1 028**	
GRAND TOTAL	**1 922**		**1 766**		**5**	**3 537**	

Depreciation and amortization (French GAAP)

DEPRECIATION/AMORTIZATION - (in € thousands)	Period from 01/01/2013 to 12/31/2013						
POSITION AND MOVEMENTS DURING THE FISCAL YEAR DEPRECIABLE/AMORTIZABLE ASSETS	*Amount at start of fiscal year*	*Increases additions*	*Decreases reversals*	*Amount at end of fiscal year*	*Straight-line depr./amort.*	*Straight-line depr./amort.*	*Extraordinary depr./amort.*
Intangible assets							
Start-up and development costs	11			11	11		
Other intangible assets	50	20	- 0	70	70		
TOTAL Intangible assets	**61**	**20**	**- 0**	**81**	**81**	-	-
Buildings on own land							
Fixtures & fittings and industrial equipment	885	209		1 094	1 094		
General facilities, fixtures and misc.	323	45		368	368		
Office, computer equipment and furniture	312	64		376	376		
TOTAL Tangible fixed assets	**1 520**	**317**	-	**1 837**	**1 837**	-	-
Expenses for purchases of equity interests							
GRAND TOTAL	**1 581**	**337**	**- 0**	**1 918**	**1 918**	-	-

DEPRECIATION/AMORTIZATION - (in € thousands)	Period from 01/01/2012 to 12/31/2012						
POSITION AND MOVEMENTS DURING THE FISCAL YEAR DEPRECIABLE/AMORTIZABLE ASSETS	*Amount at start of fiscal year*	*Increases additions*	*Decreases reversals*	*Amount at end of fiscal year*	*Straight-line depr./amort.*	*Straight-line depr./amort.*	*Extraordinary depr./amort.*
Tangible fixed assets							
Start-up and development costs	11			11	11		
Other intangible assets	41	9	-	50	50		
TOTAL Intangible assets	**52**	**9**	-	**61**	**61**	-	-
Buildings on own land							
Fixtures & fittings and industrial equipment	696	189	-	885	885		
General facilities, fixtures and misc.	252	71	-	323	323		
Office, computer equipment and furniture	258	58	5	312	312		
TOTAL Tangible fixed assets	**1 206**	**319**	**5**	**1 520**	**1 520**	-	-
Expenses for purchases of equity interests							
GRAND TOTAL	**1 257**	**328**	**5**	**1 581**	**1 581**	-	-

Provisions recorded on the balance sheet (French GAAP)

PROVISIONS RECORDED ON THE BALANCE SHEET - (in € thousands)	Period from 01/01/2013 to 12/31/2013			Period from 01/01/2012 to 12/31/2012		
	Increases additions	*Decreases reversals*	*Amount at end of fiscal year*	*Increases additions*	*Decreases reversals*	*Amount at end of fiscal year*
REGULATORY PROVISIONS	-	-	-	-	-	-
Provisions for foreign exchange losses		6		5	1	5
PROVISION FOR RISKS AND CHARGES	-	**6**	-	**5**	**17**	**5**
PROVISIONS FOR IMPAIRMENT			-			**5**
GRAND TOTAL	-	**6**	-	**5**	**17**	**5**

Due dates of receivables and debts (French GAAP)

	Period from 01/01/2013 to 12/31/2013							
RECEIVABLES - (in € thousands)	*Gross amount*	*Up to 1 year*	*1 year or more*	**DEBTS - (in € thousands)**	*Gross amount*	*Up to 1 year*	*1 to 5 years*	*1 to 5 years*
Other financial assets	628		628	* up to 1 year at origin				
TOTAL Long-term assets	628		628	* more than 1 year at origin				
Current assets				Loans and misc. financial debt				
Bad and doubtful debts				Trade and similar payables	1 791	1 791		
Other trade receivables	2	2		Staff and similar accounts	500	500		
Receivables represent. securities lent or used as collateral				Social security and other agencies	669	669		
Staff and similar accounts				Income tax				
Social security and other social agencies	14	14		Value added tax	3	3		
Government - Income tax	3 217	3 217		Guaranteed bonds				
Government - Value added tax	191	191		Other taxes and similar	75	75		
Government - Other taxes and similar payments	50	50		Debt on fixed assets and similar accounts				
Government - Misc.				Group and partners				
Group and partners				Other debt				
Misc. debtors	279	279		Debt representing borrowed securities				
TOTAL Current assets	3 753	3 753						
Pre-paid expenses	250	250		Unearned income				
GRAND TOTAL	**4 632**	**4 003**	**628**		**3 036**	**3 036**		

	Period from 01/01/2012 to 12/31/2012							
RECEIVABLES - (in € thousands)	*Gross amount*	*Up to 1 year*	*1 year or more*	**DEBTS - (in € thousands)**	*Gross amount*	*Up to 1 year*	*1 to 5 years*	*1 to 5 years*
Other financial assets	1 028		1 028	* up to 1 year at origin				
TOTAL Long-term assets	1 028		1 028	* more than 1 year at origin				
Current assets				Loans and misc. financial debt				
Bad and doubtful debts				Trade and similar payables	3 828	3 828		
Other trade receivables	316	316		Staff and similar accounts	684	684		
Receivables represent. securities lent or used as collateral				Social security and other agencies	709	709		
Staff and similar accounts				Income tax				
Social security and other social agencies	15	15		Value added tax	2	2		
Government - Income tax	3 061	3 061		Guaranteed bonds				
Government - Value added tax	812	812		Other taxes and similar	68	68		
Government - Other taxes and similar payments	9	9		Debt on fixed assets and similar accounts				
Government - Misc.				Group and partners				
Group and partners				Other debt	12	12		
Misc. debtors	223	223		Debt representing borrowed securities				
TOTAL Current assets	4 437	4 437						
Pre-paid expenses	348	348		Unearned income				
GRAND TOTAL	**5 812**	**4 785**	**1 028**		**5 304**	**5 304**		

Accrued expenses (French GAAP)

ACCRUED EXPENSES INCLUDED IN THE FOLLOWING BALANCE SHEET ITEMS – (in € thousands)	Period from 01/01/2013 to 12/31/2013
Trade and similar payables	678
Tax and social security liabilities	791
TOTAL	**1 470**

ACCRUED EXPENSES INCLUDED IN THE FOLLOWING BALANCE SHEET ITEMS – (in € thousands)	Period from 01/01/2012 to 12/31/2012
Trade and similar payables	1 748
Tax and social security liabilities	1 061
TOTAL	**2 810**

Revenue accruals (French GAAP)

REVENUE ACCRUALS INCLUDED IN THE FOLLOWING BALANCE SHEET ITEMS – (in € thousands)	Period from 01/01/2013 to 12/31/2013
Financial assets	
Receivables	
Trade and similar receivables	2
Social agencies	4
Government	50
Misc. revenue accruals	3
Other receivables	241
Cash assets	6
TOTAL	**307**

REVENUE ACCRUALS INCLUDED IN THE FOLLOWING BALANCE SHEET ITEMS – (in € thousands)	Period from 01/01/2012 to 12/31/2012
Financial assets	
Receivables	
Trade and similar receivables	58
Social agencies	5
Government	9
Misc. revenue accruals	
Other receivables	207
Cash assets	4
TOTAL	**284**

Pre-paid expenses and unearned income (French GAAP)

PRE-PAID EXPENSES AND UNEARNED INCOME (in € thousands)	Period from 01/01/2013 to 12/31/2013
Operating income or expense	250
Financial income or expense	
Extraordinary income or expense	
TOTAL	**250**

PRE-PAID EXPENSES AND UNEARNED INCOME (in € thousands)	Period from 01/01/2013 to 12/31/2013
Operating income or expense	348
Financial income or expense	
Extraordinary income or expense	
TOTAL	**348**

Share capital structure (French GAAP)

SECURITIES CATEGORIES - Period from 01/01/2013 to 12/31/2013	*Number*	*Nominal value*
1- Stocks or partnership shares composing the share capital at start of fiscal year	*6 197 876*	*619 788*
2- Stocks or partnership shares issued during fiscal year	*14 000*	*1 400*
3- Stocks or partnership shares redeemed during fiscal year		
4- Stocks or partnership shares composing the share capital at end of fiscal year	6 211 876	621 187,6

SECURITIES CATEGORIES - Period from 01/01/2012 to 12/31/2012	*Number*	*Nominal value*
1- Stocks or partnership shares composing the share capital at start of fiscal year	*4 458 710*	*445 871*
2- Stocks or partnership shares issued during fiscal year	*1 739 166*	*173 920*
3- Stocks or partnership shares redeemed during fiscal year		
4- Stocks or partnership shares composing the share capital at end of fiscal year	*6 197 876*	*619 787,6*

NOTES TO THE FINANCIAL STATEMENTS PREPARED UNDER FRENCH GAAP

1. Accounting rules and methods

(Decree 83-1020 of 11/29/1983 – Articles 7, 21, 24 beginning, 24-1, 24-2 and 24-3)

The total balance sheet before allocation for the fiscal year ended December 31, 2013 was €24.884 million.
The net accounting loss was €9.689 million.

The following notes and tables form an integral part of the year-end financial statements.

These year-end financial statements were approved by the board of directors on March 21, 2014.

The financial statements were prepared in accordance with:

- the 1999 General Chart of Accounts approved by the ministerial order of June 22, 1999
- law 83 353 of April 30, 1983
- decree 83 1020 of November 29, 1983
- accounting regulations:
  - 2000-06 and 2003-07 on liabilities
  - 2002-10 on depreciation, amortization and impairment of assets
  - 2004-06 on the definition, recognition and valuation of assets

General accounting conventions have been applied based on the principle of conservatism in accordance with the following basic assumptions:
- going concern,
- consistency of the accounting methods used from one year to the next,
- independence of fiscal years, and

in accordance with the general rules regarding the preparation and presentation of year-end financial statements.

The basic method used to determine the value of the items accounted for is the historical cost method.

1.1. Intangible assets

Start-up costs were capitalized and amortized over a three-year period.

Research and development costs are not capitalized. They are recognized as expenses incurred by the company.

1.2. Tangible fixed assets

Tangible fixed assets are recorded at their acquisition cost (purchase price and incidental expenses).

The company took advantage of the leeway offered and opted to depreciate assets that cannot be broken down into components based on their useful lives.

The company has no assets that can be broken down into components.

Depreciation is calculated on a straight-line basis according to the expected useful life.

- Software: 1 year
- Fixtures & fittings: 3-5 years (used – new)
- Misc. fixtures and facilities: 1-6 years
- Office and computer equipment: 3-5 years
- Office furniture: 5 years

Other purchases of tangible fixed assets correspond to the acquisition of parking lots, for which no impairment was recorded.

Moreover, in accordance with the General Chart of Accounts and under the lease signed with the greater Lyon area, the company revised the depreciation schedule for "Facilities and fixtures", extending the end of the depreciation period from October 12, 2014 to October 12, 2017 (expiration date of the lease).

1.3. Equity holdings and other long-term investments

Since the merger of Biodex, the company no longer has any subsidiaries.

1.4. Short-term investment securities

The company invests its funds in short-term investment securities (money market mutual funds) measured at their acquisition cost. It has also invested a portion of its liquidity in short-term term deposits at a guaranteed fixed rate.
At the end of the fiscal year, the unrealized capital gain on these investments was €1,000.

1.5. Inventories

Inventories are measured using the "first-in first-out" method.

1.6. Revenue

Revenue was €-25,000 in 2013 following the adjustment of the provisions for unbilled revenue recorded the previous year.

1.7. Changes in methods

None.

2. Highlights of the fiscal year

The year 2013 marked the end of the collaboration with the Eli Lilly group, with which the company had signed a licensing agreement in December 2011 for the development and marketing of a fast-acting insulin analog, Humalog, formulated with BioChaperone® technology.

Adocia subsequently reacquired the rights to its technology applied to insulin analogs and ownership of all the results generated during the agreement.
These 20 months of collaboration with a major player in the field of insulin enabled the company to take in €9.4 million (€7.6 million of which in up-front payments), develop an optimized formula, obtain initial clinical results and acquire expertise in the development of ultra-fast acting insulin.
Following the announcement on July 25, 2013 of the end of the collaboration, the company continued to actively develop this project and prepared a phase 2a clinical trial, the launch of which was announced in early January 2014. The purpose of this clinical trial is to confirm, on type I diabetes patients, the positive clinical results obtained during the phase I trial conducted by Eli Lilly in Singapore in July 2012.

In 2013, the company pursued the clinical development of its two other insulin projects: the formulation of a fast-acting human insulin (HinsBet®) and the formulation of a combination of long-acting insulin and fast-acting insulin. For this latter project, a phase I-II clinical trial was launched in mid-November 2013. Through this trial, conducted on 20 type I diabetes patients, it will be possible to compare the performance of the combo (combination of long-acting insulin glargine and a fast-acting insulin analog) with that of the HumalogMix® product marketed by Lilly.

For its wound healing project, and more specifically the project for the treatment of diabetic foot ulcers, in 2013 the company had not yet obtained authorization from the Indian authorities to launch the phase III clinical trial in India.

Finally, in 2013 the company obtained an exclusive license for a new technology that improves the efficacy of anti-cancer agents by targeting their action into tumors. This technology, developed by the CNRS and the University of Bordeaux, was particularly effective in pre-clinical studies.
This new platform allows the company to enter the field of oncology and its research will be focused primarily on the treatment of ovarian cancer.

(See notes 1.1 to 1.3 to the individual financial statements prepared under IFRS for the fiscal years ended December 31, 2012 and 2013 provided in Chapter 20.1 of this reference document).

3. Additional notes to certain items in the financial statements

3.1. Reimbursable advances and OSEO grants

3.1.1. OSEO Innovation agreement of March 12, 2007

As part of the Osteoporosis project, the company signed an agreement with OSEO on March 12, 2007 under which it received a reimbursable advance totaling €2.25 million for the development of a new system for local controlled release of growth factors for bone regeneration. After fulfilling all the technical and financial conditions, the company received the full amount of this reimbursable assistance in four payments made between March 15, 2007 and February 15, 2010.

Under the terms of the agreement, €0.7 million was repayable by March 31, 2013 regardless of the outcome of the program, which is unknown as of the date of this reference document. The company repaid the first €0.3 million installment in 2012 and a second payment of €0.4 million was made on April 1, 2013.

The balance of the advance (i.e. €1.55 million) will be repayable only if OSEO recognizes the technical and/or commercial success of the financed project.

(See the repayment terms in the event of the program's success or assignments of licenses or marketing in Chapter 22.1 of this reference document).

3.1.2. OSEO Innovation-ERDF agreement of July 20, 2010

As part of the Insulin project, the company signed two agreements with OSEO on July 20, 2010 for the development of a fast-acting "human" insulin formulation in connection with a phase I clinical trial for a total of €0.84 million.

(See the repayment terms in the event of the program's success or assignments of licenses or marketing in Chapter 22.2 of this reference document).

3.1.2.1. Reimbursable advance of €420,000

Under the terms of the first agreement, the company received a reimbursable advance in the amount of €0.42 million, the entirety of which was received in four payments made between July 26, 2010 and November 16, 2011.
In the event of the program's success, the company agreed to repay OSEO the sum of €0.42 million.

Since the results of this project contributed to the signing of the licensing agreement with the Eli Lilly group, on June 19, 2012 the company repaid the total amount of the advance received, i.e. €0.42 million, as provided by the agreement.

3.1.2.2. ERDF grant of €420,000

Under the terms of the second agreement, the company received an OSEO Innovation-ERDF grant totaling €420,000, the entirety of which was received in three payments made between October 18, 2010 and November 16, 2011.
The agreement stipulates no obligation to repay this grant unless the company fails to fulfill its obligations, in which case OSEO has a right to demand the repayment of the grant.

3.1.3 OSEO Innovation agreement of April 25, 2012

As part of the Insulin project, the company signed an agreement with OSEO on April 25, 2012 under which the company received a reimbursable advance totaling €0.8 million for the development of a fast-acting "human" insulin formulation and the Phase 2a clinical trial. After fulfilling all the technical and financial conditions, the company received the full amount of this reimbursable assistance on April 30, 2012.

(See the repayment terms in the event of the program's success or assignments of licenses or marketing in Chapter 22.3 of this reference document).

3.1.4 Coface-International business development insurance agreement of October 1, 2012

As part of its business development in new markets (India and China), the company signed a business development agreement with Coface (French insurance company for foreign trade) on October 26, 2012 in return for the payment of a premium equivalent to 2% of the annual budget.
Under the terms of the agreement, Coface guarantees the reimbursement of 75% of the expenses incurred during the four-year guarantee period, which runs from October 1, 2012 to September 30, 2016.
For the expenses incurred during the first insured period, i.e. from October 1, 2012 to September 30, 2013, the company received the sum of €910 on December 17, 2013.

(See the repayment terms in the event of the program's success or assignments of licenses or marketing in Chapter 22.4 of this reference document).

3.2. Income statement

No revenue was recorded for 2013. In the previous year, revenue amounted to €-2.025 million.

Operating expenses totaled €13 million, the same level as last year. Expenses include the following items (in € thousands):

- Purchases of raw materials and other supplies: 634
- Change in inventories: (22)
- Other purchases and external charges: 6,596
- Taxes: 93
- Wages and salaries: 3,745
- Social security charges: 1,656
- Depreciation and amortization: 338
- Operating provisions: 0
- Other expenses: 38

The operating loss was €13 million compared with a loss of €11 million the previous year.

Financial income and expenses totaled €0.28 million and €0.15 million, respectively, which resulted in net financial income of €0.13 million, compared with net financial income of €0.047 million the previous year.

As a result, the loss from ordinary activities before tax was €12 million compared with a loss of €11 million the previous year.

No extraordinary profit/loss was recorded for fiscal year 2013.

Thus, given the research tax credit, which amounted to €3 million, and the apprentice tax credit, which totaled €3,000, the net loss for the year was €9 million, compared with a loss of €8 million in 2012.

3.3. Balance sheet

3.3.1. Assets

The net sum of intangible assets was €3,000.
The net sum of tangible fixed assets was €862,000.
The net sum of "financial assets" was €478,000 at December 31, 2013.

The net sum of current assets was €23.54 million.
Pre-paid expenses stood at €0.25 million.

3.3.2. Liabilities

Share capital totaled €621,187.60 at December 31, 2013, compared with €619,787.60 at the end of the previous year, and additional paid-in capital totaled €49 million (same as at December 31, 2012).

Retained losses totaled €9.6 million.

Conditional advances totaled €2.4 million at December 31, 2013 compared with €2.7 million the previous year.

3.3.3 The company's debt position based on business volume and complexity

Debt stood at €3 million (compared with €5.3 million the previous year) and mainly included:

- trade and similar payables: €1.79 million
- tax and social security liabilities: €1.25 million

Pursuant to Article L. 441-6-1 of the French commercial code (*Code de commerce),* trade payables, which totaled €1.79 million, compared with €3.8 million the previous year, by due date were as follows:

Supplier category (in € thousands)	**Fiscal year 2013**	**Fiscal year 2012**
Cash payment	430	870
Payment in 30 days	544	803
Payment in 45 days	88	219
Payment in 60 days	37	47
Litigation	13	142
Suppliers, invoices pending	678	1 748

5. Proposed allocation of losses for fiscal year 2013

A proposal is made to allocate the losses for the fiscal year ended December 31, 2013 totaling €9,689,252.43 to retained losses.

As a reminder, the company has not paid out dividends over the last three years.

6. Non-tax-deductible expenses

In accordance with Article 223 (4) of the French General Tax Code (*Code Général des Impôts*), the amount of luxury and non-deductible expenses referred to in Article 39-4 of this code totaled €19,384 for the fiscal year ended December 31, 2013.

7. Off-balance sheet commitments

7.1. Retirement obligation

The company decided not to recognize a provision for its retirement obligations.

However, it chose to quantify these obligations in the financial statements prepared under IFRS in the amount of €252,000 at December 31, 2013.
(See note 3.11 to the individual financial statements prepared under IFRS provided in Chapter 20.1 of this reference document).

7.2. Lease signed with the greater Lyon area

The company's registered office is located at 115, avenue Lacassagne, 69003 in Lyon. It occupies approximately 2,032 square meters on two floors of a building that houses innovative biotech companies.
The company also signed a lease agreement for a covered parking garage, which took effect on October 13, 2011.
(See Chapter 8.1 of this reference document regarding leases signed)

The lease expense (excluding building occupancy expenses) was €346,000 and the building occupancy expenses totaled €149,000 for the fiscal year ended December 31, 2013.

7.3. Signing of two financial leases

The company owns several assets financed through leasing. It holds two agreements. The first concerns an asset with an acquisition cost of €68,000 financed for three years and the second concerns equipment with a total acquisition cost of €85,000 financed for four years. The first agreement will expire in January 2014.

8. Other Information

8.1. Bonus shares

On December 20, 2007, the ordinary shareholders' meeting authorized the board of directors to grant ordinary shares of the company, free of charge, to its employees up to a maximum of 2.5% of the share capital.

In fiscal year 2013, the following transactions were carried out:

- Issue of 14,000 shares for which the vesting periods expired and the grant conditions were fulfilled,
- No new grant of bonus shares,
- As of December 31, 2013, 7,000 of the bonus shares granted were not yet vested.

(See the grant conditions in Chapter 17.2 of this reference document)

8.2. Stock warrants

On December 20, 2007, the ordinary shareholders' meeting authorized the board of directors to issue 210 detachable stock warrants, free of charge, to consultants holding scientific positions at the company, up to a maximum of 0.5% of the share capital.

On December 13, 2013, in exercise of the authorization granted at the June 18, 2013 shareholders' meeting, the board of directors decided to issue 20,000 stock warrants to independent directors, raising the number of stock warrants issued to 20,210.
No stock warrants were subscribed for in 2013.

(See the grant conditions indicated in Chapters 15.1.4 and 21.1.5 of this reference document)

8.3. Start-up company stock purchase warrants ("BSPCE")

In accordance with the authorization granted by the company's ordinary and extraordinary shareholders' meeting on June 18, 2013, at its meeting on December 13, 2013 the board of directors decided to issue, free of charge, a total of 50,400 BSPCE to certain company employees which give a right to subscribe for 50,400 new shares, each with a par value of €0.10.

To this end, the board of directors decided to create two plans, the grant conditions of which are described in detail in Chapter 17.2 of this reference document.

8.4. Innovative startup status

Since the beginning of 2013, the company is no longer eligible as an innovative startup that carries out research and development projects.

8.5. Individual right to training

The individual right to training allows all employees to acquire credit for training hours which they can use at their own discretion, with the employer's agreement as to the choice of training.

Employees have a right to 20 hours of training per year, which can be accumulated over six years up to a maximum of 120 hours.

The number of accumulated training hours corresponding to the rights acquired by the company's employees and not used as of December 31, 2013 was 4,395.

No accumulated hours resulted in training in 2013.

The number of accumulated hours that did not result in a request for training was therefore 4,395.

8.6. Events subsequent to year end

None.

21.4. Statutory auditors' report on the individual financial statements prepared for the fiscal year ended December 31, 2013

ODICEO ERNST & YOUNG et Autres

Adocia
Fiscal year ended December 31, 2013

Statutory auditors' report
on the year-end financial statements

ODICEO
115, boulevard de Stalingrad
B.P. 52038
69616 Villeurbanne Cedex
Corporation with €275,000 in share capital

Statutory Auditor
Member of the Compagnie
Régionale de Lyon

ERNST & YOUNG et Autres
Tour Oxygène
10-12, boulevard Marius Vivier Merle
69393 Lyon Cedex 03
Simplified joint stock company with variable capital

Statutory Auditor
Member of the Compagnie
Régionale de Versailles

Adocia

Fiscal year ended December 31, 2013

Statutory auditors' report on the year-end financial statements

Dear Shareholders:

Pursuant to the mission entrusted to us by your shareholders' meetings, we present to you our report for the fiscal year ended December 31, 2013 on:

- the audit of the year-end financial statements of Adocia, as attached to this report;
- the basis for our assessments;
- the specific verifications and information required by law.

The year-end financial statements were approved by the board of directors. It is our task, on the basis of our audit, to express an opinion on these financial statements.

I. Opinion on the year-end financial statements

We have conducted our audit in accordance with the accounting standards applicable in France. These standards require the use of due diligence to provide reasonable assurance that the year-end financial statements do not contain any significant misstatements. An audit entails verifying, on a test basis or through other selection methods, evidence supporting the amounts and information contained in the year-end financial statements. It also entails assessing the accounting principles applied, the significant estimates used and the overall presentation of the financial statements. We believe that the information we have collected is sufficient and appropriate to provide a basis for our opinion.

We certify that the year-end financial statements, in accordance with French accounting rules and principles, are true and in good order and fairly present the company's net profit/loss from operations during the previous year, as well as its financial position and assets at the end of said year.

II. Basis for the assessments

Pursuant to the provisions of Article L. 823-9 of the French Commercial Code (*Code de commerce*) related to the basis for our assessments, we wish to bring the following points to your attention:

Note "2. Highlights" to the year-end financial statements describes the significant events of the previous fiscal year. As part of our assessment of the accounting rules and principles applied by your company, we have verified the appropriateness of the accounting methods and information provided in the notes to the year-end financial statements, and have ensured their proper application.

The assessments thus made are an integral part of our audit of the year-end financial statements as a whole, and therefore helped us from our opinion, as expressed in the first part of this report.

III. Specific verifications and information

In accordance with the accounting standards applicable in France, we also conducted the specific verifications required by law.

We have no observation to make as to the fairness and consistency with the year-end financial statements of the information provided in the board of directors' management report and in the documents sent to the shareholders regarding the financial position and year-end financial statements.

Concerning the information provided pursuant to the provisions of Article L. 225-102-1 of the French Commercial Code (*Code de commerce*) on compensation and benefits paid to corporate officers and commitments made to them, we have verified its consistency with the financial statements or with the data used to prepare these financial statements and, where appropriate, with the information collected by your company from the companies that control it or are controlled by it. Based on this work, we certify the accuracy and fairness of this information.

As required by law, we have ensured that the information related to the identity of holders of capital and voting rights was provided to you in the management report.

Villeurbanne and Lyon, March 24, 2014

The Statutory Auditors

ODICEO	ERNST & YOUNG et Autres
Sylvain Boccon-Gibod	Sylvain Lauria

21.5. Income for the last five years (in € thousands)

	2013	2012	2011	2010	2009
CAPITAL DURING THE FISCAL YEAR					
Share capital	621 187,6	619 787,6	445 871	444 541	399 014
Number of existing ordinary shares	6 211 876	6 197 876	4 458 710	444 541	399 014
Number of existing ordinary shares cum dividend	6 211 876	6 197 876	4 458 710	444 541	399 014
Maximum number of future shares to be created					
- by bond conversion					
- by exercise of subscription rights	7 000	23 100	41 300	310	264 054
TRANSACTIONS AND RESULTS FOR THE FISCAL YEAR (in € thousands)					
Pre-tax revenue	(26)	2 013	9 169	120	22
Profit/loss before tax, employee profit-sharing, depreciation, amortization and provisions	(12 455)	(10 732)	(4 292)	(5 966)	(5 581)
Income tax	(3 218)	(3 069)	1 855	(1 459)	(1 465)
Employee profit-sharing owed for the year	-	-	-	-	-
Profit/loss after tax, employee profit-sharing, depreciation, amortization and provisions	(9 689)	(8 029)	1 355	(4 539)	(4 633)
Distributed profit	-	-	-	-	-
EARNINGS PER SHARE (in euros per share)					
Profit/loss after tax and employee profit-sharing, but before depreciation, amortization and provisions	(1,49)	(1,24)	(0,55)	(10,14)	(10,32)
Profit/loss after tax, employee profit-sharing, depreciation, amortization and provisions	(1,56)	(1,30)	0,30	(10,21)	(11,61)
Dividend per share	-	-	-	-	-
STAFF (in € thousands)					
Average number of employees during the year	72	64	53	48	48
Total payroll for the year	3 745	3 531	2 806	2 373	2 139
Total employee benefits paid for the year (social security, social agencies, etc.)	15	-	-	-	-

21.6. Dividend payout policy

21.6.1. Dividends paid over the last three years

None.

21.6.2. Dividend payout policy

Given its positioning as a growth company, as of the registration date of this reference document, the company does not intend to implement a regular dividend payout policy.

21.7. Legal and arbitration proceedings

During the 12 months preceding the registration date of this reference document, the company was not involved in any administrative, criminal, legal or arbitration proceedings that could have a significant negative impact not reflected in its financial statements on the company, its business, its financial position, its earnings or its development nor, to its knowledge, is the company subject to the threat of such proceedings as of the registration date of this reference document.

21.8. Significant change in the financial or trading position

To the company's knowledge, there has been no significant change in the company's financial or trading position since December 31, 2013.

22. ADDITIONAL INFORMATION

22.1. Share capital

22.1.1. Amount of share capital

As of the filing date of this reference document, the Company's capital was -€621,187.60 divided into 6,211,876 fully paid common shares, each with a par value of €0.10.

22.1.2. Shares not representing capital

None.

22.1.3. Company shares pledged as collateral, guarantees or security

None.

22.1.4. Acquisition by the company of its own shares

The combined shareholders' meeting of the company held on June 18, 2013 authorized the board of directors, for an 18-month period from the date of the meeting, to implement a share buyback program under Article L. 225-209 of the French commercial code (Code de commerce) and in accordance with the General Regulation of the *Autorité des marchés financiers* (AMF) under the conditions detailed below:

Maximum number of shares that may be purchased: 10% of the share capital on the share buyback date. When the shares are acquired for the purpose of making a market and increasing liquidity, the number of shares included in the calculation of the 10% limit specified above corresponds to the number of shares purchased, less the number of shares resold over the duration of the authorization.

The objectives of the share buyback are to:

- ensure the liquidity of the company's share under a liquidity agreement to be entered into with an investment services provider, in accordance with the code of conduct recognized by the *Autorité des marchés financiers*;
- honor obligations associated with stock option, bonus share or employee savings plans or other allocations of shares to employees and managers of the company or affiliated companies;
- deliver shares upon the exercise of rights attached to marketable securities giving access to the capital;
- purchase shares for the purpose of holding them for subsequent delivery as a means of exchange or payment for a potential acquisition; or
- cancel any or all of the repurchased shares, provided resolution eight below is adopted and, if so, under the conditions specified therein.

Maximum purchase price: €30 per share. This purchase price will be adjusted, if necessary, to reflect transactions involving the capital (including capitalization of reserves and bonus issues, share splits or reverse splits) that may have occurred during the authorization period;
The number of shares acquired by the company for the purpose of holding them for subsequent delivery as a means of payment or exchange in a merger, spin-off or split-up transaction may not exceed 5% of the company's capital.

Maximum amount of funds that may be used for share buybacks: €18,000,000

The repurchased shares may be canceled.

In an agreement dated March 14, 2012, the company commissioned BIL Finance (formerly Dexia Securities France) to implement a one-year, automatically renewable liquidity agreement with an initial allocation of €500,000. This figure was supplemented on May 30, 2012 with an additional contribution of €500,000.

Over the course of fiscal year 2013, the share buyback program was therefore used only in connection with the liquidity agreement to meet the objective of making a market in the company's shares and increasing their liquidity. At December 31, 2013, the company held 40,326 shares (representing 0.65% of the capital), each with a par value of €0.10, under this agreement, for a book value of €384,694.22 measured at the purchase price of the shares and for a total par value of €4,032.60. These shares were purchased at an average price of €9.54. Over the course of fiscal year 2013, 60,539 shares were purchased and 83,061 shares were sold under this agreement. The average purchase price was €8.359 and the average sale price was €9.8676. Trading costs in 2013 were €25,000. The company did not purchase any treasury shares outside of the liquidity agreement.

The company suspended the liquidity agreement with BIL Finance on April 23, 2013, as announced in the press release of that same date. At that time, the liquidity account comprised 27,330 Adocia shares and €748,411.58 in cash.

Starting with April 24, 2013, and for a two-month period, automatically renewable for successive one-month periods, Gérard Soula, Adocia's main shareholder and chairman and chief executive officer, commissioned BIL Finance to implement a liquidity agreement, to which 10,000 Adocia shares and €30,000 were allocated

Via a press release date June 24, 2013, the liquidity agreement that Gérard Soula, Adocia's main shareholder and chairman and chief executive officer, had commissioned BIL Finance to implement since April 24, 2013 was terminated.
Furthermore, on the same press release dated June 24, 2013, the company announced the resumption of its liquidity agreement with BIL Finance. At that date of the resumption of the agreement on June 25, 2013, the resources allocated to this agreement have been reduced by €400,000 to 27,330 Adocia shares and €348,411.58.

Lastly, on December 31, 2013, the agreement between the company and DSF Markets (formerly BIL Finance) comprised 40,326 Adocia shares and €215,305.78 in cash.

22.1.5. Potential capital

As of the filing date of this reference document, there were three different types of shares giving access to the capital. Details are provided below:

Stock warrant plan (*bons de souscription d'actions* — BSA)

	$BSA_{06\text{-}2011}$	**$BSA_{09\text{-}2011}$**	**$BSA_{12\text{-}2013}$**
Date of shareholders' meeting	June 17, 2011	June 17, 2011	June 18, 2013
Date of chairman's decision	**By the shareholders' meeting**	**September 27, 2011**	**December 13, 2013**
Number of BSAs authorized	140	70	20,000
Number of BSAs issued	140	70	20,000
Total number of shares that may be subscribed (1)	1,400	700	20,000
Of which the number that may be subscribed by corporate officers	0	0	20,000
Name of non-corporate officer beneficiaries	J.M Lehn	B. Cabane	Dominique Takizawa Ekaterina Smirnyagina
Earliest BSA exercise date	June 17, 2011	September 27, 2011	January 1, 2014 for 13,333 BSAs January 1, 2015 for 3,333 BSAs January 1, 2016 for 3,333 BSAs
BSA expiration date	June 17, 2021	September 27, 2021	December 13, 2023
BSA issue price	free	free	0.588
BSA exercise price	€85.71 (or €8.571 per share) (1)	€85.71 (or €8.571 per share) (1)	€5.88
Exercise conditions	(2)	(2)	(3)
Number of shares subscribed as of the filing date of the reference document	0	0	0
Aggregate number of lapsed or canceled BSAs as of the filing date of the reference document	0	0	0
BSAs remaining as of the filing date of the reference document	140	70	20,000
Total number of shares that may be subscribed as of the filing date of the reference document	1,400 (1)	700 (1)	13,333

(1) The exercise conditions for the BSAs have been adjusted to reflect the 10-for-1 stock split approved by the shareholders' meeting of October 24, 2011. The phrase "Total number of shares that could originally be subscribed" corresponds to quantified information after accounting for this split.
(2) The BSAs may in principle be exercised over a 10-year period from their allocation date, provided the holder of the BSAs has served continuously, until the BSAs are exercised, as an external scientific advisor to the company.
(3) See section 15.3 above for the BSA exercise conditions.

As of the filing date of the reference document, the full exercise of all the BSAs allocated could lead to the creation of 15,433 shares with a par value of €0.10 (after accounting for the 10-for-1 stock split approved by the shareholders' meeting of October 24, 2011).

Bonus shares

Issue date	01/23/2008	06/06/2008	12/15/2009	03/05/2010	12/07/2010	TOTAL
Number of bonus shares issued [1]	42 000	5 600	5 600	5 600	5 600	**64 400**
Number of bonus shares canceled	2 100	-	-	-	-	**2 100**
Shares vested and held	42 000	5 600	4 200	2 800	2 800	**57 400**
Shares issued but not yet vested			1 400	2 800	2 800	**7 000**

[1] Shares are issued only to employees (who are not corporate officers). This issue vests at the end of each vesting period indicated below (*the "vesting period"*) in the following proportions:

- 25% after a two-year period following the share issue date,
- 25% after a three-year period following the share issue date,
- 25% after a four-year period following the share issue date, and
- 25% after a five-year period following the share issue date,

provided the beneficiaries meet the conditions and criteria for the issue established by the board of directors. Beneficiaries are required to hold the shares for at least two years after the applicable vesting period (*the "holding period"*). Beneficiaries must be categorized as "executives" whose "CCN" (*national collective bargaining agreement for the pharmaceutical industry*) coefficient is greater than or equal to 9A or as Project Managers, based on criteria such as the importance of the project, its degree of innovation and its complexity, as well as the management dimension of the Project Manager. They must have retained their status as employee for the entire vesting period.

Business founders' stock warrants (*Bons de souscription de parts de créateurs d'entreprise* —BSPCEs)

Issue date	12/13/2013	12/13/2013
	Plan no. 1	***Plan no. 2***
Number of BSPCEs issued [2]	28 000	22 400
Number of BSPCEs canceled	-	-
Number of warrants subscribed	28 000	22 400
Number of BSPCEs exercised	-	-

22.1.6. Authorized capital

Resolutions concerning issuances approved by the extraordinary shareholders' meeting of June 18, 2013 are summarized below:

	Period of validity/ Expiration	Ceiling (par value)	Procedures for setting the price	Date and conditions of use by the board of directors
Issuance, with preemptive rights, of shares and/or marketable securities giving immediate and/or future access to the company's capital (9)	26 months/ August 18, 2015	€125,000 (1)		The board has not used this authorization

Issuance, without preemptive rights, through a public offering, of shares and/or marketable securities giving immediate and/or future access to the company's capital and option to grant preemptive rights (10)	26 months/ August 18, 2015	€125,000 (1)	See (2)	The board has not used this authorization
Immediate or future capital increase through the issuance of common shares or any marketable securities giving access to the capital, up to a limit of 20% of the share capital per year, without shareholders' preemptive rights, by means of an offer to qualified investors or a restricted circle of investors within the meaning of Article L. 411-2 II of the French monetary and financial code (private placement) (11)	26 months/ August 18, 2015	€125,000 (1) and up to a limit of 20% of the share capital existing on the transaction date and per year	See (2)	The board has not used this authorization
Authorization granted to the board, in the event of an issuance of shares or of any marketable security giving access to the capital without shareholders' preemptive rights, to set the issue price up to a limit of 10% of the share capital and within the limits specified by the shareholders' meeting (12)	26 months/ August 18, 2015	up to a limit of 10% of the share capital per year	See (3)	The board has not used this authorization
Option to increase the number of shares to be issued in the event of a capital increase with or without preemptive rights (13)	26 months/ August 18, 2015	15% of the initial issuance (1) (4)	Same price as the initial issuance	The board has not used this authorization
Issuance of common shares or of marketable securities giving access to the capital as consideration for securities tendered should the company initiate a public offer with an exchange component (14)	26 months/ August 18, 2015	€70,000 (1)		The board has not used this authorization
Delegation of authority granted to the board to increase the share capital, up to a limit of 10% of the capital, as consideration for contributions in kind of equity securities or marketable securities giving access to the capital of third-party companies outside of a public exchange offer	26 months/ August 18, 2015	€70,000 and up to a limit of 10% of the share capital per year (1)		The board has not used this authorization
Delegation of authority granted to the board to increase the capital through the capitalization of premiums, reserves, earnings or other	26 months/ August 18, 2015	€100,000		The board has not used this authorization
Authorization given to the board to grant company stock options (18)	38 months/ August 18, 2016	180,000 shares (5)	See (7)	The board has not used this authorization
Authorization to be given to the board to issue existing or future bonus shares (19)	38 months/ August 18, 2016	180,000 shares and up to a limit of 10% of the capital existing at the time of the issue (5)		The board has not used this authorization
Authorization to be given to the board of directors to issue and grant business founders' stock warrants (BSPCEs), free of charge, to the company's employees and managers (20)	18 months/ December 18, 2014 (6)	180,000 shares (5)	See (8)	The board used this authorization to grant 50,400 business founders' stock warrants (BSPCEs) on December 13, 2013
Issue of stock warrants (BSA) to (i) members of the company's board of directors who are not employees or managers of the company or of one of its subsidiaries, based on the warrants' issue date, (ii) persons bound to the company through a service or consulting contract, or (iii) members of any committee that the board of directors may establish who are not employees or managers of	18 months/ December 18, 2014	30,000 BSAs giving access to 30,000 shares (9)	See (10)	The board used this authorization to grant 20,000 stock warrants (BSAs) on December 13, 2013

the company or of one of its subsidiaries (21)				

(1) These amounts are not an aggregate. The maximum aggregate ceiling authorized by the shareholders' meeting for capital increases in par value terms is set at €200,000. The total par value of issues of debt securities of the company giving access to the company's capital may not exceed €30,000,000;

(2) The issue price of the shares shall be at least equal to the weighted average of the price over the last three trading days prior to the date on which it is set, less, if applicable, the discount authorized by law (i.e., currently 5%) and corrected for any difference in the ex-date. The issue price of marketable securities giving access to the capital shall be such that the amount the company receives immediately plus, if applicable, the amount it is subsequently likely to receive (i.e., for each share issued as a result of the issue of these marketable securities) is at least equal to the issue price defined above;

(3) Up to a limit of 10% of the company's capital (as at the transaction date) per 12-month period, the board may disregard the price-setting conditions specified in the above resolutions and set the issue price of issued common shares and/or marketable securities giving immediate or future access to the capital as follows:

- the issue price of common shares shall be at least equal to the weighted average of the price over the last three trading days prior to the date on which it is set, possibly less a maximum discount of 20%; in any case, it may not be less than the par value of a company share on the issue date of the relevant shares,
- the issue price of marketable securities giving access to the capital shall be such that the amount the company receives immediately plus, if applicable, the amount it is subsequently likely to receive (i.e., for each share issued as a result of the issue of these marketable securities) is at least equal to the issue price defined in the above paragraph;

(4) 15% or any other percentage that may have been set by decree;

(5) 200,000 shares and not exceeding 5% of the company's share capital, on a fully diluted basis (that is, assuming all the outstanding marketable securities and other rights giving access to the company's capital are exercised). The total number of shares that may be subscribed upon exercise of the stock options granted and not yet exercised may never exceed one-third of the share capital;

(6) This authorization shall terminate and the BSPCEs that have not yet been granted by the board of directors shall automatically lapse on the earlier of the following dates: (i) December 18, 2014, or (ii) the date on which the conditions specified in Article 163 bis G of the French general tax code (Code général des impôts) cease to be met;

(7) The stock option price shall be set by the board on the option grant date as follows: the board may set the stock option price by reference to the closing sale price of a share on this regulated market on the day prior to the day on which the board decided to grant the options. However, the option price may not under any circumstances be less than ninety-five percent (95%) of the average price over the last 20 trading days prior to the day on which the board decided to grant the options;

(8) The subscription price shall be set by the board of directors when the BSPCEs are granted and shall be at least equal to the higher of the following three amounts:

- the closing sale price of a share on this regulated market on the day prior to the day on which the board decided to grant the BSPCEs;
- ninety-five percent (95%) of the average price over the last 20 trading days prior to the day on which the board decided to grant the BSPCEs;
- if one or more capital increases were carried out less than six months before the board decided to grant the relevant BSPCEs, the subscription price used for one common share of the company in the most recent of said capital increases measured on the grant date of each BSPCE;

(9) 30,000 shares and not exceeding 1% of the company's capital, on a fully diluted basis (that is, assuming all the outstanding marketable securities and other rights giving access to the company's capital are exercised);

(10) The exercise price of the BSAs shall be set by the board of directors on the BSA grant date and shall be at least equal to the weighted average price over the last 20 trading days prior to the day on which said BSA was granted by the board.

22.1.7. Information about the capital of the company which is under option or agreed conditionally or unconditionally to be put under option

To the best of the company's knowledge, there are no call or put options or other commitments to company shareholders or granted by company shareholders on company shares.

22.1.8. History of share capital

22.1.8.1 Historical changes:

The table below presents the changes in the company's capital since its creation. These historical data do not reflect the 10-for-1 stock split decided by the shareholders' meeting from October 24, 2011 to November 15, 2011. From that date, the data reflect this 10-for-1 stock split.

Issue date	Type of transaction	Capital	Issue premium	Number of shares issued	Number of shares constituting the capital	Par value	Share capital	Issue price per share before 10-for-1 stock split
12/30/2005	Incorporation (i)	€4,000,000	-	400,000	400,000	10	€4,000,000	€10
05/05/2006	Capital reduction (ii)	-€3,000,000	-	-300,000	100,000	10	€1,000,000	N/A
07/01/2006	Capital reduction (iii)	-€200,000	-	-20,000	80,000	10	€800,000	N/A
07/31/2006	Issue of shares (iv)	€600,000	-	60,000	140,000	10	€1,400,000	€10
10/19/2007	Conversion of common shares into class B preferred shares	-	-	-	140,000	10	€1,400,000	N/A
10/19/2007	Issue for cash of Class A preferred shares with ratchet BSAs attached	€933,390	€7,066,695.69	93,339	233,339	10	€2,333,390	€85.71
12/20/2007	Issue for cash of Class A preferred shares with ratchet BSAs attached	€466,680	€3,533,234.28	46,668	280,007	10	€2,800,070	€85.71
10/22/2009	Capital reduction (v)	-€2,520,063	-	-	280,007	1	€280,007	N/A
10/22/2009	Issue for cash of Class A preferred shares with Tranche 2 BSAs and ratchet BSAs attached	€43,056	€3,647,273.76	43,056	323,063	1	€323,063	€85.71
11/02/2009	Exercise of Tranche 2 BSAs	€3,616	€306,311.36	3,616	326,679	1	€326,679	€85.71
12/01/2009	Issue for cash of Class A preferred shares with Tranche 4 BSAs and ratchet BSAs attached	€15,556	€1,317,748.76	15,556	342,235	1	€342,235	€85.71
12/14/2009	Exercise of Tranche 2 BSAs	€2,333	€197,628.43	2,333	344,568	1	€344,568	€85.71
12/14/2009	Exercise of Tranche 4 BSAs	€7,778	€658,874.38	7,778	352,346	1	€352,346	€85.71
12/23/2009	Issue for cash of Class A preferred shares with Tranche 4 BSAs and ratchet BSAs attached	€46,668	€3,953,246.28	46,668	399,014	1	€399,014	€85.71

Issue date	Type of transaction	Capital	Issue premium	Number of shares issued	Number of shares constituting the capital	Par value	Share capital	Issue price per share before 10-for-1 stock split
03/05/2010	Vesting of bonus shares	€1,050	-	1,050	400,064	1	€400,064	N/A
04/06/2010	Exercise of Oreo BSAs	€5,424	-	5,424	405,488	1	€405,488	€85.71
06/01/2010	Vesting of bonus shares	€140	-	140	405,628	1	€405,628	N/A
06/18/2010	Exercise of Tranche 2 BSAs	€852	€72,172.92	852	406,480	1	€406,480	€85.71
06/18/2010	Exercise of Tranche 2 BSAs	€431	€36,510.01	431	406,911	1	€406,911	€85.71
12/10/2010	Exercise of Tranche 2 BSAs	€14,296	€1,211,014.16	14,296	421,207	1	€421,207	€85.71
12/10/2010	Exercise of Tranche 4 BSAs	€23,334	€1,976,623.14	23,334	444,541	1	€444,541	€85.71
03/04/2011	Vesting of bonus shares	€1,050	-	1,050	445,591	1	€445,591	N/A
06/20/2011	Vesting of bonus shares	€140	-	140	445,731	1	€445,731	N/A
12/15/2011	Vesting of bonus shares	€140	-	1,400	4,458,710	0.10	€445,871	N/A
02/14/2012	Issue of shares – public offering	€159,279.80	€25,134,352.44	1,592,798	6,051,508	0.10	€605,150.80	€15.88
03/07/2012	Vesting of bonus shares	€1,050	-	10,500	6,062,008	0.10	€606,200.80	N/A
03/14/2012	Issue of shares – public offering (overallotment clause)	€13,026.80	€2,055,629.04	130,268	6,192,276	0.10	€619,227.60	€15.88
06/15/2012	Vesting of bonus shares	€280		2,800	6,195,076	0.10	€619,507.60	N/A
12/19/2012	Vesting of bonus shares	€280	-	2,800	6,197,876	0.10	€619,787.60	N/A
03/26/2013	Vesting of bonus shares	€840	-	8,400	6,206,276	0.10	€620,627.60	N/A
06/18/2013	Vesting of bonus shares	€280		2,800	6,209,076	0.10	€620,907.60	N/A
12/13/2013	Vesting of bonus shares	€280	-	2,800	6,211,876	0.10	€621,187.60	N/A

(i) One-fifth of the 400,000 shares constituting the share capital were paid up on December 16, 2005, with the balance paid up on December 20, 2005.

(i) Capital reduction through the outright cancellation of 300,000 shares.

(i) Capital reduction to offset losses.

(iv) 60,000 new shares were paid up at one-quarter of their par value on subscription, with the balance paid up on November 15, 2006.

(v) Capital reduction due to losses.

22.1.8.2 Change in the company's shareholder structure since December 31, 2012

	Situation at December 31, 2013			Situation at December 31, 2012		
	Number of shares	% of capital	% of voting rights	Number of shares	% of capital	% of voting rights
Soula Family	**1 550 933**	**25%**	**30%**	**1 551 720**	**25%**	**30%**
Gérard Soula	898 463	14%	17%	899 250	15%	17%
Olivier Soula	317 490	5%	6%	317 490	5%	6%
Rémi Soula	317 490	5%	6%	317 490	5%	6%
Laure Soula	17 490	0%	0%	17 490	0%	0%
Financial investors	**2 916 042**	**47%**	**54%**	**3 077 962**	**50%**	**56%**
IdInvest fund	683 710	11%	13%	683 710	11%	13%
Amundi fund	179 890	3%	4%	341 810	6%	7%
Viveris fund	364 754	6%	7%	364 754	6%	7%
BioAM fund (Bpifrance Investissement)	341 820	6%	7%	341 820	6%	7%
Oréo Finance	191 343	3%	2%	191 343	3%	2%
Deleage Trust	68 360	1%	1%	68 360	1%	1%
SHAM [1]	386 145	6%	6%	386 145	6%	6%
Innobio (Bpifrance Investissement)	700 020	11%	14%	700 020	11%	14%
Key employees	**49 000**	**1%**	**1%**	**35 000**	**1%**	**0%**
Scientific committee (stock warrants)						
Directors (stock warrants)						
Treasury shares	**40 326**	1%		**62 848**	**1%**	-
Other shareholders*	**1 655 575**	**27%**	**16%**	**1 470 346**	**24%**	**14%**
Total	**6 211 876**	**100%**	**100%**	**6 197 876**	**100%**	**100%**

* Including any bearer shares held by the company's long-standing financial investors.

Breakdown of the company's capital and voting rights:

	Situation at December 31, 2013 on an undiluted basis			Situation at December 31, 2013 on a fully diluted basis [1]		
	Number of shares	% of capital	% of voting rights	Number of shares	% of capital	% of voting rights
Soula Family	**1 550 933**	**25%**	**30%**	**1 550 933**	**25%**	**29%**
Gérard Soula	898 463	14%	17%	898 463	14%	17%
Olivier Soula	317 490	5%	6%	317 490	5%	6%
Rémi Soula	317 490	5%	6%	317 490	5%	6%
Laure Soula	17 490	0%	0%	17 490	0%	0%
Financial investors	**2 916 042**	**47%**	**54%**	**2 916 042**	**46%**	**53%**
IdInvest fund	683 710	11%	13%	683 710	11%	13%
Amundi fund	179 890	3%	4%	179 890	3%	3%
Viveris fund	364 754	6%	7%	364 754	6%	7%
BioAM fund (Bpifrance Investissement)	341 820	6%	7%	341 820	5%	7%
Oréo Finance	191 343	3%	2%	191 343	3%	2%
Deleage Family [2]	68 360	1%	1%	68 360	1%	1%
SHAM (*)	386 145	6%	6%	386 145	6%	6%
Innobio (Bpifrance Investissement)	700 020	11%	14%	700 020	11%	14%
Key employees	49 000	1%	1%	109 200	2%	1%
Scientific committee (stock warrants)				2 100	0%	0%
Directors (stock warrants)				20 000	0%	0%
Treasury shares	40 326	1%		40 326	1%	
Other shareholders [3]	1 655 575	27%	16%	1 655 575	26%	16%
TOTAL	**6 211 876**	**100%**	**100%**	**6 294 176**	**100%**	**100%**

(1) On the date of this reference document, the dilutive instruments issued by the company consisted of (i) 64,400 shares (after accounting for the 10-for-1 stock split decided by the shareholders' meeting of October 24, 2011) issued as bonus shares by the company to key employees, of which 9,800 shares are in the vesting period as described in detail in section 21.1.5 herein; (ii) 2,100 stock warrants (BSAs) entitling holders to subscribe 2,100 shares (after accounting for the 10-for-1 stock split decided by the shareholders' meeting of October 24, 2011); (iii) 20,000 stock warrants (BSAs) entitling holders to subscribe 20,000 shares granted to independent directors; and (iv) 50,400 business founders' stock warrants (BSPCEs).

(2) The 68,360 shares are held equally by André Jean Deleage, Michel William Deleage, Emmanuel Yves Deleage and Philippe Olivier Deleage, i.e., 17,090 shares each.

(3) Including any bearer shares held by the company's long-standing financial investors.

22.1.8.3 Share price performance – Risk of price fluctuations

The share have been traded on the Euronext regulated market in Paris since February 18,2013 at €15.88 at the time of its IPO.

During 2013, the share traded at a low of €5.02 on September 27, 2013 and a high of €13.62 on February 18,2013. As of December 31,2013 the share traded €5.96.

On the first months of the 2014 year, the share moved from €5.96 to €12 on April 23,2014, the day prior to the filing date of this reference document, leading to a company's market capitalization on of €74.5 million.

22.2. Articles of incorporation and bylaws

22.2.1. Corporate purpose

The company's purpose, directly or indirectly, in France and abroad, is:

- research and development of polymer materials to create controlled-release systems for peptides and proteins of pharmaceutical interest;
- the registration, study, acquisition and granting of all patents, licenses, processes, trademarks and protection of specialized knowledge in any way arising from or relating to the domains or technologies falling within the scope of the corporate purpose;
- the design, development, manufacture, distribution, import, export and use, by any means, of medicines, proprietary drugs and other healthcare goods;
- the creation, acquisition, rental, and lease management of all businesses, the leasing, establishment, and operation of all entities, businesses, plants and workshops relating to any of the specified activities;
- the company's direct or indirect participation in all financial, real-estate or personal transactions and in any civil, commercial or industrial companies that may fall within the scope of the corporate purpose or any similar, related or complementary purpose.

22.2.2. Management and supervisory bodies

22.2.2.1 Board of directors

22.2.2.1.1 Composition of the board of directors (Articles 11.1 and 11.2 of the bylaws)

The company shall be administered by a board composed of natural persons or legal entities whose number shall be determined by the ordinary shareholders' meeting within the limits of the law.

Any legal entity may, upon appointment, designate a natural person as permanent representative to the board of directors. The permanent representative's term of office shall be the same as that of the legal-entity director that he or she represents. If the legal entity dismisses its permanent

representative, it shall immediately appoint a replacement. The same provisions shall apply in the event of the death or resignation of the permanent representative.

Directors are appointed for a three-year term, which shall expire at the close of the ordinary shareholders' meeting called to approve the financial statements for the previous fiscal year and held in the year in which the term of said director expires.

Directors may be reappointed; they may be dismissed at any time by decision of the shareholders' meeting.

Should one or more directorships become vacant due to death or resignation, the board of directors may make provisional appointments between two shareholders' meetings.

Appointments made by the board pursuant to the above paragraph shall be subject to approval by the next ordinary shareholders' meeting.

The absence of such approval shall not affect the validity of the board's prior resolutions and acts.

When the number of directors falls below the legal minimum, the remaining directors shall immediately call an ordinary shareholders' meeting so as to fill the vacant positions on the board.

An employee of the company may be named director. His or her employment contract must, however, correspond to actual employment. In that case, he or she shall not lose the benefit of his or her employment contract.

The number of directors bound to the company by an employment contract may not exceed one-third of directors in office.

The number of directors over the age of 70 may not exceed one-third of directors in office. When this limit is exceeded during a term of office, the oldest director shall be considered to have automatically resigned at the close of the next shareholders' meeting.

22.2.2.1.2 Board observers (Article 15 of the bylaws)

The ordinary shareholders' meeting may, on the proposal of the board of directors, appoint board observers (*censeurs*). The board of directors may also appoint them directly, subject to approval by the next shareholders' meeting.

The board observers, who may not number more than five, shall form a board. They shall be selected freely for their expertise.

They shall be appointed for a three-year term expiring at the close of the ordinary shareholders' meeting called to approve the financial statements for the previous fiscal year.

This advisory board shall consider matters submitted by the board of directors or its chairman for its opinion. Board observers shall attend meetings of the board of directors and take part in deliberations only in an advisory capacity; their absence shall not, however, affect the validity of the deliberations.

They shall be called to meetings of the board under the same conditions as directors.

The board of directors may pay board observers compensation out of the amount of directors' fees allocated to directors by the shareholders' meeting.

22.2.2.1.3 Meetings of the board of directors (Article 12 of the bylaws)

The board of directors shall meet as often as the interests of the company so require.

The chairman shall call directors to meetings of the board. This may be done by any means, whether in writing or verbally.

The chief executive officer may also ask the chairman to call a meeting of the board of directors to consider a specific agenda.

Additionally, directors representing at least one-third of the members of the board may validly call a board meeting. In that case, they must specify the meeting agenda.

When a works council has been formed, the representatives of this council, appointed in accordance with the provisions of the French labor code (Code du travail), shall be called to all meetings of the board of directors.

Meetings of the board shall be held either at the registered office or at any other location in France or abroad.

Decisions of the board shall be valid only if the number of members in attendance is at least equal to half the members.

Decisions of the board of directors shall be made by a majority of votes; in the event of a tie, the chairman of the meeting shall cast the deciding vote.

The board of directors may adopt its own rules of procedure which may specify, in particular, that directors attending the meeting by means of videoconferencing or other telecommunications equipment in accordance with existing regulations shall be deemed present for the purposes of calculating a quorum and a majority. This provision shall not apply to the adoption of the decisions referred to in Articles L. 232-1 and L. 233-16 of the French commercial code.

Directors shall receive the information required to fulfill their duties and mandates and may request all documents they deem necessary.

Any director may authorize, by letter, telegram, telex, fax, email or any other means of remote transmission, another director to represent him or her at a board meeting, but each director may only hold one proxy during a meeting.

Copies or extracts of the deliberations of the board of directors shall be duly certified by the chairman of the board of directors, the chief executive officer, the director temporarily delegated to perform the duties of chairman or a duly authorized proxy holder.

22.2.2.1.4 Powers of the board of directors (Article 13 of the bylaws)

The board of directors shall set the company's business strategy and oversee its implementation. Subject to the powers expressly granted to shareholders' meetings and within the limit of the corporate purpose, it shall consider all issues relating to the company's operations and make decisions on matters affecting the company.

In its relations with third parties, the company shall be bound even by acts done by the board of directors that are not within the corporate purpose, unless it can prove that the third party knew that the act was outside this purpose or could not in view of the circumstances have been unaware of it; disclosure of the bylaws shall not of itself be sufficient proof thereof.

The board of directors shall perform the audits and verifications it deems appropriate.

Furthermore, the board of directors shall exercise the special powers granted to it by law.

22.2.2.2 Executive management (Article 14 of the bylaws)

The chairman of the board of directors, or another natural person appointed by the board of directors and holding the position of chief executive officer, shall oversee the executive management of the company, which is under his or her responsibility.

The chief executive officer shall have extensive powers to act in all circumstances on behalf of the company. He or she shall exercise his or her powers within the limit of the corporate purpose and subject to those expressly granted by law to shareholders' meetings and the board of directors.

He or she shall represent the company in its relations with third parties. The company shall be bound even by acts done by the chief executive officer that are not within the corporate purpose, unless it can prove that the third party knew that the act was outside this purpose or could not in view of the circumstances have been unaware of it; disclosure of the bylaws shall not of itself be sufficient proof thereof.

The chief executive officer may not be more than 75 years old. If the chief executive officer reaches that age, he or she shall be considered to have automatically resigned. His or her term of office may be extended, however, to the next meeting of the board of directors, during which a new chief executive officer shall be appointed.

When the chief executive officer is a director, his or her term of office may not exceed his or her term as director.

The board of directors may dismiss him or her at any time. If the decision to dismiss is made without just cause, it may give rise to damages, except when the chief executive officer assumes the duties of chairman of the board of directors.

By simple decision made by a majority of votes of directors present or represented, the board of directors shall choose between the two methods of executive management referred to in the first subparagraph of the paragraph.

Shareholders and third parties shall be informed of this decision in accordance with legal and regulatory conditions.

The decision so made by the board of directors shall remain in effect until the board decides otherwise or, at its discretion, for the term of office of the chief executive officer.

When the chairman of the board of directors is responsible for the executive management of the company, the provisions applicable to the chief executive officer shall apply to him or her.

In accordance with Article 706-43 of the French code of criminal procedure, the chief executive officer may validly authorize any person of his or her choice to represent the company in criminal proceedings that may be brought against it.

On the proposal of the chief executive officer, the board of directors may empower one or more natural persons to assist the chief executive officer as vice-president.

In conjunction with the chief executive officer, the board of directors shall determine the scope and duration of the powers granted to the vice-president. The board of directors shall determine their compensation. When a vice-president is a director, his or her term of office may not exceed his or her term as director.

The vice-presidents shall have the same powers with respect to third parties as the chief executive officer; in particular, the vice-presidents may engage in legal proceedings.

There may not be more than five vice-presidents.

The vice-president(s) may be dismissed at any time by the board of directors, on the proposal of the chief executive officer. If the decision to dismiss is made without just cause, it may give rise to damages.

Vice-presidents may not be more than 65 years old. If a vice-president in office reaches that age, he or she shall be considered to have automatically resigned. His or her term of office may be extended, however, to the next meeting of the board of directors, during which a new vice-president may be appointed.

When the chief executive officer ceases to perform his or her duties or is prevented from doing so, the vice-president(s) shall continue to fulfill their roles and responsibilities, unless the board of directors decides otherwise, until a new chief executive officer is appointed.

22.2.3. Rights, privileges and restrictions attaching to shares of the company

22.2.3.1 Forms of securities (Article 7 of the bylaws)

Shareholders may choose to hold their fully paid-up shares in registered or bearer form, subject, however, to application of the legal provisions relating to the form of shares held by certain natural persons or legal entities. Shares that are not fully paid up must be held in registered form.

The shares shall be registered in an account under the terms and conditions specified in the applicable laws and regulations.

Ownership of shares delivered in registered form derives from their registration in a registered account.

22.2.3.2 Voting rights (excerpted from Article 9 of the bylaws)

Except where the law provides otherwise, and except in the case of double voting rights as set forth below, each shareholder shall have as many voting rights and may cast as many votes in shareholders' meetings as he or she owns fully paid-up shares. Each redeemable or redeemed share with the same par value, except in the case of double voting rights as set forth below, shall entitle the holder to one vote.

A voting right equivalent to twice that attributed to other shares, based on the proportion of the share capital they represent, may be attributed to all fully paid-up shares (regardless of their class) that can be proved to have been registered in the name of the same shareholder for at least two years; the conversion of preferred shares into common shares shall have no impact on the calculation of the holding period. This right shall also be attributed, in the event of a capital increase through capitalization of reserves, earnings or issue premiums, to newly issued registered shares granted as bonus shares to a shareholder for existing shares that already entitled him or her to this right.

22.2.3.3 Rights to dividends and profits (excerpted from Articles 9, 21 and 22 of the bylaws)

Each share shall entitle its holder to a share of ownership of the corporate assets, to a share of earnings and to the liquidation surplus in proportion to the number and par value of the existing shares.

Whenever it is necessary to own a certain number of shares, whether or not they are preferred shares, or marketable securities in order to exercise a particular right, shareholders or owners of marketable securities shall personally arrange to group the necessary number of shares or marketable securities.

At least five percent (5%) shall be deducted from earnings for the fiscal year, less any prior-year losses, to create a reserve fund known as the "legal reserve." This deduction shall no longer be required when the reserve fund reaches one-tenth of the share capital.

Distributable earnings shall consist of earnings for the fiscal year less prior-year losses and the deduction specified in the previous paragraph, plus earnings carried forward.

If the financial statements for the fiscal year, as approved by the shareholders' meeting, show that there are distributable earnings, the shareholders' meeting shall decide to allocate them to one or more reserve accounts whose allocation or use it controls, to carry them forward or to distribute them as dividends.

Having acknowledged the existence of reserves at its disposal, the shareholders' meeting may decide to distribute amounts from these reserves. In that case, the resolution shall expressly specify the reserve accounts from which these payments shall be drawn. However, dividends shall first be drawn from distributable earnings.

The shareholders' meeting or, alternatively, the board of directors shall set the conditions under which dividends are paid.

However, dividends must be paid no later than nine months after the close of the fiscal year.

The shareholders' meeting called to approve the financial statements for the fiscal year may give each shareholder, for all or part of the dividend paid, the choice between receiving the dividend in cash or in shares.

Similarly, the ordinary shareholders' meeting, acting in accordance with the conditions specified in Article L. 232-12 of the French commercial code, may grant each shareholder an interim dividend and, for all or part of said interim dividend, may give him or her the choice between receiving the interim dividend in cash or in shares. (…)

22.2.3.4 Preemptive rights

Shares in the company carry a preemptive right to subscribe to capital increases under the conditions specified in the commercial code.

22.2.3.5 Restrictions on voting rights

The bylaws contain no clause that restricts the voting rights attaching to the shares.

22.2.3.6 Identifiable bearer shares (Titres au porteur identifiables)

The company may, under applicable legal and regulatory conditions, at any time and at its own expense, ask any authorized body to provide it with the name or, in the case of a legal entity, the corporate name, nationality and address of holders of shares that grant an immediate or future voting right at its own shareholders' meetings, as well as the number of shares held by each of them and, if applicable, any restrictions on these shares.

22.2.3.7 Buyback by the company of its own shares

See section 21.1.3 "Acquisition by the company of its own shares."

22.2.4. Actions required to change the rights of shareholders

The rights of shareholders as stated in the company's bylaws may only be changed by an extraordinary meeting of the company's shareholders.

22.2.5. Shareholders' meetings

22.2.5.1 Holding of shareholders' meetings (Article 19 of the bylaws)

Shareholders' meetings shall be called and held under the conditions set by law.

When the company wishes to call a meeting by electronic means of communication rather than by mail, it must obtain the prior approval of the shareholders concerned, who shall provide their email address.

Meetings shall be held at the registered office or at any other location specified in the notice of meeting.

The right to attend meetings shall be governed by applicable laws and regulations and shall be subject, among others, to registration of the securities in the name of the shareholder or registered intermediary by midnight, Paris time, on the third business day prior to the meeting, either in the registered securities accounts held by the company or in bearer share accounts held by the authorized intermediary.

If a shareholder is unable to attend the meeting in person, he or she may choose one of the following three options:

- appoint a proxy under the conditions permitted by law and by regulation,
- vote by mail, or
- send a proxy to the company without naming an agent,
- under the conditions specified by law and by regulation.

The board of directors may, under the conditions specified by the applicable laws and regulations, arrange for shareholders to attend the meetings and vote by videoconference or by means of telecommunications that permit them to be identified. If the board of directors decides to implement this option for a specific meeting, this decision by the board is stated in the notice of meeting and/or notification to attend. Shareholders attending meetings by videoconference or by any of the other means of telecommunications referred to above, at the board of directors' discretion, shall be deemed present for the purposes of calculating a quorum and a majority.

Meetings shall be chaired by the chairman of the board of directors or, in his or her absence, by the chief executive officer, a vice-president if he or she is also a director, or a director specially appointed for that purpose by the board. Otherwise, the meeting shall elect its own chairman.

The duties of teller (*scrutateur*) shall be performed by the two members of the meeting who are present, have agreed to perform these duties and have the most votes. The meeting officers (*bureau*) shall appoint the secretary, who need not be a shareholder.

An attendance sheet shall be drawn up under the conditions specified by law.

The proceedings of the ordinary shareholders' meeting, when first convened, shall only be valid if shareholders present or represented own at least one-fifth of shares with voting rights. The proceedings of the ordinary shareholders' meeting, when convened a second time, shall be valid regardless of the number of shareholders present or represented.

The resolutions of the ordinary shareholders' meeting shall be adopted by a majority of votes of shareholders present or represented.

The proceedings of the extraordinary shareholders' meeting, when first convened, shall only be valid if shareholders present or represented own at least one-quarter of shares with voting rights. The

proceedings of the extraordinary shareholders' meeting, when convened a second time, shall be valid only if shareholders present or represented own at least one-fifth of shares with voting rights.

The resolutions of the extraordinary shareholders' meeting shall be adopted by a two-thirds majority of shareholders present or represented.

Copies or extracts of the minutes of the meeting shall be duly certified by the chairman of the board of directors, by a director performing the duties of the chief executive officer or by the meeting secretary.

22.2.5.2 Powers of the shareholders' meetings (Article 19 of the bylaws)

The ordinary and extraordinary shareholders' meetings shall exercise their respective powers under the conditions specified by law.

22.2.6. Provisions that may have the effect of delaying, deferring or preventing a change of control

The company's bylaws contain no provisions that may have the effect of delaying, deferring or preventing a change of control.

22.2.7. Specific provisions governing changes in the capital

The company's bylaws contain no specific provisions governing changes in its capital.

23. MAJOR AGREEMENTS

With the exception of the agreements described below, the company has not entered into any major agreements other than those signed in the normal course of business, it being understood that the company has signed several collaborative development agreements with large pharmaceutical groups for the development of new innovative formulations. However, at this stage of the company's development, none of these collaboration agreements is considered to be of major strategic importance given the insufficient technical progress made (see paragraphs 6.1 and 11.3 of this reference document).

23.1. OSEO Innovation agreement of March 12, 2007

As part of the Osteoporosis project, the company signed an agreement with OSEO on March 12, 2007 under which it received a reimbursable advance totaling €2.25 million for the development of a new system for local controlled release of growth factors for bone regeneration. After fulfilling all the technical and financial conditions, the company received the full amount of this reimbursable assistance in four payments made between March 15, 2007 and February 15, 2010.

In the event of the program's success, the company agreed to repay OSEO the sum of €2.25 million according to the following terms:

(i) The company agreed to repay OSEO the full amount lent based on the following payment schedule:

- €300,000 by March 31, 2012,
- €400,000 by March 31, 2013,
- €450,000 by March 31, 2014,
- €500,000 by March 31, 2015,
- €600,000 by March 31, 2016.

(ii) In the event of assignments of licenses or marketing, the company agreed to pay OSEO, by March 31 of each year and starting on January 1, 2010:

- 49.51% of income, excluding tax, from assignments or concessions of licenses, patents or know-how received during the previous calendar year, when such assignments or concessions concern all or part of the results of the financed program, and
- 49.51% of income, excluding tax, generated by the marketing and particularly the sale to a third party or the use by the company for its own purposes of the prototypes, pilot products and samples developed under the financed program.

In this case, the sums paid will first be deducted, by the same amount, from the last payment owed to OSEO Innovation, as specified in the above payment schedule, and, where applicable, from the next to last payment.

In the event of the program's technical or commercial failure, even if such failure is partial, given the nature of the work carried out under the Osteoporosis project, the company agreed to repay OSEO a fixed sum of €700,000 according to the following terms:

- €300,000 by March 31, 2012,
- €400,000 by March 31, 2013.

If the company fails to fulfill its obligations, OSEO would have a right to demand the repayment of the advance granted.

Under the terms of the agreement, €700,000 was repayable by March 31, 2013 regardless of the outcome of the program, which is unknown as of the date of this reference document. The company repaid the first €300,000 installment in 2012 and a second payment of €400,000 was made on April 1, 2013.
The balance of the advance (i.e. €1.55 million) will be repayable only if OSEO recognizes the technical and/or commercial success of the financed project.

In October 2012, the Company had made an application for a finding of commercial and technical failure on this issue. In March 2014, following the filing of all documents necessary for the investigation of the case, the Company received a letter from the BPI (formerly OSEO) dated March 24, 2014, indicating that the next payment mentioned in (i) was delayed to 03/31/2015. No reimbursment is therefore expected by then.

23.2. OSEO Innovation-ERDF agreements of July 20, 2010

As part of the Insulin project, the company signed two agreements with OSEO on July 20, 2010 for the development of a fast-acting "human" insulin formulation in connection with a phase I clinical trial for a total of €840,000.

(a) Reimbursable advance of €420,000

Under the terms of the first agreement, the company received a reimbursable advance in the amount of €420,000. The full amount of this assistance was received in four payments made between July 26, 2010 and November 16, 2011.

In the event of the program's success, the company agreed to repay OSEO the sum of €420,000 according to the following terms:

(i) The company agreed to repay OSEO the full amount lent based on the following payment schedule:

- €22,500 by March 31, 2014, June 30, 2014, September 30, 2014 and December 31, 2014,
- €25,000 by March 31, 2015, June 30, 2015, September 30, 2015 and December 31, 2015,
- €25,000 by March 31, 2016, June 30, 2016, September 30, 2016 and December 31, 2016,
- €32,500 by March 31, 2017, June 30, 2017, September 30, 2017 and December 31, 2017.

It is understood that these payments would, where applicable, be reduced in proportion to the sums actually paid by OSEO.

(ii) In the event of assignments of licenses or marketing, the company agreed to pay OSEO, by March 31 of each year and starting on January 1, 2010:

- 24.58% of income, excluding tax, from assignments or concessions of licenses, patents or know-how received during the previous calendar year, when such assignments or concessions concern all or part of the results of the financed program, and
- 24.58% of income, excluding tax, generated by the marketing and particularly the sale to a third party or the use by the company for its own purposes of the prototypes, pilot products and samples developed under the financed program.

In this case, the sums paid will first be deducted, by the same amount, from the last payment owed to OSEO Innovation, as specified in the above payment schedule, and, where applicable, from the next to last payment, it being understood that such repayments cannot exceed the principal amount of the assistance received.

In the event of the program's technical or commercial failure, **even if such failure is partial**, given the nature of the work carried out under the Insulin project, the company agreed to repay OSEO a fixed sum of €190,000 according to the following terms:

- €22,500 by March 31, 2014, June 30, 2014, September 30, 2014 and December 31, 2014,
- €25,000 by March 31, 2015, June 30, 2015, September 30, 2015 and December 31, 2015.

It is understood that these payments would, where applicable, be reduced in proportion to the sums actually paid by OSEO.

If the company fails to fulfill its obligations, OSEO would have a right to demand the repayment of the advance granted.

Since the results of this project contributed to the signing of the licensing agreement with the Eli Lilly group, on June 19, 2012 the company repaid the total amount of the advance received, i.e. €420,000, as provided by the agreement.

(b) ERDF grant of €420,000

Under the terms of the second agreement, the company received an OSEO Innovation-ERDF grant totaling €420,000, the entirety of which was received in four payments made between July 26, 2010 and November 16, 2011.
The agreement stipulates no obligation to repay this grant unless the company fails to fulfill its obligations, in which case OSEO has a right to demand the repayment of the grant.

23.3. OSEO Innovation agreements of April 25, 2012

As part of the Insulin project, the company signed an agreement with OSEO on April 25, 2012 under which the company received a reimbursable advance totaling €800,000 for the development of a fast-acting "human" insulin formulation and the Phase 2a clinical trial. After fulfilling all the technical and financial conditions, the company received the full amount of this reimbursable assistance on April 30, 2012.

In the event of the program's success, the company agreed to repay OSEO the sum of €800,000 according to the following terms:

(iii) The company agreed to repay OSEO the full amount lent based on the following payment schedule:

- €32,500 by March 31, 2017,
- €32,500 by June 30, 2017,
- €32,500 by September 30, 2017,
- €32,500 by December 31, 2017,
- €37,500 by March 31, 2018,
- €37,500 by June 30, 2018,
- €37,500 by September 30, 2018,
- €37,500 by December 31, 2018,
- €50,000 by March 31, 2019,
- €50,000 by June 30, 2019,
- €50,000 by September 30, 2019,
- €50,000 by December 31, 2019,
- €80,000 by March 31, 2020,
- €80,000 by June 30, 2020,
- €80,000 by September 30, 2020,
- €80,000 by December 31, 2020.

(iv) In the event of assignments of licenses or marketing, the company agreed to pay OSEO, by March 31 of each year and starting on January 1, 2014:

- 44.82% of income, excluding tax, from assignments or concessions of licenses, patents or know-how received during the previous calendar year, when such assignments or concessions concern all or part of the results of the financed program, and
- 44.82% of income, excluding tax, generated by the marketing and particularly the sale to a third party or the use by the company for its own purposes of the prototypes, pilot products and samples developed under the financed program.

In this case, the sums paid will first be deducted, by the same amount, from the last payment owed to OSEO Innovation, as specified in the above payment schedule, and, where applicable, from the next to last payment.

In the event of the program's technical or commercial failure, **even if such failure is partial**, given the nature of the work carried out under the fast-acting human Insulin project, the company agreed to repay OSEO a minimum sum of €280,000 according to the following terms:

- €32,500 by March 31, 2017,
- €32,500 by June 30, 2017,
- €32,500 by September 30, 2017,
- €32,500 by December 31, 2017,
- €37,500 by March 31, 2018,
- €37,500 by June 30, 2018,
- €37,500 by September 30, 2018,
- €37,500 by December 31, 2018.

If the company fails to fulfill its obligations, OSEO would have a right to demand the repayment of the advance granted.

23.4. Coface-International business development insurance agreement of October 1, 2012

As part of its business development in new markets (India and China), the company signed a business development agreement with Coface (French insurance company for foreign trade) on October 26, 2012 in return for the payment of a premium equivalent to 2% of the annual budget.
Under the terms of the agreement, Coface guarantees the reimbursement of 75% of the expenses incurred during the four-year guarantee period, which runs from October 1, 2012 to September 30, 2016.

The company agreed to repay the sums received from Coface according to the Terms and Conditions set out in the agreement during an amortization period that runs until September 30, 2012. The repayment terms are as follows:

- 14% of the billing amount of services provided
- 30% of the sums received from the assignment of intellectual property rights

The sums repaid will first be deducted, by the same amount, from the amount of the advance granted for the first guarantee period and then for the following periods, it being understood that such repayments:

- are limited in time (repayment of the advance over a period ending on September 30, 2021),
- will not exceed the principal amount of the total advance received.

For the expenses incurred during the first insured period, i.e. from October 1, 2012 to September 30, 2013, the company received the sum of €91,000 on December 17, 2013.

23.5. Licensing and collaboration agreement with Eli Lilly

On December 14, 2011, Adocia signed a licensing and collaboration agreement with the American Eli Lilly and Company pharmaceutical group (hereinafter "**Eli Lilly**").

This agreement concerns the development and marketing of a fast-acting insulin analog, Humalog®, formulated with BioChaperone® technology ("**BioChaperone® Humalog®**"). Under the terms of this agreement, Adocia granted Eli Lilly exclusive worldwide rights to BioChaperone® for the development, production and marketing of BioChaperone® Humalog®. This agreement covers all potential indications of BioChaperone® Humalog®. Eli Lilly will finance the development of BioChaperone® Humalog®, including the clinical trials, with Adocia and Eli Lilly managing the collaboration through a joint management committee.

This agreement was signed for a term of 10 years following the initial marketing of BioChaperone® Humalog® in any country or for the term of protection of Adocia's rights to its BioChaperone® technology, whichever is greater.

At the end of January 2012, Eli Lilly made an initial non-refundable licensing payment of $10 million to Adocia (up-front payment), i.e. €7.6 million. Additional milestone payments of up to $156 million are also planned, conditional upon the achievement of milestones related to the development, regulatory process, market release and attainment of BioChaperone® Humalog® sales targets. Adocia will also receive royalties based on a percentage of international sales of BioChaperone® Humalog® net of various charges, taxes and discounts.

Adocia and Eli Lilly decided to terminate the licensing and collaboration agreement in July 2013. Adocia therefore reacquired its rights to develop ultra-fast acting insulin analog.

23.6. Acquisition of an exclusive licence for a nanotechnology (DriveIn®)

On December 9, 2013, ADOCIA signed an exclusive and worldwide licencing agreement with CNRS, University of Bordeaux I, Polytechnic Institute of Bordeaux and Aquitaine Science Transfert (SATT Aquitaine) for a technnology called *DriveIn*.This license is granted until the expiration of the term of protection of the last patent included int the family of patents granted, i.ei October 30, 2029 (20 years from the filing date of the PCT), subject to their issue, being precised that these patent applications are pending.

As part of this agreement, ADOCIA obtained the right to operate directly or indirectly the patent application filed by Sebastien Lecommandoux and held by the signatories to this agreement (and owners of such patents), and this, in the field of human or animal health , excluding applications in the fields of cosmetics , non-therapeutic dermatology, and dietary supplements.
The patent application licensed to ADOCIA protects a nanoparticulate drug delivery technology. This innovative application covers compounds of hyaluronic acid polymers, hydrophilic natural polymer, and a hydrophobic polymer based on amino acid. It also protects the nanoparticle systems formed by these polymers, such as vesicles. This application is currently under review and Adocia will assume the procedure and the relative costs.
In consideration of the rights thus acquired, ADOCIA is committed to pay an annual fee on a percentage of revenue that would be realized, directly or indirectly, by ADOCIA.

24. INFORMATION FROM THIRD PARTIES, EXPERTS' STATEMENTS AND DECLARATIONS OF INTERESTS

24.1. Designation of experts

None.

24.2. Designation of third parties

None.

25. DOCUMENTS AVAILABLE TO THE PUBLIC

Copies of this reference document are available free of charge at the company's registered office located at 115, avenue Lacassagne, 69003 Lyon. An electronic version is also available on the company's website (www.adocia.com) and on the website of the French financial markets authority (*Autorité des marchés financiers* - AMF*)* (www.amf-france.org).

The bylaws, minutes of shareholders' meetings and other corporate documents of the company, as well as historical financial information and any assessment or statement made by an expert at the company's request which must be made available to shareholders pursuant to the applicable legislation may be consulted free of charge at the company's registered office.

Regulatory information as provided by the General Regulations of the AMF is also available on the company's website (www.adocia.com).

26. INFORMATION REGARDING EQUITY INTERESTS

As of the filing date of this reference document, the company has no equity interests in other companies.

27. GLOSSARY

AFSSAPS	Agence Française de Sécurité Sanitaire et Produits de Santé/*French Agency for the Safety of Health Products*. This authority evaluates the safety of use of health products, monitors them, controls their quality in the laboratory and inspects their sites of manufacturing, distribution and testing, and also circulates information for the correct use of health products.
Amphiphile	Chemical compound simultaneously possessing a hydrophilic group (soluble in water or a solvent) and a hydrophobic group (insoluble in water or a solvent). The hydrophilic or hydrophobic characters of the groups are related in particular to their capacity or lack thereof to form electrostatic interactions with water or a solvent.
Anionic group	Negatively charged group of ions (anions)
Ankylosis	Immobility of a joint caused by injury or disease.
Anticoagulation	Phenomenon reducing or preventing the transformation of liquid blood into a clot (a more viscous and more or less gelatinous form).
Arteriopathy	Any diseases of arteries.
Bedsore (eschar)	Skin lesion resulting from decreased blood flow following an ischemic process
Biosimilar	Generic form a drug whose patent has expired.
Chronic lesion	Significant loss of superficial skin tissues (dermis and epidermis), generally characterized by the absence of healing after 6 weeks of its occurrence and regardless of the conditions of patient management.
Coacervation	The separation of certain macromolecular solutions into two phases.
Complex	Structure formed from several independent chemical entities.
Compliance	The extent to which a patient follows the treatment prescribed.
Crohn's disease	Chronic inflammatory disease of the digestive tract.
Deamidation of asparagine	Non-enzymatic and spontaneous process that converts asparagine, an amino acid of proteins, into aspartic acid.
Dermatitis	A skin reaction caused by exposure to substances that are allergens or irritants.
EMA	European Medicines Agency. This authority evaluates and supervises the development of new drugs for human and veterinary use in the European Union.
Endothelial barrier	Selective permeability barrier enabling and regulating exchanges of molecules of varying sizes (water, salts, proteins, etc.) between the blood and tissues
Enzymatic breakdown	This process involves the destruction of intramolecular bonds of a protein and generally results in the production of smaller molecules. Enzymes, that

	are also proteins, accelerate the natural phenomenon of protein degradation in the body.
Epidermoid carcinoma	A form of skin cancer.
Erysipelas	Non-necrosing infection of the dermis or epidermis.
European Pharmacopoeia	Collection of quality control requirements of medicinal preparations drafted by the European Directorate for the Quality of Medicines and Healthcare, an organization of the European Council.
Excipient	Any substance in a drug product other than the drug substance(s).
FDA	Food and Drug Administration. American agency responsible for approving drugs and medical devices for marketing.
Glucose clamp technique	Reference method used in clinical research to measure sensitivity to insulin.
Glycoregulation	Regulation of the level of blood glucose, or glycemia, by the endocrine system.
Good Manufacturing Practices	Notion of quality assurance, established by the European Commission and applied to the manufacturing of drugs for human or veterinary use.
Graft	A chemical group bound to the molecule in question.
Granulation tissue	Temporary tissue covering a lesion during the healing process.
Growth factor	Protein required for the growth or regeneration of a tissue or organ.
Heparin	Anticoagulant substance present in the body.
ICH	International Conference of Harmonization. International body composed of American, European and Asian health authorities, as well as pharmaceutical companies.
Immunogenicity	Capacity of an antibody to cause an immune reaction.
Incidence	Number of new cases of a pathology found during a given period and for a given population.
Ischemia	Reduced blood flow to an extremity or an organ.
Islets of Langerhans	Located in the pancreas, they contain three types of cells, each secreting a different hormone: i) insulin that lowers blood glucose levels, ii) glucagon that raises blood glucose and iii) gastrin that controls the process of digestion.
IU	International Unit. In pharmacology it is the unit of measurement of the quantity of a substance, based on its biological activity. One IU of insulin is the biological equivalent of about 45.5 µg of pure crystallized insulin.
kDa (kiloDalton)	Unit used to measure the molecular weight of molecules and atoms. The

	value of one Dalton is the atomic weight of the hydrogen atom.
Leukemia	Bone marrow cancer with anarchic proliferation of white blood cells.
Ligand	In chemistry, this is an atom, ion or molecule having the capacity to bind to one or several central atoms or ions.
Lymphoma	Malignant tumor of the lymphatic system.
Marketing Authorization (MA)	Approval of a medicine by health authorities prior to its commercialization.
Multiple sclerosis	Disease of the central nervous system, in particular the brain, optic nerves and spinal cord.
Muscular dystrophy	A progressive degenerative disease of the body's muscles.
Muscular hypoxia	Insufficient oxygenation of muscle tissues.
National Consultative Ethics Committee	Independent French advisory body whose principal mission is to provide opinions and reports dealing with ethics as pertaining to scientific progress.
Necrotizing fasciitis	Infection caused by group A *Streptococcus*.
Nerve fiber (axon)	Single extension emerging from the cell body of neurons whose function is to transport nerve impulses.
Neuropathy	Any disease of the nervous system.
Osteoarticular lesion	A lesion involving both bones and joints.
Pancreas	Gland in proximity to the stomach.
Pharmacodynamics	Study of the effects of a drug on the body, in particular the interaction between its cell receptor and the therapeutic substance.
Pharmacokinetics	Study of the fate of a drug in the body and the body's effect on the drug as a function of time. The pharmacokinetics of a drug can be broken down into four phases: absorption, diffusion in the body, metabolism of the drug and its elimination by the body.
Polymer	Chemical compound formed by molecules whose feature is the repetition of one or several atoms or groups of atoms.
Polysaccharide	Complex sugar composed of several simple sugars of the same family of polymers.
Prevalence	A measure of the health status of a population at a given time, expressed as the ratio of the number of patients to the total population.
Primary dressing	Different types of dressings that are in direct contact with the lesion: sheets cut to size, paste, powder, that keep the lesion warm and moist and enable exudates to be absorbed.

Proof of concept	Demonstration of the feasibility and efficacy of a therapeutic product.
Protein	Macromolecule composed of amino acids linked by peptide bonds and that ensure myriad functions in the body.
Regenerative medicine	The use of human cells to repair or improve the functions of a damaged organ.
Rheumatoid arthritis	Chronic, inflammatory, degenerative disease characterized by the inflammation of several joints.
Sanies	Fetid purulent matter mixed with blood.
Somatic cells	All cells except germ, or sex cells.
SOP	Standard Operating Procedure. A written detailed procedure to ensure the comparability and uniformity of studies of the performance of a given pharmaceutical product.
Sorbitol	A sugar-alcohol.
Stasis	Reduction or cessation of the circulation of a fluid.
Streptococcus	A genus of bacteria, certain species of which are pathogens, i.e. sources of infections.
Transgenesis	The set of techniques used to introduce a foreign gene in the genome of an organism to obtain a genetically modified organism.
Tryptophan	An amino acid forming proteins. It is called essential because it cannot be synthesized by the body and must be provided by the diet.
UDRP procedure	Uniform Dispute Resolution Policy. Principles of the Internet Corporation for Assigned Names and Numbers (ICANN) to resolve disputes involving domain names.
United States Pharmacopeia – National Formulary	Collection of quality control requirements of medicinal preparations, excipients and medical devices drafted by the United States Pharmacopeial Convention. The FDA is responsible for ensuring compliance with these requirements in the United States. These standards have been developed and used in more than 130 counties in the world.

APPENDIX I – CHAIRMAN's REPORT ON INTERNAL CONTROL

ADOCIA

Corporation (*société anonyme*) with €621,187.60 in share capital
Registered office: 115 avenue Lacassagne - 69003 Lyon
487 647 737 Lyon trade and companies register

_____

REPORT OF THE CHAIRMAN OF THE BOARD OF DIRECTORS ON CORPORATE GOVERNANCE, INTERNAL CONTROL AND RISK MANAGEMENT

To the shareholders,

In accordance with Article L. 225-37 of the French commercial code, I am pleased to report to you, in my capacity as chairman of the board of directors, on the composition and conditions for the preparation and organization of the work of this board during fiscal year 2013 and on the internal control and risk management procedures implemented by the company.

This report, prepared by the company's administrative and finance department, was submitted to the audit committee and subsequently approved by the board of directors at its meeting of March 21, 2014.

1. Corporate governance

Until October 24, 2011, Adocia was incorporated as a simplified joint-stock company (*société par actions simplifiée*). At the time of its initial public offering, the company was converted, on October 24, 2011, into a corporation (*société anonyme*) with a board of directors, and adopted new governance rules. Shareholders appointed a six-member board of directors, five of whom had been members of the board of directors of the company in its previous form as a simplified joint-stock company.

The board of directors, at its meeting of October 24, 2011, adopted its own rules of procedure which specify, among others, the role and composition of the board, the principles of conduct and the obligations of members of the company's board of directors, and the operating procedures of the board of directors and its committees, as well as the rules for determining the compensation of their members. The board's rules of procedure can be accessed on the company's website (www.adocia.fr).

To structure its governance, the company has chosen to refer to the corporate governance code for small and midcaps as published in December 2009 by MiddleNext and approved as a reference code by the *Autorité des marchés financiers* (the "MiddleNext Code"). The board of directors, at its meeting of October 11, 2011, after reviewing the information presented in the "key issues" section of the MiddleNext Code, therefore decided to adopt this code as its corporate governance reference code.

1.1. Composition of the Board of Directors

In accordance with legal requirements and the bylaws, the board of directors is composed of at least three directors and at most 18, appointed by the shareholders' meeting for a three-year term. They may be reappointed when their term expires. In the event of a vacancy, directors may be coopted under the conditions specified in the applicable laws and regulations.

In accordance with its rules of procedure, the board of directors has at least two independent directors within the meaning of the MiddleNext Code. Members of the board are deemed independent if they have no relationship with the company, its group or its management that might adversely affect the exercise of their freedom of judgment.

The company has two independent directors within the meaning of the provisions of the MiddleNext Code, Ms. Dominique Takizawa and Ms. Ekaterina Smirnyagina.

The company intends to recruit one or more additional independent directors as part of its plan to improve its corporate governance.

The board reviews the independence of its members based on the following criteria set by the MiddleNext Code:

- the director is not an employee or corporate officer of the company, nor an employee or corporate officer of one of its subsidiaries, and has not been one over the last three years;
- the director is not a customer, supplier or banker that is material for the company or its group, or not material, for which the company or its group represents a material proportion of the entity's activity;
- the director is not a major shareholder in the company;
- the director does not have any close family ties with a corporate officer or major shareholder of the company; and
- the director has not been an auditor of the company over the last three years.

Moreover, at least one of the independent members must have specific financial or accounting expertise so that he or she may be named to the audit committee.

At December 31, 2013, the company's board of directors had seven directors and one board observer (*censeur*).

The terms of office of the directors and the board observer shall expire at the close of the shareholders' meeting called to approve the financial statements for the fiscal year ended December 31, 2013, with the exception of Ekaterina Smirnyagina who was appointed at the combined shareholders' meeting of June 18, 2013. Her term of office shall expire at the close of the shareholders' meeting called to approve the financial statements for the fiscal year ended December 31, 2015.

Name or corporate name	**Title**
Gérard Soula	Chairman of the board of directors and chief executive officer
Olivier Soula	Director and vice-president
Olivier Martinez	Director
Kurma Partners represented by Thierry Laugel	Director

BPI France Investissement represented by Laurent Arthaud	Director
Dominique Takizawa	Independent director
Ekaterina Smirnyagina	Independent director
Viveris Management represented by Jérôme Féraud	Board observer

A list of other offices held by the company's directors can be found in section 14.1.2. of the reference document.

On October 24, 2011, the board of directors decided to appoint Mr. Gérard Soula as chairman of the board of directors and chief executive officer. As chairman, he is responsible for organizing and directing the work of the board of directors, on which he reports to the shareholders' meeting, and for ensuring the proper functioning of the company's bodies. As chief executive officer, he is responsible for the executive management of the company, represents the company in its relations with third parties, and has the powers granted to him by law to act in all circumstances on the company's behalf.

On December 19, 2012, the board of directors decided to appoint Mr. Olivier Soula as vice-president. The vice-president has the same powers as the chief executive officer with regard to third parties.

On February 25, 2014, the board of directors received the resignation of Mr. Thierry Laugel.
As the minimum number of directors has been met, an ordinary shareholders' meeting does not have to be called to fill this vacancy on the board of directors.

1.2. Roles and responsibilities of the board of directors

The board is subject to the provisions of the French commercial code, articles 11 to 13 of the company's bylaws and the rules of procedure that it has adopted.

These rules can be accessed on Adocia's website (www.adocia.fr).

The board is responsible, among others, for:

- setting the company's business strategy and overseeing its implementation. Subject to the powers expressly granted to shareholders' meetings and within the limit of the corporate purpose, it considers all issues relating to the company's operations and makes decisions on matters affecting the company,
- appointing the chairman of the board, the chief executive officer and the vice-presidents, and determining their compensation,
- authorizing the agreements and commitments referred to in Articles L. 225-38 and L. 225-42-1 of the French commercial code, and
- approving the report of the chairman of the board on corporate governance and internal control.

It monitors the quality of the information provided to shareholders and to the markets.

1.3. Conditions for the preparation and organization of the work of the board

To contribute effectively to the work and deliberations of the board, each member shall receive the documents he or she deems necessary. Requests of this nature shall be made to the chairman or, if applicable, to any other company executive (chief executive officer or vice-president).
Each member of the board is authorized to meet with the company's key executives, provided that he or she so inform the chairman of the board and the chief executive officer in advance.
The board is regularly informed by the chief executive officer of the company's and the group's financial position, cash position, financial commitments and significant events.
Lastly, any new member of the board may request training on the specific aspects of the company and its group, their business lines and their business sectors.

The members of the board may be called to a meeting by any means, even verbally.

All documents or draft documents providing information on the agenda and on all matters submitted to the board for review are sent, delivered or made available to board members within a reasonable time frame before the meeting.

A packet detailing the contents of the items on the agenda, prepared by executive management, is provided to each director during the meeting.

Minutes are drawn up for each meeting, and a draft is sent to the directors for comment. The final version of the minutes is approved at the next meeting and signed by the chairman and another board director who attended the meeting. Representatives of the works council attend the meetings, and the company's statutory auditors also attend meetings dealing with the closing of the annual and interim financial statements. The board of directors is assisted by three standing committees whose responsibilities and operating procedures are specified in the rules of procedure: the audit committee, the compensation committee and the scientific advisory board. The rules of procedure also provide for the possibility of creating any other committee, whose composition and responsibilities it shall determine, as often as the interests of the company so require.

In accordance with recommendation 15 of the MiddleNext Code, the board conducts an annual assessment of its operations. The board of directors, appointed on October 24, 2011, laid down the rules for conducting this evaluation in its rules of procedure.

1.4. Report on the activities of the Board during fiscal year 2013

Over the course of the past year, the company's board of directors met seven times, on March 6, 15 and 26, June 18, September 4 and 26, and December 13. The chairman of the board chaired these seven meetings, and the attendance rate for all members was 94%.

The following main points were addressed at the meetings:

- Updates on acquisition projects
- Update on the business and the status of various projects
- Financial updates:
  - Quarterly revisions
  - 2013-2016 three-year plan
  - Presentation and approval of the 2014 budget
- Report of the Compensation Committee:
  - Approval of compensation
  - Grant of BSPCEs and BSAs to directors
- Vesting of bonus shares
- Items to be submitted to the shareholders' meeting:

- Appointment of a new director
- Determination of directors' fees
- Renewal of the financial authorizations and delegations to be granted to the board of directors

1.5. Audit committee

The board of directors of the company, in its previous form as a simplified joint-stock company, had established an audit committee. The board of directors of the company, in its new form as a corporation, decided at its meeting of October 24, 2011 to maintain this already-established audit committee.

The audit committee, which is independent from the company's executives, is responsible for assisting the board of directors and ensuring the fairness of the financial statements, the quality of internal control, the relevance of the information provided and the proper performance by the auditors of their duties.

The audit committee is responsible, among others, for:
- monitoring the financial reporting process;
- monitoring the effectiveness of the internal control and risk management systems;
- monitoring the statutory audit of the annual financial statements and the consolidated financial statements by the statutory auditors;
- making a recommendation concerning the statutory auditors whose appointment is proposed at the shareholders' meeting and reviewing the terms of their compensation;
- monitoring the independence of the statutory auditors;
- reviewing the conditions under which derivatives may be used;
- periodically reviewing the status of significant legal proceedings; and
- in general, providing any advice and making any appropriate recommendations to the board of directors in the above areas.

The audit committee is, if possible, composed of at least two members appointed by the board of directors. The term of office of the audit committee members is concurrent with their term as member of the board of directors. Members of the audit committee are chosen from among the members of the board of directors and, to the extent possible, two-thirds are independent members, including one with specific financial or accounting expertise; all members have a minimum level of expertise in finance and accounting.

As of the filing date of this reference document, the members of the audit committee are:
- Ms. Dominique Takizawa, independent member with financial and accounting expertise, and
- Mr. Olivier Martinez, director.

Ms. Dominique Takizawa chairs this committee.

Ms. Takizawa is the member of the board with "specific financial or accounting expertise," due to her nearly 25 years of experience in the pharmaceutical industry and the executive management positions she held at Sanofi Pasteur, Biomérieux and Institut Mérieux.

Having two members on this committee was deemed sufficient, given the total number of directors of the company. The audit committee's rules of procedure, adopted on October 24, 2011 after approval by the board of directors, specifies the audit committee's roles and responsibilities and its organizational arrangements, including the minimum number of times the committee shall meet

each year. It also specifies that the committee may interview any member of the company's board of directors and perform any internal or external audit on any matters it deems to be within its responsibility. The chairman of the audit committee shall so inform the board of directors in advance. In particular, the audit committee has the right to interview those individuals who contribute to the preparation of the financial statements or to the audit thereof (vice-president finance, chief financial officer and key finance department managers). It has the right to direct, independent and confidential consultation with the statutory auditors.

The audit committee met three times in 2013, on January 15, March 15, and September 4, 2013.

1.6. Compensation Committee

The board of directors of the company, in its previous form as a simplified joint-stock company, had established a compensation committee. The board of directors of the company, in its new form as a corporation, decided at its meeting of October 24, 2011 to maintain this committee.

The compensation committee is responsible, among others, for:

- reviewing the main objectives suggested by executive management with respect to the compensation of executives of the company who are not corporate officers, including bonus share issues and stock option plans;
- reviewing the compensation of executives who are not corporate officers, including bonus share issues and stock option plans, pension and benefit plans and benefits in kind;
- making recommendations and proposals to the board concerning:
    - the compensation, retirement and insurance plans, non-cash benefits, and other financial entitlements, including severance pay, of the members of the board of directors. The committee suggests the amounts and structure of the compensation and, in particular, the rules for determining the variable component, taking into account the company's strategy, objectives and results, as well as market practices, and
    - bonus share plans, stock subscription or purchase options and any other similar profit-sharing program and, in particular benefits granted to specific members of the board of directors,
- reviewing the total amount of directors' fees and how they are allocated among the members of the board of directors, as well as the conditions for reimbursement of any expenses incurred by members of the board of directors,
- preparing and presenting any reports that may be required by the board of directors' rules of procedure, and
- preparing any other compensation-related recommendations that may be requested by the board of directors.

In general, the committee provides any advice and makes any appropriate recommendations in the above areas.

The compensation committee is, if possible, composed of at least two members appointed by the board of directors; no member of the board of directors serving in a management capacity within the company may be a member of this committee. The term of office of the compensation committee members is concurrent with their term as member of the board of directors.

As of the date of this reference document, the members of the compensation committee are:

- Ms. Ekaterina Smirnyagina
- Mr. Laurent Arthaud

In the performance of its duties, the committee may ask the chairman of the board to provide it

with assistance from any of the company's senior managers whose expertise may facilitate dealing with a matter of business on the agenda.

The committee met once during fiscal year 2013.

1.8. Principles and rules that determine corporate officer compensation

The company has implemented all the MiddleNext Code recommendations regarding the compensation of corporate officers and non-executive directors.

Compensation is presented in detail in chapter 15 of the 2013 reference document.

For fiscal year 2013, the variable component of the compensation of the chief executive officer and vice-president depended on several qualitative objectives relating to oversight of financial management, the development of collaborations, the launch of certain clinical trials, the signature of feasibility contracts and the acceleration of the company's business development.

The board of directors evaluated the extent to which these objectives had been met at its meeting of December 13, 2013 and determined, on the proposal of the compensation committee, the amount of compensation to be awarded for the year.

1.9. Other elements of governance

Provisions relating to attendance at shareholders' meetings are included in Article 19 of the bylaws available on the company's website. Information referred to in Article L. 225-100-3 of the French commercial code that is likely to have an impact in the event of a public offering is detailed in the reference document.

2. Risk management and internal control procedures implemented by the company

When preparing this part of the report, the company followed the implementation guide for the reference framework on internal control adapted for midcaps and small-caps published by the AMF on July 22, 2010.

2.1. General risk management principles

A) Definition

Adocia continues to formalize its risk management system. This system seeks to identify all the risks and risk factors that could affect the company's activities and processes and to define the resources to be used to manage these risks and keep them at or reduce them to an acceptable level for the company. It is intended to cover all types of risks and to apply to all of the company's and the group's activities.

B) Goals of risk management

Adocia has adopted the definition of risk management proposed by the AMF [71], which states that risk management is a management tool of the company that helps:

[71] Implementation guide for the reference framework on internal control adapted for midcaps and small-caps and updated on July 22, 2010

- create and preserve the company's value, assets and reputation;
- secure decision-making and the company's processes to attain its objectives;
- encourage consistency between the company's actions and its values; and
- ensure that the company's employees have a shared vision of the main risks.

C) Components of the risk management system

The risk factors the company has identified to date are detailed in chapter 4 of the 2013 reference document.

2.2. Coordination of risk management with internal control

Risk management aims to identify and analyze the main risks and risk factors that could affect the company's activities, processes and objectives and define the resources to be used to keep these risks at an acceptable level, in particular by implementing the preventive measures and controls that are part of the internal control system.

At the same time, the internal control system relies on risk management to identify the main risks that need to be controlled. The company has been preparing and developing an internal control system since its founding, while the formalization of the risk management system is more recent. The company is now implementing an initiative to coordinate the two systems, which aims to identify the control procedures to be addressed in the key processes of the company that are likely to be affected by risks qualified as "major."

2.3. General principles of internal control

A) Definition

Adocia has adopted the definition of internal control proposed by the AMF[72], which states that internal control is a system that the company implements in order to ensure:

- compliance with laws and regulations;
- implementation of the instructions and directions given by executive management;
- proper functioning of the company's internal processes;
- reliability of financial information; and

in general that contributes to control over its activities, the efficiency of its operations and efficient use of its resources.
Over the course of the fiscal year, Adocia continued to implement an internal control process aimed at "internally ensuring the relevance and reliability of the information used in and disseminated to the company's activities."

B) Components of internal control and stakeholders

<u>Organization</u>

The internal control system is based on a clear organization of responsibilities, standards, resources and procedures implemented. The company has had a quality assurance system since its founding. The processes for all business segments are described in procedures (*Standard Operating*

[72] Implementation guide for the reference framework on internal control adapted for midcaps and small-caps and updated on July 22, 2010

Procedures, or SOPs), operating methods, notices and forms. These written documents describe the conduct of business, define the resources and responsibilities of the stakeholders, specify the company's know-how and provide specific instructions on how to carry out a particular operation.

All of the company's stakeholders are involved in the internal control system.

Project management and business monitoring procedures.

The company has set up a specific organization to monitor projects and ensure that the objectives set by executive management are met within the specified time frames and budgets. For each project it develops, the company names a project leader who reports to the R&D director and who may seek out the expertise of the different departments within the company, in order to complete the work defined by executive management. He or she is responsible for defining the research programs, validating the objectives with executive management, ensuring they are achieved on schedule and coordinating with any partners.

In 2006, the company also established a scientific advisory board which is responsible for reviewing the company's major scientific directions. It proposes methods and strategies for achieving the company's scientific objectives. It evaluates the work conducted by the company and the results obtained.
The scientific advisory board meets one to two times a year. The work of the company's scientific department is presented at these meetings. Based on the data presented, the board's members make recommendations to the R&D director, Mr. Olivier Soula.

The external members of the scientific advisory board are Mr. Jean-Marie Lehn and Mr. Bernard Cabane.

Operational process procedures

All documentation relating to the quality system is saved to a dedicated intranet in order to maximize access to the documents and their ongoing adaptation to changes in the business (document lifecycle management). The objective is the continual improvement in the quality of the company's or the group's business processes, for operational, management and support processes alike.

The quality assurance system covers the following areas:

- quality assurance, health and safety, risk management;
- administrative, legal, social and financial matters, including internal control. The intention is to also include communications and rules relating to the company's listing on Euronext;
- pharmaceutical, pre-clinical and clinical research and development;

With respect to information systems, procedures that have been incorporated into the quality system define the rules relating to access to and the protection and storage of information. An IT Charter has also been put in place.

C) Financial reporting procedures

The company has set up the following organization to limit its financial management risks:

- The company's executive management and, more specifically, the employees of the Finance Department are tasked with improving internal control and incorporating the recommendations of the external auditors and the audit committee,

- The company maintains an internal separation between the production and oversight of the financial statements and brings in independent experts to evaluate complex accounting items,
- A chartered accountant is asked to verify the half-yearly and annual work, for the individual financial statements and the financial statements presented under IFRS,
- Payroll management is subcontracted to an independent specialized firm.

Oversight of internal control, regular reviews

The company's executive management has put in place specific internal control procedures that consist of regular reviews of key information for each activity. For each of the areas listed below, information deemed material for the corresponding activities has been identified and selected. It must reflect the reality of the activity and be used to track this activity both quantitatively and qualitatively, including compliance with the standards that govern it. This key information must be verifiable and documented. It should be updated every month by the people who conduct the work. This system covers the following areas:

- information about Research and Development projects (pre-clinical, clinical, pharmaceutical);
- financial reporting and transactions involving the capital;
- the company's legal aspects, regulatory aspects and intellectual property;
- communication of accounting and financial information, as well as scientific and corporate information;
- quality and information systems;
- human resources and payroll.

These reviews are first conducted by the company's management committee, which is composed of the chairman and chief executive officer, the R&D director, the chief financial officer and the business development director. This committee meets at least once a week and reconciles the data with the reporting. The aim of these reviews is to ensure that the information for each of the items in the scope fairly reflects the group's activity and position.
The operations committee also reviews the key information for each activity. It meets every three weeks and is made up of the members of the management committee and all of the company's department heads.

In general, all of the company's accounting options are defined by the chief financial officer, discussed with executive management and the statutory auditors and then presented to the audit committee and discussed therein. This ensures that the company's practices are fully compliant with French and international (IFRS) standards and that the financial statements are presented in a consistent manner.

At the end of each year, the chief financial officer prepares a detailed budget for the following fiscal year, which is then approved by executive management. This budget is presented to the board of directors. At the end of each quarter, the accounting teams prepare the closing of the individual financial statements of the companies in the group.

The budget reviews conducted with all operational managers ensure an analytical validation of the entries and a review of all expenditures, and the chief financial officer prepares a report for executive management and the directors. This report is presented and discussed periodically at the meetings of the board of directors.

However, it should be noted that the internal control system implemented by the company cannot provide an absolute guarantee that its objectives will be met.

Internal control stakeholders

All of the company's stakeholders, governance bodies and employees are involved in the internal control system.

Since the company's founding, executive management has played a leading role in defining and implementing the internal control system and subsequently risk management.

2.5. Limitations on risk management and internal control and areas of improvement

In 2014, the company will continue to implement its risk management system and to improve its monitoring of the identified action plans. At the same time, the company will work to update its internal control system to reflect changes in its internal organization and its business as well as closer coordination with the risk management process.

The board of directors has approved this report which will be presented to the shareholders' meeting called to approve the financial statements for fiscal year 2013.

3. Representation of men and women on the board of directors

In accordance with Act no. 2011-103 of January 27, 2011 on the balanced representation of men and women on boards of directors and supervisory boards and on gender equality, currently two of the six members of the board of directors are women, Ms. Dominique Takizawa and Ms. Ekaterina Smirnyagina.

_____

Chairman of the Board of Directors

Adocia
Fiscal year ended December 31, 2013

Statutory auditors' report, prepared in accordance with Article L. 225-235 of the French Commercial Code (*Code de commerce*), on the report of the Chairman of the board of directors of Adocia

ODICEO
115, boulevard de Stalingrad
B.P. 52038
69616 Villeurbanne Cedex
Corporation with €275,000 in share capital

Statutory Auditor
Member of the Compagnie
Régionale de Lyon

ERNST & YOUNG et Autres
Tour Oxygène
10-12 boulevard Marius Vivier Merle
69393 Lyon cedex 03
Simplified joint stock company with variable capital

Statutory Auditor
Member of the Compagnie
Régionale de Versailles

Adocia

Fiscal year ended December 31, 2013

Statutory auditors' report, prepared in accordance with Article L. 225-235 of the French Commercial Code (*Code de commerce*), on the report of the chairman of the board of directors of Adocia

Dear Shareholders:

In our capacity as statutory auditors of Adocia and in accordance with the provisions of Article L. 225-235 of the French Commercial Code (*Code de Commerce*), we present to you our report on the report prepared by your company's chairman as provided by Article L. 225-37 of the French Commercial Code for the fiscal year ended December 31, 2013.

It is the chairman's responsibility to prepare and submit to the board of directors for approval a report that describes the internal control and risk management procedures implemented at the company and provides the other information required by Article L. 225-37 of the French Commercial Code related, in particular, to the corporate governance scheme.

It is our responsibility:

- to give you our observations based on the information contained in the chairman's report regarding the internal control and risk management procedures related to the preparation and treatment of accounting and financial information, and

- to certify that this report contains the other information required by Article L. 225-37 of the French Commercial Code, it being understood that it is not our responsibility to verify the fairness of this information.

We have performed our work in accordance with the accounting standards applicable in France.

Information regarding the internal control and risk management procedures related to the preparation and treatment of accounting and financial information

The accounting standards require that we follow certain procedures to assess the fairness of the information regarding the internal control and risk management procedures related to the preparation and treatment of accounting and financial information contained in the chairman's report. These procedures entail:

- reviewing the internal control and risk management procedures related to the preparation and treatment of accounting and financial information that forms the basis of the information provided in the chairman's report and the existing documentation;

- reviewing the work involved in preparing this information and the existing documentation;

- determining whether any major weaknesses in internal control related to the preparation and treatment of accounting and financial information identified by us in the course of our audit have been properly disclosed in the chairman's report.

Based on this work, we have no observation regarding the information about the company's internal control and risk management procedures related to the preparation and treatment of accounting and financial information contained in the chairman of the board of directors' report, which was prepared in accordance with the provisions of Article L. 225-37 of the French Commercial Code.

Other Information

We certify that the chairman of the board of directors' report contains the other information required by Article L. 225-37 of the French Commercial Code.

Villeurbanne and Lyon, March 24, 2014

The Statutory Auditors

ODICEO	ERNST & YOUNG et Autres
Sylvain Boccon-Gibod	Sylvain Lauria

ANNEXE III - Independent verifier's report on consolidated social, environmental and societal information presented in the management report

Adocia

Year ended the 31 December 2013

Independent verifier's report on consolidated social, environmental and societal information presented in the management report

This is a free translation into English of the original report issued in the French language and it is provided solely for the convenience of English speaking users. This report should be read in conjunction with, and construed in accordance with, French law and professional standards applicable in France.

To the shareholders,

In our quality as an independent verifier of which the admissibility of the application for accreditation has been accepted by the COFRAC, under the number n° 3-1050, and as a member of the network of one of the statutory auditors of the company Adocia, we present our report on the consolidated social, environmental and societal information established for the year ended on the 31 December 2013, presented in chapter 19 of the management report (corresponding to paragraph 8.3, 8.4 and 17.7 of the Document of Reference), hereafter referred to as the "CSR Information," pursuant to the provisions of the article L.225-102-1 of the French Commercial Code (*Code de commerce*).

Responsibility of the company

It is the responsibility of the Board of Directors to establish a management report including CSR Information referred to in the article R. 225-105-1 of the French Commercial Code (*Code de commerce*), in accordance with the protocols used by the company consisting in internal instructions and rules (hereafter referred to as the "Criteria"), and of which a summary is included where needed in the text.

Independence and quality control

Our independence is defined by regulatory requirements, the Code of Ethics of our profession as well as the provisions in the article L. 822-11 of the French Commercial Code (*Code de commerce*). In addition, we have implemented a quality control system, including documented policies and procedures to ensure compliance with ethical standards, professional standards and applicable laws and regulations.

Responsibility of the independent verifier

It is our role, based on our work:

- to attest whether the required CSR Information is present in the management report or, in the case of its omission, that an appropriate explanation has been provided, in accordance with the third paragraph of R. 225-105 of the French Commercial Code (*Code de commerce*) (Attestation of presence of CSR Information);

- to express a limited assurance conclusion, that the CSR Information, overall, is fairly presented, in all material aspects, in according with the Criteria;

Our verification work was undertaken by a team of two people between March and April 2014 for an estimated duration of two weeks.

We conducted the work described below in accordance with the professional standards applicable in France and the Order of 13 May 2013 determining the conditions under which an independent third-party verifier conducts its mission, and in relation to the opinion of fairness and the reasonable assurance report, in accordance with the international standard ISAE 3000[10].

1. Attestation of presence of CSR Information

We obtained an understanding of the company's CSR issues, based on interviews with the management of relevant departments, a presentation of the company's strategy on sustainable development based on the social and environmental consequences linked to the activities of the company and its societal commitments, as well as, where appropriate, resulting actions or programmes.

We have compared the information presented in the management report with the list as provided for in the Article R. 225-105-1 of the French Commercial Code *(Code de commerce).*

In the absence of certain consolidated information, we have verified that the explanations were provided in accordance with the provisions in Article R. 225-105-1, paragraph 3, of the French Commercial Code *(Code de commerce).*

We verified that the information covers the consolidated perimeter, namely the entity and its subsidiaries, as aligned with the meaning of the Article L.233-1 and the entities which it controls, as aligned with the meaning of the Article L.233-3 of the French Commercial Code (Code de commerce).

Based on this work, we confirm the presence in the management report of the required CSR information.

2. Limited assurance on CSR Information

Nature and scope of the work

We undertook three interviews with the people responsible for the preparation of the CSR Information in the different departments of Finance, Human Resources and Quality-Safety-Environment, in charge of the data collection process and, if applicable, the people responsible for internal control processes and risk management, in order to:

- Assess the suitability of the Criteria for reporting, in relation to their relevance, completeness, reliability, neutrality, and understandability, taking into consideration, if relevant, industry standards;

- Verify the implementation of the process for the collection, compilation, processing and control for completeness and consistency of the CSR Information and identify the procedures for internal control and risk management related to the preparation of the CSR Information.

We determined the nature and extent of our tests and inspections based on the nature and importance of the CSR Information, in relation to the characteristics of the Company, its social and environmental issues, its strategy in relation to sustainable development and industry best practices.

For the CSR Information which we considered the most important[11]:

-At the level of the consolidated entity, we consulted documentary sources and conducted interviews to corroborate the qualitative information (organisation, policies, actions, etc.), we implemented analytical procedures on the quantitative information and verified, on a test basis, the calculations and the compilation of the information, and also verified their coherence and consistency with the other information presented in the management report.

10 ISAE 3000 – *Assurance engagements other than audits or reviews of historical information*

11 Environmental and Societal information: preventative measures, recycling and waste management, energy consumption, business ethics (measures undertaken in favour of consumers' health and safety).

Social information: employment (total headcount and breakdown, hiring and terminations), health and safety at the work place, work accidents, notably their frequency and their severity, training policies.

For the other consolidated CSR information, we assessed their consistency in relation to our knowledge of the company.

Finally, we assessed the relevance of the explanations provided, if appropriate, in the partial or total absence of certain information.

We consider that the sample methods and sizes of the samples that we considered by exercising our professional judgment allow us to express a limited assurance conclusion; an assurance of a higher level would have required more extensive verification work. Due to the necessary use of sampling techniques and other limitations inherent in the functioning of any information and internal control system, the risk of non-detection of a significant anomaly in the CSR Information cannot be entirely eliminated.

Conclusion

Based on our work, we have not identified any significant misstatement that causes us to believe that the CSR Information, taken together, has not been fairly presented, in compliance with the Criteria.

Observations

Without qualifying our conclusion above, we draw your attention to the following points:

- Definitions and reporting procedures were not systematically formalised, notably for the calculation of environmental indicators and the number of hours of training.

Paris-La Défense, the 24 April 2014

French original signed by:

Independent Verifier ERNST & YOUNG et Associés	
Partner, Sustainable Development Christophe Schmeitzky	Partner Bruno Perrin