INNOVATIVE MEDICINE FOR EVERYONE EVERYWHERE
A French société anonyme (corporation) with €693,124,40 in share capital

Registered office: 115 avenue Lacassagne
69003 Lyon, France
Lyon Trade and Companies Registry No. 487 647 737

This registration document was filed with the Autorité des Marchés Financiers (the “AMF”) on April 12th, 2019 in accordance with Article 212-13 of its General Regulation. It may be used to support a financial transaction if supplemented by a securities note approved by the AMF. This document was prepared by the issuer and is the responsibility of its signatories.

Copies of this registration 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 on the AMF website (www.amf-france.org).
NOTICE

In this registration document, the terms “Adocia” or 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 and, when appropriate, its subsidiary, Adocia Inc., a company incorporated in the state of Delaware, whose head office is located at 2090 Dipinto Avenue, Henderson, NV 89052, U.S.A.

The consolidated financial statements prepared under IFRS for the fiscal year ended December 31, 2018 are presented on pages 126 to 158 of this registration document. The statutory auditors’ report on the consolidated financial statements prepared under IFRS for the fiscal year ended December 31, 2018 is presented on pages 159 to 165 of this registration document.

The corporate financial statements prepared under French GAAP for the fiscal year ended December 31, 2018 are presented on pages 166 to 179 of this registration document. The statutory auditor’s report on the corporate financial statements prepared under French GAAP for the fiscal year ended December 31, 2018 is presented on pages 180 to 185.


- The consolidated consolidated financial statements ended December 31, 2017 and the related statutory auditors’ reports presented respectively in paragraph 4.1 and 4.2 of the 2017 registration document filed with the AMF on April 19th, 2018 with reference D.18-0347.
- The consolidated consolidated financial statements ended December 31, 2016 and the related statutory auditors’ reports presented respectively in paragraph 20.A of the 2016 registration document filed with the AMF on April 11th, 2017 with reference D.17-0363

Are incorporated by reference in this registration document.

The non-included parts of this(ese) document(s) are either irrelevant for the investor or covered elsewhere in the registration document.

A glossary containing the definitions of certain technical terms used in this registration document, as well as an index of abbreviations used, can be found in paragraph 6.6. Terms indicated by an asterisk (*) are defined in the glossary.
DISCLAIMER

Market and competition information
This registration document contains, in particular in section 1.3 “Description of Activities”, information about the Company’s markets and competitive position. This information is taken, in particular, 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 registration 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 may change or be modified due to uncertainties associated with, in particular, the economic, financial, competitive and regulatory environment. This information is provided in the various sections of this registration document and includes data related to the Company’s intentions, estimates and objectives with respect to, among other things, the market in which it operates and its strategy, growth, results, financial position, cash position and forecasts. The forward-looking information in this registration document is provided only as of the date of this registration 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 mentioned in any forward-looking information. It should be noted 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 paragraph 1.5 “Risk Factors” of this registration 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, results or outlook. Furthermore, other risks not yet identified or not deemed significant by the Company as of the date of this registration document may also have a material adverse impact.
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# Presentation of Adocia and its activities

## 1 PRESENTATION OF ADOCIA AND ITS ACTIVITIES

### 1.1 Selected financial information

#### Condensed income statement

<table>
<thead>
<tr>
<th></th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating revenue</td>
<td>53,930</td>
<td>27,177</td>
</tr>
<tr>
<td>Of which revenue</td>
<td>47,389</td>
<td>19,469</td>
</tr>
<tr>
<td><strong>PROFIT (LOSS) FROM ORDINARY OPERATING ACTIVITIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial income (loss)</td>
<td>2,050,7</td>
<td>(335,4)</td>
</tr>
<tr>
<td>Profit (loss) before tax</td>
<td>11,758</td>
<td>(8,516)</td>
</tr>
<tr>
<td>Tax</td>
<td>(4,144)</td>
<td>(35)</td>
</tr>
<tr>
<td>Net income (loss)</td>
<td>7,615</td>
<td>(8,550)</td>
</tr>
<tr>
<td><strong>TOTAL NET PROFIT (LOSS)</strong></td>
<td>7,458</td>
<td>(8,741)</td>
</tr>
</tbody>
</table>

#### Condensed balance sheet

<table>
<thead>
<tr>
<th></th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-current assests</strong></td>
<td>9,058</td>
<td>9,069</td>
</tr>
<tr>
<td>of which: land, building, fixtures and facilities</td>
<td>7,399</td>
<td>7,327</td>
</tr>
<tr>
<td>of which: laboratory equipment</td>
<td>942</td>
<td>1,253</td>
</tr>
<tr>
<td><strong>Current assets</strong></td>
<td>60,984</td>
<td>44,692</td>
</tr>
<tr>
<td>of which: cash and cash equivalents</td>
<td>39,841</td>
<td>34,778</td>
</tr>
<tr>
<td><strong>TOTAL ASSETS</strong></td>
<td>70,043</td>
<td>53,761</td>
</tr>
<tr>
<td><strong>Equity</strong></td>
<td>45,848</td>
<td>36,857</td>
</tr>
<tr>
<td><strong>Non current liabilities</strong></td>
<td>9,340</td>
<td>8,022</td>
</tr>
<tr>
<td>of which: long-term financial debts</td>
<td>4,892</td>
<td>5,781</td>
</tr>
<tr>
<td><strong>Current liabilities</strong></td>
<td>14,854</td>
<td>8,882</td>
</tr>
<tr>
<td><strong>TOTAL LIABILITIES</strong></td>
<td>70,043</td>
<td>53,761</td>
</tr>
</tbody>
</table>

#### Condensed cash flow statement

<table>
<thead>
<tr>
<th></th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net cash flow generated by operating activities</td>
<td>6,313</td>
<td>(22,227)</td>
</tr>
<tr>
<td>Net cash flow in connection with investment transactions</td>
<td>(1,034)</td>
<td>(1,685)</td>
</tr>
<tr>
<td>Net cash flow in connection with financing transactions</td>
<td>(216)</td>
<td>653</td>
</tr>
<tr>
<td><strong>Changes in net cash</strong></td>
<td>5,063</td>
<td>(23,259)</td>
</tr>
<tr>
<td>Cash and cash equivalents at the start of the year</td>
<td>34,778</td>
<td>58,037</td>
</tr>
<tr>
<td>Cash and cash equivalents at year-end</td>
<td>39,841</td>
<td>34,778</td>
</tr>
</tbody>
</table>
1.2 About Adocia and its evolution

1.2.1 Legal presentation of the company

The company’s legal name is Adocia.

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

It 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 decision of the general shareholders’ meeting on October 24, 2011.

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 closing date for its fiscal year is December 31.

The company’s registered headquarters is located at 115 Avenue Lacassagne, 69003 Lyon, France.

The company’s contact information is shown below:

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

1.2.2 General presentation of the company

1.2.2.1 Mission

Adocia’s goal is to deliver “Innovative medicines for everyone, everywhere.”

Adocia is a clinical biotechnology company specializing in the development of innovative formulations of pre-approved therapeutic proteins and peptides. In the diabetes field, Adocia’s portfolio of injectable products for treatment of diabetes, is among the largest and most differentiated of the industry, featuring six clinical-stage products and one in preclinical stage. Additionally, Adocia expanded its portfolio to include the development of treatments of obesity and short bowel syndrome.

The BioChaperone® patented technological platform aims to improve the efficacy and/or safety of therapeutic proteins, while also making them easier for patients to use. Adocia adapts BioChaperone for each protein for a given application.

Adocia’s clinical pipeline contains five innovative insulin formulations for the treatment of diabetes: two ultra-rapid insulin lispro analogs (BioChaperone® Lispro U100 and U200), a rapid-acting human insulin (HinsBet® U100) and a combination of long-acting insulin glargine and rapid-acting insulin lispro (BioChaperone® Combo) and a prandial combination of human insulin with amylin pramlintide (BioChaperone® PramInsulin). It also includes an aqueous formulation of human glucagon (BioChaperone® Glucagon) for the treatment of hypoglycemia. Adocia’s preclinical pipeline includes combinations of insulin glargine with GLP-1 receptor agonists (BioChaperone® Glargine GLP-1) for the treatment of diabetes, a ready-to-use combination of glucagon and a GLP-1 receptor agonist BioChaperone®
1.2.2.2 Significant events in the development of the company’s business

As the results of these research efforts and their commercial development take many years, for the first ten years the company’s annual financial statements have mainly reflected research and development costs which, for the most part, have been financed by capital increases, Bpifrance repayable advances and grants and the research tax credit.

Since its inception on December 16, 2005, and before its IPO, the company raised over €27 million through capital increases subscribed, in particular, by its 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 Paris regulated market and raised more than €27.4 million (excluding transaction costs). In March 2015, it completed a private placement of nearly €32 million by issuing new shares to investors specialized in the healthcare sector, particularly in the United States.

In 2009, the Company recorded its first revenue when it concluded research and collaboration 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 collaboration agreement, thereby recovering its rights to develop an ultra-rapid analog insulin and enabling it to conduct its own clinical studies to establish proof of concept.

Following the clinical results obtained in late 2013 and throughout 2014, Adocia convinced Eli Lilly to renew their collaboration. On December 19, 2014, the two companies signed a licensing agreement for the development of an ultra-rapid insulin called BioChaperone® Lispro. At the time the agreement was signed, the Company received a non-repayable up-front payment of $50 million (€41 million).

The years 2015 and 2016 were marked by intense activity under this partnership with the completion of six clinical studies on the BioChaperone Lispro formulation and the receipt of a $10 million milestone payment following the positive results of the bioequivalence study of the concentrated formulation of BioChaperone Lispro.

Throughout 2016, the Company focused its efforts entirely on diabetes by discontinuing its monoclonal antibodies and DriveIn programs and launching new BioChaperone Combo projects, combinations of long-acting insulin glargine with GLP-1 and, recently, combinations of prandial insulins.

On January 26, 2017, the Company announced that Eli Lilly was ending the collaboration on BioChaperone Lispro. Adocia has recovered all its rights to this product and is looking for a new partner to continue phase 3 development.

In 2017 Adocia achieved key milestones in the development of its products, by demonstrating a better fast-off profile for BioChaperone Lispro than for the Novo Nordisk ultra-rapid insulin Fiasp®, successfully completing the first clinical trial for the BioChaperone Glucagon project and demonstrating the dose linearity of BioChaperone Combo. The company also announced the expansion of its portfolio to new therapeutic fields other than diabetes, with the launch of two new projects for the treatment of obesity and short bowel syndrome.

In April 2018, Adocia signed with the Chinese company, Tonghua Dongbao Pharmaceuticals Co. Ltd, a strategic alliance for the development and commercialization of BioChaperone® Combo and BioChaperone® Lispro in China and in certain other countries. These licensing agreements have a total potential value of $ 135 million (Adocia is
expected to receive double-digit royalties on the future sales of both products) including $50 million when the partnership was signed. In June 2018, the companies also signed two global supply agreements for Insulin Lispro and Insulin Glargine. Thus, Adocia will be able to carry out its BioChaperone Lispro et BioChaperone Combo projects in Europe, in the US and in Japan.

In 2018, Adocia carried on with the development of both products in this new partnership. The company also further developed its portfolio and successfully lead the first clinical trial on BioChaperone Pramlintide Insuline in people with type 1 diabetes.

In legal affairs, 2018 was also marked by the two-parts arbitration procedure launched against Eli Lilly & Co., which are detailed in paragraph 1.3.7.3.

1.2.3 Organizational chart

1.2.3.1 Organization of the Company

At the date of issue of this registration document, the organizational chart for the Company is as follows:

1.2.3.2 Subsidiaries, branches and secondary establishments

In February 2015, the company founded Adocia Inc., a subsidiary in the United States, a company incorporated in the state of Delaware, whose head office is located at 2090 Dipinto Avenue, Henderson, NV 89052, U.S.A. Adocia wholly owns its subsidiary Adocia Inc., which at the date of the present registration document had two employees: a marketing director and a business development director. The objective is for the subsidiary to facilitate interaction with the US market and to locate the Company's advocacy activities in the United States. M. Stephen Daly is US General Manager.

Stephen Daly has more than 30 years of experience in commercialization and business development for pharmaceutical and biotech products across multiple therapeutic categories. Before Adocia, he served as the Vice President of Commercial at Halozyme Therapeutics for their ultra-rapid insulin program. Stephen Daly's experience in the diabetes field also includes several years at Amylin Pharmaceuticals in marketing and brand leadership for Byetta® and Symlin®.
Presentation of Adocia and its activities

At the date of this registration Document, the Company does not have a branch or a secondary establishment.

1.2.3.3 Management

ADOCIA is managed by an executive committee made up of four members: Gérard Soula, CEO, Valérie Danaguezian, CFO, Olivier Soula, Deputy General Manager – R&D Director, Rémi Soula, Business Development and Legal.

They 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,

Dr. Gérard Soula, PhD, MBA – President and CEO: cf. paragraph 3.1.4 of the current reference document.

Dr. Olivier Soula, PhD, MBA – Deputy General Manager – R&D Director: cf. paragraph 3.1.4 of the current reference document.

Dr. Rémi Soula: Director of Business Development and Legal

Rémi Soula holds a doctorate in polymer chemistry from CPE Lyon. He did a post-doctorate at Max Planck Institute in Berlin. He also holds an MBA at HEC Paris. He began his career with Flamel Technologies as a Senior researcher in the synthesis of new polymers. After 3 years at Flamel, he co-founded Adocia with Gérard and Olivier Soula.

Today he is Director of Business development and Legal. He is the co-author of 30 patents and 6 scientific publications

Mrs. Valérie Danaguezian: Administrative and Financial Director

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. In 1991, she joined Sanofi Pasteur where she was in charge of the group’s financial consolidation, eventually being promoted as Director of the group’s research and development expenditures management control. In 2003 she joined Flamel Technologies and held the position of administration and financial officer for 3 years. In 2006 Valérie Danaguezian joined Adocia as CFO and member of the Executive team. She 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.

1.2.4 Investments and real estate

The company outsources a significant portion of its research and development activities. Its investments in fixed assets are therefore relatively low in value compared with its research and development expenditures, with the exception of the real estate investments presented in the section below.

<table>
<thead>
<tr>
<th>In (€) thousands</th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intangible assets</td>
<td>70</td>
<td>77</td>
</tr>
<tr>
<td>Property, plant and equipment</td>
<td>5</td>
<td>861</td>
</tr>
<tr>
<td>Other tangible assets</td>
<td>764</td>
<td>709</td>
</tr>
<tr>
<td>Non-current financial assets</td>
<td>250</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1 089</strong></td>
<td><strong>1 648</strong></td>
</tr>
</tbody>
</table>
1.2.4.1 Major investments

- **Description of real estate**

  The Company is headquartered in Lyon, 115 avenue Lacassagne in the 3rd arrondissement (district) of the city of Lyon. The Company has been located at these premises since it was founded, initially as a tenant of the city of Lyon (Métropole de Lyon), and then as owner. In February 2016, to make its presence at this site permanent, the Company acquired the building with a total area of 7,120 m², the land on which the building is located and parking spaces. The acquisition of this property for a total of €5.5 million was financed by a bank loan. In 2017, the company added to its installation on the site by acquiring a hangar adjacent to the main building for €0.5 million and developing a green space in the interior courtyard for €0.3 million.

  In 2018, after the signature of the partnership with the Chinese company Tonghua Dongbao Pharmaceuticals Co. Ltd, the Company initiated refurbishing on two floors of 450 sqm each, mainly dedicated to the Analytical Department.

- **Other property, plant and equipment**

  The principal property, plant and equipment that the company holds is described in note 2 to the notes to the corporate financial statements prepared in accordance with IFRS, in chapter 4 of this reference document.

1.2.4.2 Major current and future investments

Over the course of 2019, the Company plans to finalize the design of the additional 900 sqm floorspace for new labs and offices of the Analytical Department.

Adocia also plans to purchase the scientific material needed for the research and development activities of its current and future projects.

Further refurbishment of the building would require new financial income.

1.3 Description of activities

Adocia is a French biotechnology company founded in December 2005 by Gérard, Olivier and Remi Soula. It focuses on the treatment of diabetes and other metabolic diseases with innovative formulations of approved proteins and peptides, using its BioChaperone® technology. Adocia’s portfolio of injectable treatments for diabetes, featuring five clinical-stage products and two preclinical products, is among the largest and most differentiated of the industry.

Adocia’s mission is to ‘Deliver more physiologic treatments to people with diabetes and other metabolic diseases in a simple and affordable way to help them avoid the long-term consequences of their disease.’

Diabetes is a global pandemic, affecting in 2017 more than 425 million people worldwide\(^1\). Despite significant progress made in the treatment of diabetes over the last 30 years, there is still a significant medical need, with it estimated that nearly 79% of people with diabetes experience severe complications\(^2\). The complexity of treatments and their costs place additional constraints on the lives of those who live with diabetes and may be responsible for a decline in their compliance, as well as a deterioration in the long term in quality of care (for example, linked to treatment abandonment).

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\(^1\) International Diabetes Federation, 2017

\(^2\) Hazel-Fernandez & al; American Journal of Managed Care. 2015
For the same reasons, the capacity of healthcare systems to cope with the enormous costs of this disease is in question, in the context of an overall increase in pressure on healthcare costs. In 2012, in the United States, the costs associated with diabetes amounted to $245 billion, including $29 billion for drugs and medical devices. In its annual results presentation for 2017, Novo Nordisk estimated that medicine and devices global costs for the treatment of diabetes were above $80 billion.

Adocia therefore believes that any new diabetes treatment must meet a threefold challenge:

- **Offer better performance**, through more ‘physiologic’ treatment approaches to address the disease in its complexity;
- **Facilitate the use of treatments**, to maximize the chances of patient compliance without placing further daily constraints on the patient;
- ** Guarantee affordable prices**, to ensure the greatest number of patients can access the best treatment and to guarantee the sustainability of our healthcare systems.

To meet this threefold challenge, Adocia is adopting an original strategy which consists of improving the efficacy and/or safety of already-approved therapeutic proteins and peptides while facilitating their use by patients. To do this, Adocia has developed its proprietary formulation technology, BioChaperone®. The formulation approach is simple to implement and provides the opportunity to improve and combine in an original way already-approved protein. It also takes advantage of the track record of already-used therapeutic proteins in terms of safety, efficacy and production infrastructure. Thus, it enables Adocia to develop innovations by decreasing risk margins, accelerating clinical development and reducing the amount of investment required (at the clinical and production stages) compared to a strategy to develop novel proteins. Its relatively low cost-intensive business model enables Adocia to develop innovative treatments with improved performance while enabling attractive drug pricing in an extremely competitive environment.

By adapting BioChaperone to each protein to meet the technical challenges posed, Adocia has developed a portfolio of innovative formulations of metabolic hormones for the treatment of diabetes among the most differentiated on the market. Each product aims to meet the specific needs of people living with diabetes. Adocia’s goal is to develop its products until their entry into phase 3 clinical studies in order to maximize the value of its projects prior to licensing out to potential partners in the field of diabetes and other metabolic diseases, whether this be one of the established leaders of the field, or new entrants wishing to immediately take position in the market with differentiated bio-betters rather than standard biosimilars.

Since April 2018, Adocia entered a partnership with Chinese company Tonghua Dongbao Pharmaceuticals Co. Ltd, which acquired the rights to develop and commercialize the BioChaperone Lispro et BioChaperone Combo insulin programs in China and other Asian and Middle-East territories.

### 1.3.1 The BioChaperone® technological platform

Adocia has designed and developed a technological platform based on novel polymers, oligomers, and innovative small molecules, called BioChaperone®. These compounds have the property of spontaneously combining with certain therapeutic proteins. This non-covalent combining helps increase the solubility and efficacy of the therapeutic protein and protects it from enzymatic breakdown.

BioChaperone technology is derived from the functional mechanism of heparin. This natural polysaccharide forms molecular complexes with growth factors, increasing their solubility, protecting them from enzymatic breakdown and thereby extending their time of action. The goal of the first generation of BioChaperone molecules developed by Adocia was to mimic the interaction properties of heparin with growth factors whilst avoiding its anticoagulant effect. Its was also aimed at increasing reaction versatility in order to diversify the proteins with which BioChaperone could react.

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The first innovative BioChaperone polymers were composed of a sugar backbone (e.g., dextran or pullulan) modified by both anionic groups* (carboxylates with a negative electric charge for instance) and by hydrophobic amino acids. Adocia then extended its BioChaperone family to include other shorter compounds (oligomers and small molecules) presenting the same properties. BioChaperone compounds have no intrinsic biological activity and should therefore be registered with regulatory authorities as new excipients.

BioChaperone compounds form complexes with proteins by binding non-covalently to their surface (adsorption). The complex forms spontaneously and is based on hydrophobic and electrostatic interactions and on the formation of hydrogen bonds. These BioChaperone polymers interact reversibly and non-degradatively with the proteins. The complex forms spontaneously when the two constituents are simply mixed in aqueous solution. This process occurs immediately and does not require heating or the use of an organic solvent.

The formulation-based approach presents the advantage of being easily industrializable as it relies on the addition of BioChaperone in the formulation process to the other excipients (preservatives, salt, etc.), and does not require adaptation of the industrial tools. Furthermore, the BioChaperone chemical synthesis processes are simple and low in cost compared to the therapeutic proteins themselves. These two aspects make it possible to envisage manufacturing costs for the BioChaperone formulations in parallel with those of the original formulations.

Four key properties of the BioChaperone technology, via the formation of the complex with the protein or peptide, have been demonstrated:

- Increased solubility of proteins or peptides that are relatively insoluble at physiological pH;
- Increased stability of proteins or peptides during storage;
- Protection of proteins or peptides against enzymatic breakdown; and
- Stabilization of the activity of proteins or peptides in the presence of cells.

Pharmaceutical products developed using BioChaperone technology are therefore designed to be more effective, easier to use and sometimes offer new uses at prices comparable to existing treatments.

At present, Adocia research teams have developed more than 500 BioChaperone compounds, an impressive collection that grows in size over time. The main distinctions among these compounds are their size, nature, and the number of anionic and hydrophobic grafts. This collection of molecules was rapidly extended to enable...
interactions with several classes of therapeutic proteins, notably the insulins and other metabolic hormones used in the treatment of diabetes.

BioChaperone technology is at present protected by 39 patent families for BioChaperone molecules and formulations. The first of the patents protecting formulations tested in clinical studies will expire in 2033.

1.3.2 Pipeline presentation

Since its creation, Adocia has developed a broad portfolio of injectable treatments for type 1 and 2 diabetes patients based on its BioChaperone technology. In January 2018, Adocia sought to extend its portfolio to include new therapeutic indications that could benefit from BioChaperone technology and the knowledge accumulated by the Company over the previous twelve years.

At present, Adocia’s clinical portfolio features five innovative insulin formulations for the treatment of diabetes: two ultra-rapid insulin analogs (BioChaperone Lispro U100 and U200), a rapid-acting human insulin (HinsBet U100), a combination of long-acting insulin glargine and rapid-acting insulin lispro (BioChaperone Combo), a combination of human insulin with pramlintide, an amylin analog, amylin being a synergetic hormone to prandial insulin (BioChaperone Pramlintide Insulin) and a ready-to-use aqueous formulation of human glucagon (BioChaperone Glucagon).

In 2018, Adocia granted the Chinese company Tonghua Dongbao Pharmaceuticals Co. Ltd, two licenses for the development and commercialization of BioChaperone Lispro et BioChaperone Combo insulin programs. These two agreements cover China, and some Asian and Middle-East territories. Adocia retains the rights to develop and license these two insulin programs in worldwide markets outside of the territories covered by these agreements, including the United States, Europe, Latin America and Japan.

Adocia also has in preclinical development two combinations of insulin glargine with GLP-1s (BioChaperone Glargine Dulaglutide and BioChaperone Glargine Liraglutide), a ready-to-use aqueous formulation of teduglutide, a GLP-2 analog for the treatment of short bowel syndrome (BioChaperone Teduglutide), and a combination of glucagon and a GLP-1 receptor agonist for the treatment of obesity (BioChaperone Glucagon GLP-1).

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<tr>
<th>Diabetes clinical pipeline</th>
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<td><strong>In vitro</strong></td>
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<td><strong>BC Lispro U100</strong></td>
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<td><strong>BC Lispro U200</strong></td>
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BC: BioChaperone; GLA: glargine; LIS: lispro; Pram: pramlintide; recom: recombinant human insulin; GLP-1: GLP-1 receptor agonist; GLP-2: GLP-2 receptor agonist; Gluc: glucagon; SBS: short bowel syndrome.

Products licensed to Tonghua Dongbao in China and other territories (excluding US, EU, Japan).
1.3.3 BioChaperone portfolio for the treatment of diabetes

1.3.3.1 Diabetes

Using its proprietary BioChaperone technological platform, Adocia is developing innovative formulations of therapeutic proteins for the treatment of diabetes.

Adocia develops new, more effective, easier to use, and more affordable injectable treatment options to improve the long-term quality of life for people living with diabetes.

- Epidemiology

Diabetes represents a group of global chronic diseases with a high rate of expansion, in particular in emerging countries. The International Diabetes Federation\(^4\) forecasts an increase by 48% of the number of people with diabetes worldwide between 2017 and 2045. (among people aged between 20 and 79 years), that is an increase from 425 million people with diabetes to 629 million. Although Europe (+15%) and North America (+36%) should experience growth rates inferior to the global average, emerging countries should face an acute raise of the number of people with diabetes.

By 2045 the proportion of people with diabetes should be over 8% in most regions of the world, except for Africa.

![Prevalence of diabetes by region (in million people, 2017-2045)](image)

*Figure 1: Estimates of the number of people with diabetes (in millions) among people aged between 20 and 79 years worldwide in 2017 and forecasts for 2045. The percentages show growth rates from 2017 to 2045 per region. Source: International Diabetes Federation, 2017*

- Disease and complications

Diabetes is a chronic disease where the patient experiences high levels of sugar in the blood (hyperglycemia) due to a deficiency or total lack of insulin, a pancreatic hormone.

Insulin plays a major role in the control of glycemia, by enabling the capture of circulating glucose by cells. In a subject without diabetes, the surge of glycemia following the ingestion of a meal is immediately associated with a rapid increase of endogenous insulin concentration in the blood, which enables the capture of the glucose by the cells and consequently maintains the glycemia level in the blood in a range comprised between 4.4 mmol/L (0.80 g/L) and 7 mmol/L (1.4 g/L). The control of glycemia is considered as ideal when blood glucose stays within this range.

However, if the blood glucose concentration dips under 0.80 g/L, the subject enters into an hypoglycemic state (which is hazardous, and could potentially be lethal) and when this concentration goes over 1.4g/L, she enters into an hyperglycemic state (which can lead to ketoacidosis in the short term and to numerous complications in the long term). In a person with diabetes, the regulation of blood glucose is deficient, which results in chronic exposure to hyperglycemic states. With time chronic hyperglycemia is responsible for micro- and macrovascular complications.

There are two main types of diabetes, known as type 1 and type 2 diabetes.

Different types of diabetes

**Type 1 diabetes** is an autoimmune disease, most commonly diagnosed in young people. Type 1 diabetes has been estimated to affect 10% of people with diabetes\(^5\). A person with type 1 diabetes makes antibodies which attack the beta cells of the pancreas, responsible for producing insulin in the islets of Langerhans. When a large majority of beta cells are destroyed (about 90%), treatment with insulin becomes unavoidable. Type 1 diabetes cannot be considered a ‘genetic disease’; in 90% of new cases there is no parental history at all of type 1 diabetes and the risk of developing type 1 diabetes if one of the two parents has it is lower than 2–3%\(^6\).

**Type 2 diabetes** is characterized primarily by resistance of cells to insulin, i.e., insulin resistance. Type 2 diabetes has been estimated to affect 90% of people with diabetes\(^7\). Type 2 diabetes is a progressive disease: insulin resistance leads firstly to excess insulin production, which degrades the islets of Langerhans. Once this degradation is initiated, the amount of insulin produced decreases. Type 2 diabetes is considered asymptomatic and is only discovered when measuring blood glucose levels (glycemia). It is estimated that the majority of patients to be diagnosed have already lost half of their beta cells. Genetic predisposition is a predominant factor and being overweight is an aggravating cause of type 2 diabetes.

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\(^5\) Business Insights - The Diabetes Market Outlook to 2016–May 2011

\(^6\) Diabetology Department, Prof. Altman, Georges Pompidou European Hospital (http://www.hegp.fr/diabeto/causetype1.html)

\(^7\) Business Insights - The Diabetes Market Outlook to 2016–May 2011
Other forms of diabetes called secondary forms (owing to the fact they are a consequence of other disorders or pathologies) do exist although their prevalence is marginal: genetic insulin secretion defects, genetic insulin sensitivity defects, diabetes due to pancreatitis or pancreatic cancer, drug-induced diabetes, etc. Pregnancy can also cause diabetes which, even if it disappears after childbirth, can nonetheless be a precursor to type 2 diabetes.

**A complex hormonal disorder**

Although insulin is a life-saving treatment for people with type 1 diabetes, as insulin triggers the metabolism of ingested glucose, the reality of hormonal deregulations due to diabetes is more complex than a simple lack of insulin.

Indeed, in a person who does not have diabetes, glycemias are regulated by a multitude of metabolic hormones, including insulin, acting in synergy to keep glycemia levels within a very precise range.

![Figure 3: Schematic representation of the secretion pattern of 4 key metabolic hormones around mealtime: insulin, amylin, GLP-1 and glucagon. Source: Adocia, adapted from Toff-Neilsen et al., J. Clin Endocrinol Metab 2001;86:3717-3723; Cummings DE et al., Diabetes 2001;50:1714-1719; Aronoff SL et al., Diabetes Spectrum 2004; 17(3): 183–190.](image)

In particular, four hormones play a key role in controlling glycemia levels: Insulin, amylin and GLP-1 are hypoglycemic agents, while glucagon is a hyperglycemic agent (Cf. figure 3)

- **Insulin and amylin** act in synergy. Insulin and amylin are co-secreted by the beta cells of the pancreas, at the ‘basal’ rate between meals, and at a higher level each time food is consumed, the so-called ‘prandial’ rate. Insulin acts on the liver, the muscles and the adipose tissues to promote uptake by these organs of sugar in the blood stream. Amylin works by suppressing the secretion of glucagon in the pancreas, promoting a sensation of satiety in the brain and slowing gastric emptying.

- **GLP-1** also has an action that works in synergy with those of insulin and amylin. It is mainly produced in the intestines following a meal. GLP-1 has several effects which all contribute to slowing the rate at which glucose enters the bloodstream. Firstly, via receptors in the pancreas, GLP-1 stimulates the secretion of insulin and suppresses the secretion of glucagon. Secondly, by affecting the central and peripheral nervous system, GLP-1 slows gastric emptying and induces a feeling of satiety.

- **Glucagon**, produced by alpha cells in the pancreas, is a hyperglycemic agent; that is, it promotes the release of glucose from the muscles and liver into the bloodstream. This is particularly useful between meals and during periods of exertion (physical or mental).

Combined, these four hormones keep glycemia levels within a very precise range, avoiding both hypoglycemia, which can be immediately debilitating or even fatal if severe, and hyperglycemia, responsible in the long-term for severe complications.

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In each of these four classes, at least one compound has been approved by the FDA. We shall only mention here those with a short action, for postprandial use. These compounds are:

- Prandial insulins: recombinant human insulin (named also « rHI », several brands worldwide) or analogs (insulin lispro, Humalog®, Eli Lilly; or Admelog®, Sanofi), insulin aspart (Novolog/NovoRapid®, Novo Nordisk); insulin glulisine (Apidra®, Sanofi)
- Pramlintide (Symlin®, AstraZeneca), an amylin analog;
- GLP-1 receptor agonists: exenatide (Byetta®, AstraZeneca), lixisenatide (Lyxumia®, Sanofi)\(^9\).
- Human glucagon (Glucagon®, Eli Lilly, and Glucagen®, Novo Nordisk)

In people with type 1 diabetes, this precise hormonal regulation is severely impaired (see figure 1): not only does the destruction of beta cells in the pancreas lead to the absence of insulin and amylin secretion, GLP-1 secretion by intestinal cells is also reduced. In the absence of glucagon suppressants i.e., GLP-1 and amylin, glucose is abnormally secreted at mealtimes.

Prandial hyperglycemia therefore has at least three causes: glucagon secretion, which leads to the release of sugars even before the person starts eating, faster gastric emptying resulting in a massive surge of glucose, and the absence of insulin, which prevents the uptake of these endogenous and exogenous sugars. This might explain in part why prandial insulin injection alone is not enough to completely control post-prandial hyperglycemia in a person with diabetes.

Complications of diabetes

Cardiovascular complications are the main cause of mortality in patients with type 2 diabetes: cardiovascular morbidity and mortality are multiplied by a factor of 2–3 in men and 4–5 in women. About 20% of cerebrovascular accidents (stroke) occur in people with diabetes. In the long term, diabetes can damage the heart, blood vessels, eyes, kidneys and nerves\(^10,11\):

- Heart disease and strokes are responsible for the death of 50% of people with diabetes;
- Kidney failure is responsible for the death of 10–20% of people with diabetes;
- Diabetic retinopathy is a significant cause of blindness resulting from accumulating damage to the small vessels in the retina; after approximately 15 years, 2% of people with diabetes are losing their sight and about 10% have a serious visual impairment;
- Diabetic neuropathy is nerve damage caused by diabetes; up to 50% of people with diabetes experience it. Common symptoms are tingling, pain, numbness or weakness in the feet and hands. Neuropathy, associated with poor blood circulation, increases the risk of venous ulcers and foot ulcers, which may lead to amputation;
- The overall risk of death is at least twice as high in people with diabetes.

1.3.3.2 Diabetes treatment - Insulinotherapy

Diabetes is a global pandemic affecting hundreds of millions of people which continues to grow at a significant rate, mainly due to changing lifestyles (more urban, more sedentary, with diets higher in fat and sugars) for many populations throughout the world. Historically, the injectable diabetes treatment market has been dominated by

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9 Among the GLP-1 receptor analogs, there are also long-acting products, whose action is pharmacologic but not physiological, in particular Ozempic® (Semaglutide, Novo Nordisk, weekly injection), Victoza® (liraglutide, Novo Nordisk, daily injection), Trulicity® (dulaglutide, Eli Lilly, weekly injection), Bydureon® (long-acting exenatide formulation, AstraZeneca, weekly injection), and Tanzeum® (abligrutide, GlaxoSmithKline, weekly injection).

10 Diabetology Department, Prof. Altman, Georges Pompidou European Hospital (http://www.hegp.fr/diabeto/causetype1.html)

11 DTTC study, NEJM, 1993, 329(14); EDIC study NEJM, 2005, 353(25)
three major players: Eli Lilly, Novo Nordisk and Sanofi, with all three initially focusing on insulin and, more recently, on GLP-1s. However, the dominance of these three players may well come to change under the influence of several major trends, including treatment personalization and commoditization.

According to Novo Nordisk, the global market for diabetes treatment with injectable products (insulins, GLP-1 analogs, glucagon) grew by 18.1% per year between 2008 and 2018, accounting for $29 billion\(^2\), i.e., more than 50% of the total market for antidiabetic medications. (cf. figure 4).

This domination of injectable medicinal products, particularly insulin, compared to other drug classes, is explained simply by the fact that insulin is absolutely needed to control glycemia in patients with type 1 diabetes, and that the use of insulin is also ultimately unavoidable for patients with type 2 diabetes.

![Global diabetes care market by treatment class](image)

**Figure 4: Global diabetes market per therapeutic class and changes between 2008 and 2018 OADs: Oral antidiabetic drugs; GLP-1: GLP-1 receptor agonists; insulin: insulin; CAGR: compound annual growth rate, over 10 years. The DKK-USD exchange rate on August 31, 2008, was DKK1 to $0.198. On August 31, 2018, the exchange rate was DKK1 to $0.156. (Source: Novo Nordisk, Investors Presentation First Nine Months of 2018, November 2018).**

It is important to remember that treatments differ for type 1 and type 2 diabetes. In type 1 diabetes, treatment with insulin is unavoidable, as pancreatic beta cells are destroyed and there is no more production of insulin. The treatment should cover both the regulation of continuous glycemia due to hepatic glycogenesis between meals (basal glucose) and the regulation of post-prandial glycemia. This is achieved by two types of products: the so-called ‘basal’ or ‘long-acting’ insulins, injected once or twice per day, and the so-called ‘rapid-acting’ or ‘prandial’ insulins, injected with every meal. A third type of product, called ‘premix,’ injected twice per day, maintains both basal and prandial regulation. Premixes are based on prandial insulin, a part of which is rendered less rapid by coacervation with protamine. However, premixes are a suboptimal solution compared to individually using basal insulin (which lasts longer) and prandial insulin (which acts more rapidly).

Historically, purified animal insulin was used as the first insulinotherapy (early 20th century), followed in the 1980’s by human recombinant insulin (Humulin®, Lilly; Novolin®, Novo Nordisk; Insuman®, Sanofi) and, more recently, since the end of 1990’s by modified insulin analogs to either accelerate their prandial action (insulin lispro: Humalog®, Lilly; Admelog®, Sanofi insulin aspart: Novolog®/NovoRapid® Novo Nordisk; insulin glulisine: Apidra®, Sanofi), or to lengthen their basal action (insulin glargine: Lantus® and Toujeo®, Sanofi and Abasaglar®, Lilly; insulin detemir: Levemir®, Novo Nordisk; insulin degludec: Tresiba®, Novo Nordisk). Premixed insulins made from human recombinant insulin and insulin analogs (Humalog® Mix, Eli Lilly and Novomix®, Novo Nordisk) have also been developed.

\(^2\)Estimations from annual reports. On the diagram below, this market is valued at $49 billion dollars according to IMS data, reported by Novo Nordisk, a figure that does not take into account discounts granted to payers.
In people with type 2 diabetes, disease progression is accompanied by treatment intensification: patients at first receive oral antidiabetic drugs and then move onto GLP-1 receptor analogs (that promote the secretion of insulin) and insulins (basal at first, then basal and prandial or premix).

1.3.3.3 The injectable diabetes treatment market: challenges and trends.

Despite insulin treatment for people with type 1 diabetes, and the large range of treatments for those with type 2 diabetes, there is still a significant medical need in these two indications.

Trend #1: improve the quality of life and extend the lifespan of patients by focusing on more specific criteria

It has been demonstrated that improving glycemic control can help limit the disease's short- and long-term consequences. Generally, there is a strong trend in the endocrinologist community to start evaluating new treatments on more diverse aspects than glycated hemoglobin (HbA1c) alone, which reflects only an average of glycemia over 3 months.

For instance, it has been proposed to pay closer attention to:

- Time-in-target-range: “time-in-range”, the glycaemic range being typically set between 70-140mg/mL; the notion of time in range permits a more precise representation of the glycemias variations that patients endure and their impact on their quality of life;
- Risk of hypoglycemia (the definition of which was recently reviewed by several scientific societies);
- Hypoglycemia is a major risk for patients treated for diabetes and presents related risks;
- Long-term benefits of certain drugs: for instance, cardiovascular benefits observed with new classes such as GLP-1 receptor agonists and and SGLT-2 inhibitors.

More generally there is also a need to actively promote and support patient involvement to avoid treatment misuse or discontinuation.

Trend #2: Integrate technologies and drug therapies

Interest given to finer indicators of glycemic variability has, amongst others, been made possible with the rapid evolution of technology: development of increasingly accurate continuous blood glucose monitoring (CGM) devices, ability to use Big Data data to address patient behavior, development of decision support algorithms (eg IBG Star Sanofi) or control pumps (eg BetaBionics), etc. For a short while, companies such as Eli or BigFoot in collaboration with other companies (like Dexcom) have been developing complete solutions (also known as “artificial pancreas” or “closed-loop systems”) including a continuous blood glucose monitoring (CGM) system, an insulin pump and an algorithm that automatically takes into account blood glucose measurements and injects the right dose of insulin.

Similar systems using “smart” pens rather than pumps are also under development. More generally, the various major players in insulin have recently partnered with big data companies to develop new diabetes monitoring and management solutions (Sanofi-Google partnerships, Medtronic-IBM Watson, Novo Nordisk-Glooko ...). The development of these new solutions could have a significant impact on the market in the years to come.

Trend #3: Market commoditization

At the same time, the diabetes market is becoming more commoditized given the combined effect of the approval of the first biosimilars and the pressure on healthcare systems to constrain rapidly increasing costs. Within the field of insulin, the first biosimilar of glargine, a basal insulin (Basaglar®, Eli Lilly) has recently been introduced to the European (2015) and American (2016) markets, a few years after similar products were introduced to the Chinese

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13 DTTC, NEJM study, 1993, 329(14); EDIC NEJM study, 2005, 353(25)
14 Travaux de consensus de l’ADA (American Diabetes Association) et de l’EASD (European Association for the study of diabetes), Travaux de l’EMA (European Medical Agency), interventions d’associations comme le JDRF (Juvenile Diabetes Research Foundation) ou DiaTribe...
(Basalin®, Gan & Lee) and Indian (Basalogs, Biocon) markets. As of the third quarter of 2018, Basaglar had acquired an 11% market share of the global basal insulin market. That market actually lost 4% of its global value over a year following the introduction of Basaglar in the US and EU.

In April 2018, Sanofi also launched on the US market the first FDA-approved insulin lispro biosimilar, Admelog®. Several new entrants and historical players in insulin are positioning themselves globally in the biosimilars field, such as Mylan and Biocon (Semglee®, insulin glargine, approved in Europe in 2018 and launched in the UK in November 2018 and in Japan in 2017, in registration in the US), or Sandoz and Gan & Lee who signed in 2018 a partnership to develop and commercialize biosimilars of insulins glargine, aspart and lispro in multiple markets, including the US and Europe.

At a regional level, one should also mention TUL, Fosun WangBang or Tonghua Dongbao Pharmaceuticals Co. Ltd in China, or Biocon and Wockhardt in India. In the GLP-1 field, Teva announced in January 2017 its intention to marker a biosimilar of liraglutide (Victoza®, Novo Nordisk).

The commoditization of these markets has begun to have a downward impact on historical product revenues, particularly for basal insulins, but is also pushing for innovation, in order to develop products “immune” from the competition of biosimilars. For example, Novo Nordisk and Eli Lilly, world leaders in prandial insulins with Novolog and Humalog products, developed two high-speed insulins, Fiasp® (approved in 2018) and LY900014 (in Phase 3). Similarly, Novo Nordisk and Sanofi have developed a new generation of basal insulins, Degludec® and Toujeo®, which outperform the historic products Lantus® and Detemir®.

By developing innovation using already-approved products, Adocia is responding to these two trends in the diabetes market, which should lead to offering better treatments to patients while making them affordable for as many people as possible.

### 1.3.3.4 BioChaperone Lispro U100 and U200

- **Ultra-rapid insulins for a more physiologic action**

Ultra-rapid insulin is an insulin that has a more rapid absorption profile than rapid-acting insulin analogs currently on the market. Currently marketed insulin analogs must be injected 5–15 minutes before meals, whilst human recombinant insulin must be injected 30 minutes before. This is in contrast to what happens in a non-diabetic person, for whom insulin secretion is immediate and proportionate to the meal, which limits glycemic excursion and its long-term effects. To mimic this ‘physiologic’ action profile, injected prandial insulins should ideally start acting very rapidly and for a duration limited to a few hours (to avoid any mismatch between insulin concentration in the blood and glycemia).

A mealtime injection, or right-after-mealtime injection, would enable patients to better determine the appropriate insulin dose because the exact contents of the meal would be known, and also to avoid overdosing or delayed dosing, which can lead to hypoglycemia or hyperglycemia respectively, which both have severe short and long-term consequences. This would also give patients some flexibility in terms of the time of injection, which is important in day-to-day life.

To respond to this need, **Adocia has developed two ultra-rapid insulin lispro formulations: BioChaperone Lispro U100 (standard insulin concentration: 100 IU/mL) and BioChaperone Lispro U200 (twice as concentrated solution, i.e., 200 IU/mL)**. These two products could offer a significant medical benefit to all users of prandial insulin. They may, however, be of particular importance for specific populations of people with diabetes:

- **Children**: it is particularly difficult to predict exactly when a child will eat and in what quantities. To avoid the risk of severe hypoglycemia, parents tend to inject insulin to their children with diabetes at mealtimes or after meals, which, together with prandial insulins currently on the market, can result in hyperglycemia. In the long-term, chronic hyperglycemia is correlated to serious complications of diabetes.

- **Insulin pump users**: the development of ultra-rapid insulin is a key element to facilitate the development of fully-automated insulin pumps (also called an ‘artificial pancreas’ ‘closed-loop systems’ or ‘automated insulin delivery systems’) that deliver insulin automatically, in real time, depending on the patient’s blood
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• Glucose levels. Concentrated ultra-rapid insulin may also facilitate the miniaturization of devices and/or increase autonomy between refills.

- People with type 2 diabetes: BC Lispro U200, an ultra-rapid insulin concentrate, may also improve glycemic control for these people whilst also limiting the volume required for each injection.

• Results obtained with BC Lispro U100 & U200

To date, BioChaperone Lispro has been successfully tested in 9 clinical studies, in more that 250 people with type 1 or type 2 diabetes. BioChaperone Lispro has been repeatedly shown to display an ultra-rapid profile compared to reference analog insulins aspart and lispro, whereas it was injected via syringes or insulin pumps and also showed superiority on some pharmacodynamic and pharmacokinetic parameters over Fiasp®, the only commercialized ultra-rapid insulin.

Phase 2a clinical results – Pharmacokinetic and pharmacodynamic study in people with type 1 diabetes (n=36)

The objective of this study was to compare the pharmacokinetic and pharmacodynamic profiles of the BioChaperone Lispro U100 complex to those of Humalog® U100. In April 2014, Adocia announced the results of this study, which showed the 30% faster onset of action and 69% better early metabolic effect of BioChaperone Lispro compared to Humalog in 36 patients with type 1 diabetes. These results are consistent with the pharmacokinetics of BioChaperone Lispro, which reaches its concentration peak 35% faster than Humalog; the amount of insulin present in the blood for the first 30 minutes is also 170% greater when it is formulated with BioChaperone.

Phase 2a clinical results – Second pharmacokinetic and pharmacodynamic dose-response study in people with type 1 diabetes (n=37)

In May 2014, Adocia initiated a second Phase 2a clinical study that aimed to evaluate the linearity of the effect of BioChaperone Lispro U100 for various doses in a range covering the needs of the majority of patients (0.1, 0.2 and 0.4 IU/kg). Positive results from this study were announced in September 2014. In this usual dose range, BioChaperone demonstrated the ultra-rapid linearity of its pharmacokinetic profile with respect to the dose (normalization test). The ultra-rapid effect was also observed in all pharmacodynamic profiles, whatever the dose tested.

The results of these two studies convinced Eli Lilly to enter into a new collaboration with Adocia. On December 19, 2014, Adocia and Eli Lilly announced they had signed a global licensing agreement for the development of an ultra-rapid insulin, BioChaperone Lispro. The agreement covered the development of two formulations: BioChaperone Lispro U100 and U200. Since signing the agreement, Eli Lilly and Adocia have successfully completed six clinical studies of BioChaperone Lispro U100 and U200. Lilly announced its decision to withdraw from this agreement on January 26, 2017.

Phase 2a clinical results – Study of the response to a standardized meal in people with type 1 diabetes (n=38)

Adocia and Lilly jointly announced in January 2015 that Adocia would initiate the first clinical study under this partnership. This Phase 1b/2a study aimed to evaluate the improvement in postprandial glycemic control obtained with BioChaperone Lispro compared to Humalog in 38 patients with type 1 diabetes after a standardized meal. The results of this study were jointly announced by both companies in June 2015. They showed a 61% reduction in postprandial glycemic excursions compared to Humalog. This study also confirmed the ultra-rapid pharmacokinetic profile of BioChaperone Lispro by demonstrating that insulin lispro’s speed of absorption was significantly faster. Early exposure also increased by 168% at the same dose for BioChaperone Lispro compared to Humalog.

The results of this study were the subject of an oral presentation given by Dr. Tim Heise (Profil Neuss) at the American Diabetes Association’s 76th Scientific Sessions (June 2016, New Orleans, USA) and a further oral presentation by Dr.

15 For more information on legal procedures opposing Adocia and Lilly following the termination of this contract, please see section « Litigation » 1.3.7.3 of the present reference document
Heise at the European Association for the Study of Diabetes 52nd Annual Conference (September 2016, Munich, Germany).

**Figure 5:** Comparison of the effect on postprandial glycemia of BioChaperone Lispro U100 vs. Humalog U100 in 38 people with type 1 diabetes. Glycemia is measured for six hours after injecting the treatment at the time of consuming a standardized liquid meal.

**Phase 1b clinical results – Study evaluating the potential for bioequivalence of the BioChaperone Lispro U200 formulation compared to BioChaperone Lispro U100, based on their pharmacokinetic and pharmacodynamics profiles in healthy volunteers (n=26)**

In June 2014, Adocia announced it was developing BioChaperone® Lispro U300, a concentrated insulin lispro formulation at 300 IU/mL of insulin lispro with BioChaperone. Preclinical data demonstrated that BioChaperone Lispro U300 had an ultra-rapid action compared to Humalog 100 IU/mL. This ultra-rapid action was equivalent to that obtained with BioChaperone Lispro U100 in the same model.

As part of the partnership with Lilly, a 200 IU/mL formulation, BioChaperone® Lispro U200, was developed, with Eli Lilly marketing a Humalog formulation at this concentration, Humalog U200. Further to positive preclinical results, BioChaperone Lispro U200 was clinically tested in a pilot bioequivalence study comparing it to BioChaperone Lispro U100, the positive results of which were announced in December 2015.

This pilot study aimed to demonstrate the potential for bioequivalence between the two products.

BioChaperone Lispro U200 fulfilled all the study’s predefined endpoints (two standard bioequivalence parameters, Cmax and AUCLispro0–infinity), and two parameters characterizing the ultra-rapid action (AUCLispro0–1 h and early t50%Cmax Lispro). These positive feasibility results support the development of BioChaperone Lispro U200, based on the demonstration of bioequivalence.

These positive results led to a $10 million milestone payment from Eli Lilly in December 2015.
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Figure 6: Mean pharmacokinetic profiles (variation in insulin level in the blood) of BioChaperone Lispro U100 (light blue curve) and BioChaperone Lispro U200 (dark blue curve) obtained from 26 healthy volunteers.

The results of this study were the subject of an abstract published in the Diabetes Care scientific journal at the American Diabetes Association’s 76th Scientific Sessions (June 2016, New Orleans, USA).

Positive topline results for the Phase 1b clinical study: repeated administration of BioChaperone Lispro U100 in people with type 1 diabetes (n= 36)

In March 2016, Adocia and Lilly jointly announced the positive results of a Phase 1b clinical study comparing the effects of BioChaperone Lispro and Humalog injected daily, at each meal, either at the time of the meal, or 15 minutes before, or 15 minutes after, on postprandial glycemic control in people with type 1 diabetes over a period of two weeks. This study showed: (i) at the beginning of the 14-day treatment period, BioChaperone Lispro U100 showed a 31% reduction in glycemic excursions over the first two hours compared to Humalog, when the treatments where injected when a solid meal was consumed and; (ii) after 14 days of treatment, a reduction of 42% in glycemic excursions during the first two hours compared to Humalog, when the treatments were injected at the mealtimes. This study was presented during multiple scientific conferences, and was also published in a peer-reviewed journal.

Positive topline results for the Phase 1b clinical study: repeated administration of BioChaperone Lispro U100 in people with type 2 diabetes (n=51)

In April 2016, Adocia and Lilly jointly announced the positive results of a Phase 1b study comparing the effects on postprandial glycemic control of BioChaperone Lispro and Humalog injected daily at mealtimes for 14 days in people with type 2 diabetes. BioChaperone Lispro demonstrated an ultra-rapid pharmacokinetic profile with a statistically significant increase of 83% in exposure to insulin lispro during the first 30 minutes post injection, compared to Humalog. On the basis of a post-hoc analysis including four meal tests per patient for each treatment (days 1, 2, 13 and 14), BioChaperone Lispro also showed a statistically significant decrease of 22% in glycemic excursions for the first two hours, compared to Humalog.

Main results from this study were published in Diabetes Care following the 77th Scientific Sessions of the American Diabetes Association (June 2017, San Diego, USA).

Positive topline results for a Phase 1 clinical study: evaluation of BioChaperone Lispro U100 in healthy Japanese subjects (n=15)

In May 2016, Adocia and Lilly jointly announced the positive results of a Phase 1 study evaluating BioChaperone Lispro U100 ultra-rapid insulin in Japanese subjects. This study aimed to compare the pharmacokinetic and pharmacodynamic profiles of BioChaperone Lispro to those of Humalog in 15 healthy Japanese subjects under

euglycemic clamp conditions. Although the study was not designed to perform statistical analysis, the results show an acceleration in the pharmacokinetic and pharmacodynamic profiles of BioChaperone Lispro compared to Humalog, as well as the linearity of insulin exposure as a function of the dose administered. The results of the study should allow for the inclusion of Japanese diabetes patients into the Phase 3 program in compliance with the global registration plan planned for this product.

**Positive topline results for Phase 1b clinical study: evaluation of BioChaperone Lispro U100 in people with type 1 diabetes using an insulin pump vs. Humalog® (n=44)**

In December 2016, Adocia and Lilly jointly announced the success of a Phase 1b clinical study comparing the effects of BioChaperone Lispro and Humalog on postprandial glycemic control in people with type 1 diabetes using an insulin pump. During this study, BioChaperone Lispro U100 demonstrated a statistically significant increase in insulin exposure over the first 30 minutes after a mealtime bolus compared to Humalog. The accelerated absorption of BioChaperone Lispro U100 was also observed in the three insulin delivery devices tested (Roche Accu-Chek® Spirit, Medtronic Paradigm® Veo™ and a syringe with insulin).

**Positive topline results for the Phase 1b clinical study: evaluation of BioChaperone Lispro U100 in people with type 1 diabetes using an insulin pump vs. Fiasp® and Novolog® (n=42)**

In December 2017, Adocia announced the success of a Phase 1b clinical study comparing BioChaperone Lispro both to the rapid-acting insulin Novolog® (Novo Nordisk) and to the recently approved ultra-rapid insulin aspart formulation Fiasp® (Novo Nordisk) in patients with type 1 diabetes. This study was the first direct comparison of two ultra-rapid insulin formulations. Forty-two participants received, under euglycemic clamp conditions, single doses of these three products via an insulin pump during three separate visits. The objectives of the study included comparing the glucodynamic effects and pharmacokinetic profiles obtained with the three treatments.

BioChaperone Lispro satisfied the primary endpoint, showing a statistically significant increase of 63% in metabolic effect during the first hour compared to Novolog®. This result confirms the ultra-rapid profile observed in previous studies when compared to Humalog®. Furthermore, BioChaperone Lispro showed a statistically significant ‘faster-off’ metabolic profile compared to the other two products, reaching the late half-Tmax 18 minutes before Fiasp® and 22 minutes before Novolog®. BioChaperone Lispro also showed an early metabolic effect similar to that of Fiasp® during the first hour.

Thus, BioChaperone Lispro has demonstrated a reproducible absorption profile through several studies, several populations and several modes of administration.

Results from this study were made public in an abstract in the scientific journal Diabetes Care following the 78th Scientific Sessions of the American Diabetes Association (June 2018, Orlando, USA), an oral presentation during the 54th Annual Conference of the European Association for the Study of Diabetes (October 2018, Berlin, Germany) and in a peer-reviewed publication17.

**Ongoing study using iLet™ bionic pancreas (n=30)**

In January 2019, Adocia announced the initiation of a first home-use trial testing the ultra-rapid insulin BioChaperone Lispro with BetaBionics automated insulin delivery system, the iLet™.

The iLet is a so called “Hybrid Closed-Loop” system, that consist of an autonomous, infusion pump that use clinically tested mathematical dosing algorithms driven by machine learning, to calculate and dose insulin as needed, based on data from a continuous glucose monitor. The iLet to be used in this trial will be set in an insulin-only configuration (another version allows the co-infusion of glucagon)

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The use of an ultra-rapid insulin in a hybrid closed-loop system should improve the reactivity and so the efficiency of this system to control glycemia.

This, multi-arm, cross-over, USA-only clinical trial, will recruit up to 30 people with type 1 diabetes to participate in three 7-day study arms comparing the pharmacokinetic and pharmacodynamic profiles of insulin lispro, insulin aspart, and BioChaperone Lispro in the bionic pancreas between and within subjects. The co-primary outcomes will be mean continuous glucose monitoring glucose (CGMG) and fraction of time spent with CGMG <54 mg/dl.

Results are expected in 2019.

- **Partnership with Tonghua Dongbao Pharmaceuticals Co. Ltd**

Adocia and the Chinese insulin leader Tonghua Dongbao Pharmaceuticals Co. Ltd announced in April 2018 a strategic partnership whereby Adocia granted exclusive development and commercialization rights to Tonghua Dongbao for BioChaperone® Combo and BioChaperone® Lispro in China and other Asian and Middle East countries.

Adocia received an upfront payment of $10 million for BioChaperone Lispro. Additionally, Adocia is entitled to receive development milestone payments up to $35 millions and to receive double-digit royalties on the sale of this product in the designated territories. Tonghua Dongbao will also reimburse some of Adocia’s expenses for research and development activities performed during the terms of the agreements.

Adocia retains the rights to develop and license BioChaperone Lispro in worldwide markets outside of the territories covered by these agreements, including the United States, Europe and Japan. Adocia remains responsible for the development and the manufacturing of BioChaperone® pharmaceutical excipients.

In June 2018, Tonghua Dongbao Pharmaceuticals Co. Ltd also agreed to manufacture and supply insulin glargine and insulin lispro to Adocia worldwide, excluding China, to support the development of Adocia programs in these regions. This agreement gives us full control, over the further development of BioChaperone Lispro. This also opens additional collaboration opportunities with biopharmaceutical companies focused in diabetes with no existing insulin manufacturing facilities and, also, device companies integrating synergies between innovative medicines, devices and care management systems.

Additional information about these contracts and the company Tonghua Dongbao Pharmaceuticals Co. Ltd are available in the section 1.3.7. of this document.

**Achieved partnership with Eli Lilly:**

BioChaperone Lispro program was previously licensed to the American company Eli Lilly: first between December 2011 and January 2013 (partnership terminated by common agreement) and then between December 2014 and January 2017 (partnership terminated by Eli Lilly, that gave priority to an internal project, LY90014). Some legal procedures are ongoing facing Adocia to Eli Lilly: they are detailed in the section “Litigations” 1.3.7.3 of this document.

Follow the termination of the second partnership, Adocia took back the full ownership of the rights that were licensed and continued the development of this product.

- **Next steps**

Based on BioChaperone Lispro’s strong clinical dossier, Adocia is seeking a new partner for entry into phase 3 and commercialization of the product in territories excluded from the licensing agreement with Tonghua Dongbao Pharmaceuticals Co. Ltd. (THDB), which is to say mainly the US, EU, Latin America and Japan.

Adocia intends to launch in 2019 a so-called “bridging study” enabling to demonstrate the comparability of THDB’s insulin lispro API with the one used in former formulations of BioChaperone Lispro (insulin lispro used in Humalog, Lilly). This will allow the use of all previous clinical data gathered for BioChaperone Lispro in its Phase 3 registration process.
• **Competition**

Several companies have sought to develop an ultra-rapid insulin with an action profile close to the physiologic activity of insulin.

**Novo Nordisk** has developed a high-speed formulation of insulin aspart called Fiasp®. In 2016, Fiasp received the approval of the European Medicines Agency for its launch on the European market for the treatment of type 1 and type 2 diabetes. Following a request for additional information from FDA (Complete Response Letter), Novo Nordisk resubmitted its file early in 2017 and Fiasp was approved by the FDA in September 2017. Fiasp has been available in the United States since January 2018 at a price similar to that of Novolog. In the third quarter of 2018, Fiasp recorded $26 million in sales in Europe and the United States.

A Phase 1b study of Fiasp in 52 patients with type 1 diabetes showed that the product had early pharmacokinetic and pharmacodynamic profiles significantly faster than insulin aspart. On the other hand, this does not translate into a fast-out / fast-off effect (faster insulin release / shorter duration activity), as has been shown for BioChaperone Lispro U100 in several Phase Studies 1b. This latter effect is desirable as it may reduce the risk of hypoglycaemia. In Phase 3 studies, Fiasp confirmed its high-speed absorption profile, but did not show superiority in terms of hypoglycaemia compared to insulin aspart.

In 2017, at the same time as the collaboration with Adocia ended, **Eli Lilly** announced that it had developed a competing high-speed insulin project LY900014 (insulin lispro formulated with treprostinil and citrate, among other excipients). The first results were presented at the ADA annual conference in June 2017. LY900014 has faster pharmacokinetic and pharmacodynamic profiles than Humalog (insulin lispro) in the first few minutes after injection. Nevertheless, Lilly has not demonstrated a more significant fast-out / fast-off effect than insulin lispro, unlike BioChaperone Lispro. Lilly announced in 2018 that it had achieved the primary objectives of the two Phase three trials in people with type 1 or type 2 diabetes. Thus, compared to Humalog, LY900014 met the non-inferiority criterion for the reduction. glycated hemoglobin (HbA1c) and demonstrated better glucose control after a meal. Lilly announced that the detailed results will be presented at a future conference and that the regulatory file will be submitted to the FDA in 2019.

**Mannkind**, founded in 1991, developed Afrezza, an inhalable human insulin with a high-speed profile, whose peak concentration is observed 12 to 15 minutes after inhalation. On June 27, 2014, the FDA approved the use of Afrezza to improve glycemic control in adults with diabetes. This approval, however, was accompanied by restrictions on patient populations (not recommended for smokers and patients with ketoacidosis) that could use Afrezza and a “black box warning” (warning about the potential risk of a drug, which should be included in the list), explicitly on the packaging, regarding the risk of bronchospasm associated with treatment. In addition, the FDA requested that Mannkind carry out four postmarketing clinical trials. An Afrezza marketing agreement with Sanofi in 2014 was terminated on April 4, 2016. Since then, Mannkind has continued to market Afrezza by its own means. Afrezza’s sales for the years 2016 to 2018 remained very weak, although slightly increasing.

Finally, in January 2019, the company **Arecor** announced the initiation of its first human study of its high-speed insulin (AT-247).

Other competing projects have been abandoned, in particular the association between human insulin and hyaluronidase developed by Halozyme (which refocused its activities on the applications of hyaluronidase in oncology at the end of 2014) and the high-speed formulations BIOD-250 and BIOD-238 developed by Biodel (which was the subject in 2016 of a “reverse-merger” operation by Albireo, which resulted in the deprioritization of Biodel’s historical activities).

### 1.3.3.5 BioChaperone Combo: a safer alternative to premixed insulin for treatment intensification in people with type 2 diabetes.

Type 2 diabetes is a progressive disease requiring progressive treatment intensification. At present, 50% of patients on basal insulin do not meet their glycemic control targets.\(^1\)

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\(^1\) Sanofi communication – Q3 2015 presentation
Presentation of Adocia and its activities

To improve glycemic control, the patient may be recommended to add a prandial component to his/her treatment regimen. This can be achieved via the addition of prandial insulin to the basal insulin, or by replacing basal insulin with premixed insulin. Premixed insulin is a fixed combination of a soluble fraction and a precipitated fraction of the rapid-acting prandial insulin analog. It is usually injected twice per day. It is thus an easier regimen than multiple insulin injections: one product only, twice per day at a fixed ratio (rather than two products, four times per day at variable doses).

Premixed insulins are therefore particularly recommended for elderly patients. They are also widely used in emerging countries. However, they do not offer ideal medical performance owing to a delayed and prolonged prandial action, a basal action profile of less than 24 hours and an elevated risk of hypoglycemia.

To meet the medical need for a regimen as simple as that of premixed insulin but as effective as a multiple-injection regimen, Adocia has developed BioChaperone Combo, a combination of insulin glargine (basal, Lantus, Sanofi) and insulin lispro (prandial, Humalog, Eli Lilly) at neutral pH. For a longtime, it was technically impossible to actually combine the gold-standard basal acting insulin, insulin glargine, and a rapid acting insulin into the same product, as they could not be formulated in the same pH range. BioChaperone technology makes it possible to solubilize insulin glargine at neutral pH and thus make it compatible with any prandial insulin.

By truly combining a basal insulin and a prandial insulin without changing their individual pharmacodynamic profiles, BioChaperone Combo could advantageously replace premix insulins in populations using them.

- Clinical results obtained with BioChaperone Combo

To date, BioChaperone Combo has been successfully tested in 5 clinical studies in 143 people with type 1 or type 2 diabetes, and repeatedly showed a faster prandial profile and longer basal profile compared to an analog insulin premix (HumalogMix 75/25).

Phase 1b clinical results – First pharmacodynamic and pharmacokinetic study in people with type 1 diabetes (n=20)

In the first quarter of 2014, Adocia announced positive results for a study that had aimed to compare the pharmacodynamic and pharmacokinetic profiles of BioChaperone Combo to those of HumalogMix (insulin lispro premix 75/25, Eli Lilly) in people with type 1 diabetes under euglycemic clamp conditions. The following positive results were obtained: onset of action of BioChaperone was at least 30% faster than that of HumalogMix; the duration of action observed for BioChaperone Combo was longer than 30 hours in the majority of patients but only 18 hours with HumalogMix; and BioChaperone Combo was well tolerated.

Phase 1b clinical results – Evaluation of the effects of BioChaperone Combo on postprandial glycemic control in people with type 1 diabetes (n=28)

In early November 2015, Adocia announced positive results for a Phase 1b clinical study evaluating postprandial effects of BioChaperone Combo in 28 patients with type 1 diabetes. This randomized double-blind crossover study compared the effect on postprandial glycemia of individualized doses of BioChaperone Combo and HumalogMix™75/25 (Eli Lilly), injected at the start of a standardized meal. The study fulfilled its primary endpoint, demonstrating that BioChaperone Combo decreased postprandial glycemia significantly more than Humalog Mix™75/25 during the first two hours (∆AUCBG(0–2h)). The minimal blood glucose level observed during the period was also significantly better controlled with BioChaperone Combo vs. Humalog® Mix™ 75/25. Although this study was not designed to measure differences in the incidence of hypoglycemic episodes between the two treatment groups, a reduced number of hypoglycemic events was observed with BioChaperone Combo vs. Humalog® Mix™ 75/25.
The results of this study were the subject of an oral presentation given by Dr. Steve Edelman (University of California, San Diego) at the American Diabetes Association’s 76th Scientific Sessions (June 2016, New Orleans, USA) and a poster at the European Association for the Study of Diabetes 52nd Annual Conference (September 2016, Munich, Germany).

Phase 1b clinical results – Pharmacokinetic and pharmacodynamic study of people with type 2 diabetes comparing BioChaperone Combo to HumalogMix 75/25™ and to the dual injection of Lantus and Humalog. (n=24)

In late November 2015, Adocia announced positive topline results for a Phase 1b study comparing the pharmacokinetic and pharmacodynamic profiles of BioChaperone Combo to those of HumalogMix 75/25™ and to the dual injection of Lantus and Humalog in patients with type 2 diabetes.

This randomized, double-blind, crossover phase 1b clinical study evaluated BioChaperone Combo in 24 patients with type 2 diabetes under euglycemic clamp conditions. The topline results consisted of comparing the pharmacodynamic profile of BioChaperone Combo to that of Humalog Mix75/25™ (Eli Lilly) and to separate, simultaneous injections of Lantus (insulin glargine, Sanofi) and Humalog (insulin lispro, Eli Lilly). The two key parameters in this comparison were the early prandial effect (AUCGIR(0–2h)) and the delayed basal effect (AUCGIR(24–30 h)) of these three treatments.

In this study, BioChaperone Combo demonstrated a significantly superior early prandial action and a longer metabolic effect compared to Humalog Mix75/25™, which confirms results previously obtained during the first pharmacokinetic and pharmacodynamics study conducted in patients with type 1 diabetes.
Furthermore, this study also established the proof-of-concept that BioChaperone Combo has a similar effect to that of the dual injection of Lantus and Humalog on these two parameters in people with type 2 diabetes.

The results of this study were presented in a poster discussed by Dr. Eda Cengiz (Yale School of Medicine) at the American Diabetes Association’s 76th Scientific Sessions (June 2016, New Orleans, USA) and an oral presentation by Dr. Simon Bruce, Medical Director at Adocia, at the 52nd annual conference of the European Association for the Study of Diabetes (September 2016, Munich, Germany).

Phase 1b clinical results – Evaluation of the effects of BioChaperone Combo on postprandial glycemic control in people with type 2 diabetes. (n= 39)

In June 2017, Adocia announced the positive topline results for a study intended to measure the effect of BioChaperone Combo injected at mealtimes on postprandial glycemic control in patients presenting type 2 diabetes compared to that obtained with Humalog Mix25™ premixed insulin (Eli Lilly), and with separate injections of Lantus (Sanofi) and Humalog (Eli Lilly).

Firstly, BioChaperone Combo showed a statistically significant decrease of 18% in glycemic excursions for the first two hours after the meal compared to Humalog Mix25™. The number of hypoglycemic episodes per patient was also significantly lower with BioChaperone Combo than with Humalog Mix25™. Moreover, BioChaperone Combo led to at least as good postprandial glycemic control as that achieved with simultaneous and separate injections of Lantus and Humalog, and a similar number of hypoglycemic episodes per patient.

Phase 1b clinical results – BioChaperone Combo dose-proportionality study in people with type 2 diabetes. (n= 32)

In January 2018, Adocia announced positive topline results for a Phase 1b study evaluating the relationship between insulin exposure and hypoglycemic response to the BioChaperone Combo 75/25 dose for three different doses in people with type 2 diabetes. During his study, 32 participants were randomly allocated a sequence of four treatments: one of the three doses of BioChaperone Combo 75/25 (0.6 IU/kg; 0.8 IU/kg or 1.0 IU/kg) or a single dose of Humalog Mix25™ at 0.8 IU/kg. BioChaperone Combo exhibited dose-proportional exposure and a linear relationship of hypoglycemic response to the dose when tested at 0.6, 0.8 and 1.0 IU/kg in people with type 2 diabetes. These results are essential to complete the regulatory dossier. The study also confirmed previous results showing that BioChaperone Combo acts significantly faster (prandial effect) and lasts significantly longer (basal effect) than HumalogMix.
Partnership with Tonghua Dongbao Pharmaceuticals Co. Ltd


The BioChaperone Combo agreement includes an upfront payment of $40 million, up to $50 million development milestone payments and double-digit royalties on the sale of this product in the designated territories. Tonghua Dongbao Pharmaceuticals Co. Ltd will also reimburse some of Adocia's expenses for research and development activities performed during the terms of the agreement.

Adocia retains the rights to develop and license BioChaperon Combo in worldwide markets outside of the territories covered by these agreements, including the United States, Europe, Latin America and Japan. Adocia remains responsible for the development and the manufacturing of BioChaperone® pharmaceutical excipients.

In June 2018, Tonghua Dongbao Pharmaceuticals Co. Ltd agreed to manufacture and supply insulin lispro and insulin glargine APIs to Adocia worldwide, excluding China, to support the development of Adocia's portfolio in these territories.

This agreement gives us full control, outside China, over the further development of BioChaperone Combo. This also opens additional collaboration opportunities with biopharmaceutical companies focused in diabetes with no existing insulin manufacturing facilities.

Further details on these contracts and the company Tonghua Dongbao Pharmaceuticals Co. Ltd are available under the section 1.3.7 of the present reference document

Next steps

Adocia is actively seeking a partner to further develop and market BioChaperone Combo, for territories non licensed to Tonghua Dongbao Pharmaceuticals Co. Ltd.

Competition

Premixed insulins, which are prandial insulins of which some is precipitated with protamine, should be considered as direct competitors to BioChaperone Combo. These products include: HumalogMix® (Eli Lilly, made from insulin lispro) NovoMix®/NovologMix® (Novo Nordisk, made from insulin aspart), in addition to, in emerging countries, premixed insulins made from human insulin, which remain widely used (e.g., Humulin® 70/30 for Eli Lilly and Novolin® 70/30 for Novo Nordisk, as well as many locally-developed products). These products now represent an estimated combined turnover of $4 billion for the three largest players, $2.2 billion for analog premixes19 and $1.8 billion for human insulin premixes20. It should be noted that in China, 65% by volume of insulin sold consists of premixed insulin (according to estimates by IQVIA in 2017). Whilst the exact turnover of Chinese companies in the Chinese market is not known, it is acknowledged that the Chinese market is underestimated.

However, as previously explained, these products have several disadvantages, particularly in terms of:

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19 Overall turnover estimates for 2017, based on annual reports published by Eli Lilly and Novo Nordisk. NovoMix/NovologMix: Turnover in 2015 reported as $10.257 MDKK, estimated at $1.552 billion (based on the $/DKK average exchange rate per trimester). HumalogMix: Turnover in 2017 for Humalog (prandial and premix) reported as $2.865 billion. After the survey of the ratios between Humalog and HumalogMix in volume based on IQVIA data from 2017 in Europe, in the US and in China. The estimated turnover of HumalogMix in 2017 was $629 million. This equates to a total of $2.181 billion. This figure is probably underestimated, as in emerging markets some players have already marketed analog insulin premixes, such as Gan & Lee in China (lisprox).

20 For premixed human insulin, we used the ratio between human prandial insulin and premixed human insulin reported in the same presentation by Novo Nordisk, i.e., 40% prandial and 60% premix. By applying this ratio to the total sales of Novo Nordisk's human insulin (Novolin DKK10.072 million, i.e., 1.526 billion), Lilly (Humulin, 1.335 billion) and Sanofi (Insuman, 1.211 million), we obtain a total of $1.789 billion for premixed human insulin. This figure is probably underestimated, as in emerging markets, many other players are producing and marketing human insulin, in particular in premixed forms in the Asian and Latin American markets (e.g., Gan & Lee, DongBao, Fosun WangBang in China; Biocon in India; R-Pharm in Russia; Julpharm in the Middle East, etc.).
Presentation of Adocia and its activities

- **A delayed prandial action** compared to their benchmark insulin (human or analog). This delay leads to reduced postprandial glycemic control and an elevated risk of hypoglycemia linked to an overly slow transition between the prandial and basal effects. In clinical studies published to date, BioChaperone Combo and Ryzodeg present a similar onset of action to prandial insulin analogs.

- **An overly slow basal action**, always less than 24h, meaning two injections per day are required. With BioChaperone Combo, it is possible to gradually intensify treatment, switching from basal insulin to a single daily injection of BC Combo (at the time of the main meal of the day), then to two injections when disease progression requires it.

BioChaperone Combo may thus represent a superior solution to premixed insulin, at a similar price, to facilitate patient access to a better-performing and safer treatment, particularly in emergent countries wherein these products remain dominant.

**Novo Nordisk** has developed Ryzodeg®, the only other product truly combining a basal insulin (insulin degludec) and a prandial insulin (insulin aspart), Ryzodeg was tested in multiple clinical studies, either against a premixed insulin aspart, NovoMix®, against Lantus, or against the combination of Levemir and NovoLog. These results demonstrated the Ryzodeg is well tolerated in patients with type 1 and type 2 diabetes, and that this product can improve glycemic control vs Lantus and reduce the incidence of hypoglycemic episodes vs Novomix, confirming the expected benefits of a ‘true’ combo compared to premixed insulin. In 2013, Novo Nordisk obtained marketing authorizations for Tresiba and Ryzodeg in Europe and Japan. Ryzodeg is the first dual insulin combo product to enter the market. Tresiba and Ryzodeg were only approved in the United States in September 2015 after Novo Nordisk published positive interim results from the additional cardiovascular safety studies of Tresiba which the FDA had requested during the first submission of the regulatory dossier. Ryzodeg is now available in more than 25 countries. The pricing strategy of Novo Nordisk takes into account the investment consented in developing Tresiba and Ryzodeg is currently sold at a premium compared to Novomix.

BioChaperone Combo, the formulation developed by Adocia combining insulin glargine and lispro, benefits from the large amount of positive data on the safety of insulin glargine and lispro (Lantus® and Humalog®). BioChaperone Combo may also benefit from a competitive advantage in terms of cost, as the product is based on two insulins which fell in the public domain and benefit from large manufacturing infrastructure.

In 2018, Adocia secured its sourcing of lispro and glargine insulins from Tonghua Dongbao Pharmaceuticals Co. Ltd. of China.

1.3.3.6 **HinsBet®**

- **A rapid and cost-effective prandial insulin**

Seventy-seven percent of people with diabetes live in low- and middle-income countries where human insulin is the main type of insulin used. For these patients with diabetes, there is a real need for prandial insulin at an affordable price which acts as rapidly as insulin analogs.

HinsBet® U100 is a standard concentration human insulin formulation incorporating BioChaperone® to accelerate its action profile.

Some people with type 2 diabetes are severely resistant to insulin and their treatment may require daily doses of insulin two or three times higher than those normally administered to people with type 2 diabetes, i.e., more than 200 units per day.

It is difficult for these patients to use conventional insulin analogs or human insulin at 100 IU/mL, such as Humalog® or Humulin®, as the volumes involved for the administrations are too large.

The main option for insulin-based treatment for these highly insulin-resistant individuals in the United States is Humulin® U500 (Eli Lilly), a human insulin formulation at 500 IU/mL, that is, five times more concentrated than
standard products on the market. This product has rapidly growing revenues in the United States where estimates for 2014 amounted to more than $300 million\textsuperscript{21}.

- Clinical results obtained with HinsBet U100

Two formulations were developed for HinsBet: one conventional formulation, that enabled the clinical proof-of-concept to first be demonstrated, and an optimized formulation, which was tested in two clinical studies in people with type 1 diabetes.

Phase 1b clinical results – Pharmacokinetic and pharmacodynamic study of people with type 1 diabetes comparing HinsBet U100 (BioChaperone rHI) to Humalog (insulin lispro) and Humulin (rHI). (n=36)

In February 2015, Adocia announced positive topline results for this crossover double-blind study comparing the pharmacokinetic and pharmacodynamic characteristics of HinsBet with those of Humulin and Humalog. Thirty-six patients with type 1 diabetes received a single 0.2-U/kg dose of HinsBet, Humulin and Humulin under euglycemic clamp conditions. The results showed that HinsBet was significantly faster acting than human insulin in patients with type 1 diabetes: onset of action 70% sooner and double the early metabolic effect. The three formulations were well tolerated and did not induce any local reaction.

This rapid action of HinsBet is comparable to that of Humalog in the first hour, which is critical when it comes to prandial glycemic control.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure9.png}
\caption{Taux d’infusion du glucose (GIR)}
\end{figure}

Phase 1b clinical results – Evaluation of the effects of HinsBet U100 on postprandial glycemic control in people with type 1 diabetes. (n= 36)

On October 27, 2016, Adocia announced positive topline results for this study, which compared the postprandial effect of HinsBet U100 to those of Humalog and Humulin, injected at the same time as a mixed standardized meal. The clinical study achieved its principle objective of demonstrating the superiority of HinsBet over Humulin in terms of postprandial glycemic control one hour after the meal (glycemia level one hour after the meal: BG\textsubscript{1h}=228 mg/dL with HinsBet vs. 253 mg/dL with Humulin, LSM ratio 0.9, 95% CI, p=0.0002). HinsBet also showed a similar effect to that of Humalogin terms of postprandial glycemic control for the first hour after the meal. In addition, HinsBet significantly reduced postprandial glycemic excursions for the first hour compared to Humulin (AUC\textsubscript{BG0-1h}=174 h*mg/dL avec HinsBet vs. 192 h*mg/dL with Humulin, LSM ratio 0.9, 95% CI, p=0.0002). No significant differences

\textsuperscript{21} RED BOOK 2013 - Truven Health Analytics - Thomson Reuters
were observed between HinsBet and Humalog for this last parameter (AUC$_{BG0-1h}$ = 174 h*mg/dL with HinsBet vs. 172 h*mg/dL with Humalog, LSM ratio 1.0, 90% CI, p=0.5373).

- **Next steps**

On the basis of these positive phase 1b results and given the particular potential of HinsBet in emergent countries with greater user demand for human insulin, Adocia intends to find one or several partners with which to continue HinsBet development in these markets.

- **Competition**

The global market for human prandial insulin for the three main players (Novo Nordisk, Sanofi and Eli Lilly) is currently estimated at $1.238 billion. Compared with conventional recombinant human insulin, HinsBet presents the advantage of an onset of action equally fast as that of an analog, for a cost similar to that of human insulin. HinsBet would therefore likely outperform human insulin in markets where it remains significant.

Ultimately, HinsBet will also compete with insulin analog biosimilars (aspart, lispro, glulisine). At present, an insulin lispro biosimilar developed by Sanofi (Admelog®) is approved in Europe and the United States, and some rapid-action insulin analog biosimilars have been approved (for instance a biosimilar of insulin lispro in China developed by Gan & Lee) or are in development (insulin lispro for Biocon in the preclinical stage in India) in emergent countries. Sanofi is also developing an insulin aspart biosimilar (phase 1). However, HinsBet should continue to enjoy a competitive advantage in terms of pricing, since human insulin production remains less expensive than that of insulin analogs.

1.3.3.7 **BioChaperone Glucagon**

- **An aqueous formulation of human glucagon for the acute and chronic treatment of hypoglycemia**

Glucagon is one of the main hormones regulating the metabolism. Its role is schematically the opposite to that of insulin. In a person without diabetes, glucagon is secreted in the event of hypoglycemia or during exertion in order to keep blood glucose at a normal level.

**Severe hypoglycemia** is defined by a blood glucose lower than 50-54 mg/dL. It is insulin’s most feared short-term adverse event (due to overdosing). Its symptoms may include dizziness, transient cognitive impairment, convulsion and, in the most severe cases, coma and death. Due to those symptoms, treating severe hypoglycemia very often requires the help of a third party.

In the therapeutic field, human glucagon is the only approved treatment for severe hypoglycemia. Unfortunately, human glucagon is very unstable in aqueous solution and the only commercially-available products at present are the emergency (rescue) kits composed of lyophilized human glucagon that can be reconstituted just prior to injection by following several steps. Recent studies evaluating the ease-of-use of these kits have shown that in 80% of cases, users fail to correctly reconstitute and/or administer the recommended dose.

By using proprietary BioChaperone® technology, Adocia intends to develop a stable aqueous solution of human glucagon. Such a solution could both be used as part of the emergency treatment of hypoglycemia (in a ready-to-use device) and in the context of a dual hormone artificial pancreas (DHAP). In the latter, using glucagon may help to significantly increase the time spent within the targeted glycemic range. Additionally, the joint use of glucagon and insulin may help bring about devices that are completely autonomous, using algorithms that react automatically to glycemic variations, without the patient directly intervening. Recently, several research groups (academic and

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22 Cf. Calculation for human insulin premixes. The proportion of prandial human insulin is estimated here to be 40% of reported sales. Once again, the turnover figures for local players (Gan & Lee, DongBao, Fosun WangBang, Biocon, R-Pharm, BioMM, Bioton, etc.) have not been reported, suggesting that this figure is probably underestimated.

23 Locemia, 2015
industrial, such as Beta Bionics or Inreda Therapeutics) have developed such “smart” pumps and have clinically demonstrated their potential benefits in comparison to pumps using insulin alone\textsuperscript{24}, particularly with regards to reduced glycemic variability and the reduced risk of hypoglycemia. However, all these teams are currently limited by the absence of a commercially available glucagon solution. Most of the studies up until now have been conducted using lyophilized glucagon reconstituted every day, what would not be acceptable for a daily use, or with developing products which are not yet approved by a regulatory authority Adocia is also seeking to develop BioChaperone Glucagon for other indications, including congenital hyperinsulinism and chronic hypoglycemia following bariatric surgery.

Adocia hopes to be able to soon offer an aqueous solution of human glucagon. Using human glucagon also presents Adocia the additional advantage of being able to take advantage of the track record of this approved peptide compared to glucagon analogs developed by some competitors (e.g. Eli Lilly, Zealand Pharma).

- **Clinical results obtained with BioChaperone Glucagon**

  **Phase 1 clinical results – Evaluation of the safety, pharmacokinetics, and pharmacodynamics of BioChaperone Glucagon in patients with type 1 diabetes (n=24)**

  In November 2017, Adocia announced positive topline results for this first study of BioChaperone Glucagon in human participants. A subcutaneous injection of 1 mg BioChaperone Glucagon showed acceptable safety and tolerability profiles, validating the primary objective of the study. In all groups, the most common adverse event was nausea, with eight events observed in 25 patients with BioChaperone Glucagon vs. five events in 24 patients with Glucagen\textsuperscript{®} Hypokit\textsuperscript{®}. The median time to reach a clinically risk-free level of glucose of 70 mg/dL was 11 min for BioChaperone Glucagon and almost 7 min for the reconstituted commercial product Glucagen\textsuperscript{®}. All patients achieved hypoglycemic resolution within 35 minutes of injection.

- **Next steps**

  Adocia plans to initiate a second Phase 1/2 study during the second quarter of 2019. This study could be the last one before starting the program in Phase 3 development. In parallel, Adocia is selecting a high quality and easy-to-use injection device for BioChaperone Glucagon.

- **Competition**

  Two major applications are envisaged for the BioChaperone Glucagon formulation.

  - Treatment of severe hypoglycemia
  - Chronic use (bi-hormonal artificial pancreas, indications in need of a glucagonotherapy

  For the treatment of severe hypoglycemia, there are currently two products on the market: Glucagon\textsuperscript{®} (Eli Lilly) and GlucaGen\textsuperscript{®} Hypokit\textsuperscript{®} (Novo Nordisk). These both come in emergency kits and require the real-time reconstitution of lyophilized glucagon and injection with a syringe. There are between seven and nine stages to the procedure. In a real emergency situation, wherein the patient is unconscious, these devices have proven to be extremely difficult to use for third parties, even more so if they have not been trained in their use. In a study of 130 parents of people with type 1 diabetes in a simulated hypoglycemic emergency, 69% of them had difficulty handling the emergency kit (GlucaGen Hypokit)\textsuperscript{25}. Due to the difficulty using these products, they remain underprescribed and underused, leading to frequent interventions by emergency teams. The response time can be fatal. Severe hypoglycemia results in more than 300,000 hospitalizations in the United States each year\textsuperscript{26}. Several companies, including Adocia, are developing ready-to-use alternatives for emergency treatment.

\textsuperscript{24} For example, c.f. El Khatib et al., 77-OR, ADA 76th Scientific Sessions June 10–14th, 2016, USA. et Russell et al, The Lancet (2016) 4(3):233-2

\textsuperscript{25} Harris, G et al Practical Diabetes Int. 2001: 18;22-25.

\textsuperscript{26} Report from the CDC, 2014
Presentation of Adocia and its activities

Locemia has developed a single-use nasal spray presentation which in principle is easier to use for the untrained user. This product was acquired by Eli Lilly, for an undisclosed sum, in October 2015. Lilly filed this product for registration with the US and European regulatory authorities during the second quarter 2018. Meanwhile, Lilly ended in 2018 the development of a soluble glucagon analog formulation.

Furthermore, several companies are developing liquid forms for use in emergency situations or for use with an artificial pancreas.

Xeris developed a human glucagon liquid formulation with the help of the organic solvent DMSO. It intends to develop this product in the form of a pen for emergency situations, a mini-pen for moderate hypoglycemic episodes, and a cartridge for use in pumps (artificial pancreas or other chronic uses of glucagon). At this stage, two Phase 3 studies and a Phase 3b study have been successfully completed. Xeris entered pre-registration stage in the US in Q2 2018. Furthermore, the company completed a Phase 2 study using glucagon pumps to treat post-bariatric hypoglycemia and initiated in April 2018 a Phase 2 study using glucagon pumps in people with type 1 diabetes with hypoglycemia unawareness. Xeris has also obtained the ‘orphan medicinal product’ indication from the FDA for use in the treatment of congenital hyperinsulinemia and started a Phase 2 for this indication in December 2018.

Zealand Pharma is developing a glucagon analog, dasiglucagon, for three main indications: for the treatment of severe hypoglycemia; for use in a DHAP; and for the chronic treatment of congenital hyperinsulinism (in a glucagon pump). At the end of 2017, it started Phase 3 studies on HypoPal®, a prefilled ready-to-use pen for the emergency treatment of severe hypoglycemia. Preliminary positive results for this study were announced in February 2018. Zealand plans to market HypoPal® in Europe and the United States in 2020/2021. Furthermore, it recently announced the preparation of a Phase 2b study using the Beta-Bionics artificial pancreas, iLet™. Finally, it has obtained an ‘orphan drug’ indication by the FDA for the use of dasiglucagon to treat congenital hyperinsulinism, a project which entered Phase 3 in December 2018.

Compared to an analog, BioChaperone Glucagon should offer the advantage of using human glucagon, the safety and efficacy of which have been demonstrated with the Glucagon® and Glucagen® products.

1.3.3.8 BioChaperone Pramlintide Insulin: multi-hormonal prandial combinations for the treatment of type 1 diabetes

- Provide high-performance, easy-to-use multi-hormone therapy for people with type 1 diabetes to improve long-term outcomes

Although insulin is a vital treatment for people with type 1 diabetes, even the best-controlled patients present significant glycemic variations and frequently do not achieve the targets set by their physician. This may result in an increase in the risk of severe complications in the long term, such as cardiovascular disease, retinopathy, renal failure and neuropathy.

In fact, in people who do not have diabetes, insulin is secreted synchronously and acts in synergy with other hormones, such as amylin and GLP-1, to control glycemia. In type 1 diabetes, ultimately, neither insulin nor amylin are secreted, and GLP-1 secretion is deficient. It is therefore possible that the use of insulin alone cannot address all the metabolic deficiencies related to diabetes.

Pramlintide (Symlin®, AstraZeneca), a rapid-acting amylin analog, was approved in 2005 for the treatment of diabetes (type 1 and 2) as a supplement to intensive insulin therapy. In phase 3 clinical studies, this molecule has been shown, when used as a supplement to insulin therapy, to improve HbA1c (-0.2% by people with type 1 after 6 mo.) and reduce prandial insulin use (-22% in the same study) and weight gain compared to insulin alone (-3 kg in the same study)27.

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Unfortunately, to the extent that insulin therapy for type 1 diabetes requires high patient compliance, with frequent glycemia monitoring and at least four injections of insulin daily, the introduction of an additional injectable treatment is often synonymous with a significant deterioration in quality of life and an increase in the cost of treatment, which can lead to its abandonment.

The combination of this molecule with insulin could therefore prove to be an elegant solution to maximize the medical benefit whilst maintaining patient compliance and controlling health costs. Developing such a combination is Adocia’s objective for the BioChaperone Pramlintide Insulin program.

Currently, the prandial insulin and pramlintide formulations are not compatible. Adocia has therefore used its expertise to develop BioChaperone so pramlintide can be solubilized and stabilized in neutral pH solution, enabling it to be combined with prandial insulin.

Our BioChaperone formulation strategy, based on actual clinical results, showing a clear medical benefit when hormones are administered separately, could reduce development time. The BioChaperone Pramlintide Insulin project could also support a competitive pricing strategy, taking advantage proteins already approved and in the public domain.

- Clinical results obtained by BioChaperone Pramlintide Insulin

**Phase 1 clinical results – Evaluation of safety, pharmacokinetics and pharmacodynamics of BioChaperone Pramlintide Insulin in people with type 1 diabetes (n=24)**

In September 2018, Adocia announced positive pharmacodynamic and safety topline results from the Phase 1 study of BioChaperone Pramlintide Insulin (BC Pram Ins), the ready-to-use co-formulation of pramlintide and human insulin. This randomized, double-blind, active comparator-controlled, three-period cross-over study, enrolled 24 participants with type 1 diabetes. Subjects were randomly allocated to a sequence of three treatments, administered at the time of the intake of a standardized mixed meal. This study aimed to investigate the pharmacokinetics, pharmacodynamics, and the safety and tolerability of a single fixed dose of BC Pram Ins (containing 7.5U insulin and 45 μg pramlintide), compared on the one hand to separate and simultaneous injections of human insulin (7.5U, Humulin®, Eli Lilly) and pramlintide (45 μg, Symlin®, AstraZeneca), and on the other hand to an injection of rapid-acting insulin analog lispro (7.5U, Humalog®, Eli Lilly).

Treatment with BC Pram Ins resulted in a statistically significant 97% reduction of blood glucose excursions over the first two hours compared to Humalog (Mean(±SD) DeltaAUCGIR 0_2h = 4 (63) mg*hour/dL vs. 126(74) mg*hour/dL; p<0.0001) and a comparable postprandial glycemic control to that of the separate injections of Humulin and Symlin (LS- Mean DeltaAUCGIR 0_2h = 21 (66) mg*hour/dL, n.s.)

All treatments were well tolerated. Notably, the overall number of hypoglycemia was similar between treatments (BC Pram Ins: n=4; Symlin + Humulin: n=3; Humalog: n=3) and there were no warnings on gastro-intestinal side-effects with any of the administered treatments. As a reminder, hypoglycemia and gastro-intestinal side effects have been previously associated with Symlin® clinical use.
Presentation of Adocia and its activities

- **Next steps**

Adocia plans to initiate a second phase 1 /2 study during the first semester of 2019.

- **Competition**

To date and to our knowledge, only **Biozeus**, a Brazilian biotechnology company, and **Xeris Pharmaceuticals**, a biotech company known for its ready to use glucagon program for different indications, are developing at the preclinical level a combination of insulin and amylin.

**AstraZeneca**, which owns the commercial product **Symlin** (pramlintide), has successfully conducted Phase 1 clinical trials on the joint administration, with two independent pumps, of prandial insulin and pramlintide. These studies were partially funded by the Juvenile Diabetes Research Foundation (JDRF). These results support Adocia’s approach of combining the two products in a single formulation for better results.

**Novo Nordisk** is also developing a new long-acting amylin analog, which is currently tested in 2 Phase 1 clinical trials, alone and in combination with Novo Nordisk’s last generation GLP-1, semaglutide. This product is intended for use in overweight or obese patients, but not in patients with diabetes.

**Zealand Pharma** in collaboration with Boehringer Ingelheim, is also developing a long-acting amylin analog for people with obesity as well as for people with type 2 diabetes. A phase 1 study planned in 2017 was cancelled and the project is registered as in preclinical development.

### 1.3.3.9 BioChaperone Glargine GLP-1

- **Combinations to intensify treatment in people with type 2 diabetes using basal insulin**

Basal insulin remains an essential treatment for patients with uncontrolled type 2 diabetes using oral antidiabetic agents. However, according to some estimates, 50% of people with diabetes using basal insulin alone as an injectable treatment do not meet their glycemic target.

As the underlying mechanisms of action of basal insulin and GLP-1 receptor agonists (GLP-1s) are complementary, combinations of the two agents have been developed as one product, once-daily treatment intensification options for these patients. In Phase 3 clinical studies, these combinations demonstrated improved glycemic control whilst reducing the incidence of adverse reactions compared to each agent used separately (hypoglycemia level similar to or lower than basal insulin alone and less gastrointestinal adverse reactions GLP-1 alone). Two basal insulin-GLP-1 combinations were approved by the FDA in November 2016 (Xultophy® by Novo Nordisk and Soliqua® by Sanofi).

In September 2016, Adocia announced the launch of a new BioChaperone program to combine basal insulin and GLP-1. This program benefits from the expertise gained through the BioChaperone Combo project because it relies on BioChaperone’s ability to solubilize insulin glargine at physiologic pH. This makes it possible to combine it with the two GLP-1 market leaders: liraglutide (Victoza®, Novo Nordisk, daily administration) and dulaglutide (Trulicity®, Eli Lilly, weekly administration), in order to develop two potential candidates:

- BioChaperone® Glargine Liraglutide, with a strong potential price advantage, as it is based on two proteins in, or about to enter, the public domain, and
- BioChaperone® Glargine Dulaglutide, with a strong potential for best-in-class performance, based on the excellent pharmacologic profile of dulaglutide and glargine.

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28 Control of Postprandial Hyperglycemia in Type 1 Diabetes by 24-Hour Fixed-Dose Coadministration of Pramlintide and Regular Human Insulin: A Randomized, Two-Way Crossover Study, Riddle et al., Diabetes care, 2018

These two candidates, which are intended for daily use, may help improve glycemic control whilst also reducing the number of injections and limiting costs for the patient.

- **Preclinical results and next steps**

  Adocia generated positive stability and preclinical results for the program BioChaperone Glargine GLP-1.

- **Competition**

  Two combinations of basal insulin and a GLP-1 agonist were recently approved for the treatment of type 2 diabetes. Xultophy™ (insulin degludec and liraglutide, **Novo Nordisk**) was approved in Europe in September 2014 and in the United States in November 2016. Soliqua®/Suliqua® (basal insulin and lixisenatide, **Sanofi**) was approved in the United States and Europe in November 2016.

  In both cases, these products may be used to intensify treatment after using basal insulin or a GLP-1 agonist alone. The two combinations demonstrated in phase 3 clinical studies significant advantages compared to basal insulin: lower HbA1c, weight loss, less nausea than GLP-1 used alone. In the case of Xultophy, the product helps patients to lose weight. In the case of Soliqua, the product is neutral with regard to weight gain (compared to the increase in weight when using insulin). Furthermore, using a combination makes it possible to limit the number of injections to one per day and, in the American healthcare system, to also limit the cost borne by the patient (by requiring only a single “copay” payment per product).

  The two companies launched their products on the US market in early 2017. While Novo Nordisk fixed a price for Xultophy corresponding to the sum of the Victoza and Tresiba prices, less a reduction of about 20%, Sanofi was more aggressive, fixing a pricing structure which is equivalent to the average price of a GLP-1, a price (before negotiations) about 33% lower than that of Xultophy. Indeed, as Sanofi had already amortized its investments in insulin glargine (now in the public domain), it has more leeway to set its prices. Conversely, Novo Nordisk must recoup the investments in the development of insulin degludec and liraglutide and must also protect the independent Tresiba (insulin degludec) and Victoza (liraglutide) brands.

  Compared to these products, BioChaperone Basal GLP-1 formulations could be positioned at potentially similar performance levels. Moreover, in the case of BioChaperone Glargine Liraglutide, the product could have an advantage in terms of pricing similar to, or even higher than, Soliqua, by using two molecules that are going to be in the public domain.

  One last competitor product in development is the combination developed by the Korean company **Hanmi** of a weekly insulin (LAPS-Insulin, currently in the phase 1) and a weekly GLP-1 (efpeglenatide). This combination was licensed to Sanofi in November 2015, as well as each component independently (including a once-monthly version of efpeglenatide), under an agreement including an initial payment of $434 million (€400 million) and expected to total $4.2 billion (€3.5 billion). In January 2017, Sanofi announced its was relinquishing the rights to LAPS-insulin and concentrating on the development of efpeglenatide (the weekly injectable version entered phase 3 in 2017). This announcement resulted in Hanmi refunding Sanofi $250 million (€196 million) and a reduction of the total potential amount of the agreement to €2.72 billion. For its part, Hanmi is responsible for the development of the weekly LAPS-insulin/efpeglenatide combination, a product for which Sanofi retains a licensing option. Hanmi also has to bear some of the development costs of efpeglenatide, which was not the case in the initial agreement. This combination of insulin and GLP-1 is currently in preclinical development.

### 13.4 BioChaperone Glucagon GLP-1 for the treatment of obesity

- **Providing a powerful and easy-to-use multi-hormonal treatment to optimize lasting weight loss in obese people**

  Obesity is defined as an excessive accumulation of fat in adipose tissue negatively impacting the well-being and health of the person. A person is diagnosed as obese when his or her body mass index (BMI) is more than 30 kg/m².
The increase in weight is the consequence of an imbalance between energy intake and expenditure. This imbalance results from a complex combination of environmental, behavioral and genetic factors.

The World Health Organization (WHO) estimates that there were 650 million obese adults in the world in 2016, or 13% of the world's population. This number has nearly tripled since 1975 and continues to grow. The obesity rate varies from one country to the next with, for example, 39.2% of adults obese (and 65% overweight) in the United States.

Obesity increases the risk of developing many other diseases, including type 2 diabetes, non-alcoholic steatohepatitis (NASH), dyslipidemia, sleep apnea, cardiovascular disease and several types of cancer. These risks increase for overweight people (BMI > 25 kg/m²) and increase with weight gain. The World Obesity Federation estimates that obesity and its complications led to nearly $800 billion in healthcare expenditure worldwide in 2017. This expenditure could reach $1,200 billion by 2025.

It is generally accepted that a 10–15% loss of body mass significantly reduces the comorbidities associated with obesity. To lose weight, the first recommendation is to have enough regular physical activity and to follow a special diet. However, weight loss is often difficult to maintain, both because it requires often significant behavioral changes, and because the body tends to return to the original weight, for various physiological reasons, which results in discouragement in obese people. Medical treatment is prescribed to patients with BMI greater than 30 kg/m² or, if there are two cardiovascular risk factors, a BMI > 27 kg/m². In the event of morbid obesity, bariatric surgery may be prescribed. This consists of reducing the volume of the stomach.

Today, only 2% of obese patients use medication. This low percentage is due to the limited efficacy of the medicinal products available and the lack of persistence of their effects over time. These treatments, oral or injected subcutaneously, can lead to a rapid loss of 3 to 10% of body weight, but this loss is rarely stabilized in the long term. Some of these treatments are also associated with adverse reactions (nausea, cardiac risk, diarrhea, etc.). Mechanisms of action include a decrease in the food bolus, a limitation of nutrient absorption, or an increase in energy expenditure.

Among the available treatments, one of the most effective is Saxenda® (liraglutide, GLP-1 receptor agonist, Novo Nordisk). Saxenda® is currently the only GLP-1 treatment for obesity and has met with significant commercial success.

Recent studies have shown that a multi-hormonal approach targeting both GLP-1 receptors and other metabolic hormone receptors, such as glucagon or GIP, could increase energy expenditure, promote significant weight loss and improve blood glucose control in obese people. Based on these results, several companies have initiated the development of co-agonists or combinations allowing this multi-hormonal approach.

Based on this promising research and its BioChaperone Glucagon formulation, Adocia has developed BioChaperone Glucagon GLP-1, a two-in-one combination of human glucagon and exenatide (Byetta®, AstraZeneca), a GLP-1 receptor agonist. It has been previously shown that the combination of glucagon and GLP-1 RA works by increasing satiety, slowing gastric emptying and increasing energy expenditure (Figure 11). In contrast to the multi-agonist approaches, Adocia’s formulation approach makes it possible to rely on the efficacy and safety profiles of two approved molecules, while favoring the choice of the best ratio between these two molecules to optimize the product profile.

30 Key facts about being obese and overweight, WHO, October 2017
32 World Obesity Federation, 2017
33 Glandt & Raz, J. Obes, 2011;2011:636181
34 Liraglutide is also the active ingredient, used at a lower dose, in the hypoglycemic treatment Victoza® (Novo Nordisk) for the treatment of type 2 diabetes.
In vitro results and next steps

On the basis of promising in vitro stability results, BioChaperone Glucagon GLP-1 is currently in preclinical development, with the goal of starting the first human clinical trial in the second semester of 2019.

Competition

The competition includes both products already approved for the treatment of obesity, and multi-hormonal treatments currently under development.

This market of the treatment of obesity is growing strongly (+120% per year since the end of 2015), due to the rapid increase of the obese population, the emergence of more effective products like Saxenda® (liraglutide, Novo Nordisk) and growing awareness of the value of drug approaches. Five products are currently approved for the treatment of obesity, for a global market still relatively limited, $500 million in 2017.

- Saxenda® (liraglutide, Novo Nordisk), the only injectable treatment approved in the US since 2015, currently accounts for 75% of the value of the US market in clinical trials, Saxenda showed a decrease in body weight of 5-7.5% over 12 months.
- BelviQ® (API, Arena/Eisai) is an oral appetite suppressant enabling limited weight loss (around 3%). This treatment is only available in the United States.
- Qsymia® (phentermine and topiramate, Vivus) is an oral combination showing the best weight loss efficacy among oral treatments, but the effect disappears on average less than one year after the start of treatment.
- Xenical® (API, Roche) blocks the absorption of triglycerides.
- Contrave® (bupropion and naltrexone, Nalpropion) is an oral combination that reduces appetite and increases energy expenditure. Following the bankruptcy of Orexigen. The company Nalpropion acquired their assets (including Contrave) in April 2018.

There are currently 33 products in clinical development to treat obesity, with various approaches in terms of mechanism of action and expected efficacy.

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Figure 11: Combined effects of glucagon and GLP-1 on the human body

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36 Analysis of sales in the third quarter of 2017. $101 million in sales for Saxenda in a $139 million market (BelviQ + Saxenda + Qsymia + Contrave).
Among the products in development, semaglutide from Novo Nordisk, a new GLP-1 agonist already approved for the treatment of diabetes, has shown positive weight loss results in Phase 2 studies. This product recently approved for patients with Type 2 diabetes entered into a Phase 3 for treating obese patients.

Eli Lilly also presented promising results of a co-agonist GLP-1 and GIP (the tirzepatide) by patients with type 2 diabetes during the EASD international conference in October 2018. Eli Lilly plans to start soon the clinical development of this product for obese patients.

1.3.5 BioChaperone Teduglutide for the treatment of short bowel syndrome

- Simplifying chronic treatment injections for people with severe short bowel syndrome

Short bowel syndrome (SBS) is a serious disease caused by either a congenital defect, intestinal obstruction or extensive surgical resection of the intestinal tract, resulting in a functional small intestine less than 200 cm in length (the average length of the small intestine is 6.1 m in a healthy person). Sufferers have an intestine which is too short to absorb enough ingested food, leading to not only malnutrition and weight loss but also dehydration, severe diarrhea, abdominal pain, and fatigue. In the long term, various complications may occur including anemia or hyperkeratosis. Short bowel syndrome is most often the result of resection of the small intestine, which is itself a result of inflammatory diseases or intestinal tumors. More rarely, there are cases of congenital short bowel syndrome (birth with a small intestine less than 75cm long).

In its most severe forms (intestine less than 1 m), SBS requires supplementary parenteral or enteral nutrition to compensate for the effects of diarrhea, malabsorption of nutrients, intestinal dilatation and intestinal dysmotility. This supplementary nutrition can also sometimes lead to severe complications, particularly involving the liver. Approximately 20,000 people with SBS in the United States and Europe need parenteral nutrition. In these individuals, Gattex®/Revestive® (teduglutide, GLP-2 analog, Shire) can be prescribed to improve intestinal absorption and reduce the need for parenteral nutrition, which seriously disrupts patients’ lives.

Indeed, GLP-2 promotes the growth of intestinal villi, reduces intestinal flow and reduces acid secretions in the stomach. However, teduglutide is unstable in aqueous solution and is only available in the form of a lyophilized powder to be reconstituted before each daily injection. Reconstituting the product before injection involves 22 steps and the use of 6 different objects (syringes, needle, vial, Figure 13). This complicated procedure takes time and can result in mishandling, misinjection, or even injury. A ready-to-use solution could therefore have significant benefits for people with short bowel syndrome.

Figure 13: Detail of the material necessary for the reconstituting of Gattex®/Revestive® before injection. (Excerpt from the instruction leaflet).

- In vitro results and next steps

On the basis of promising in vitro results, BioChaperone Teduglutide is currently in preclinical development, with the goal of starting the first human clinical trial in the second semester 2019.
• Competition

Today, the only competitor product on the market is Gattex® (teduglutide) itself, which has recently addressed a significant medical need. Sales reached $219.4 million in 2016, and $335 million in 2017. The market has been growing strongly since the launch of Gattex and is expected to reach in excess of $500 million at its peak. The annual cost for medication with Gattex® is approximately $350,000 per year in the United States and €240,000 per year in France.

Two GLP-2 analog projects are currently in clinical development for the treatment of short bowel syndrome. Zealand Pharma is developing glepaglutide, a stable analog of GLP-2 in liquid form. Gelpaglutide entered Phase 3 in October 2018. In addition, Therachon acquired in September 2018 the apraglutide formerly developed by Glypharma. Apraglutide is a long-acting GLP-2 analog with the potential to reduce injections to once or twice a week. This compound has the same disadvantage as teduglutide i.e., instability in liquid form, and is being developed as a powder for reconstitution. Glypharma had announced positive toxicity and safety results in Phase 1 clinical study in healthy subjects. A new analog GLP-2 announced by Hanmi in January 2019 entered in Phase 1 during Q1 2019.

1.3.6 Intellectual property

1.3.6.1 Innovation policy

Adocia’s mission is to create and develop inventions that are subsequently licensed.

These inventions involve in particular innovative therapeutic treatments based on the combination of our processing technology (BioChaperone®) with therapeutic protein agents.

Since its founding, Adocia has created inventions in several therapeutic domains based on its BioChaperone® technology, such as the healing of chronic wounds and the treatment of diabetes with insulin therapy. In 2016 the Company refocused its business on the treatment of diabetes, which is reflected in its patent portfolio.

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, employee training, and its work methods. More specifically, researchers receive both internal and external training related to IP.

The inventions that Adocia develops are cross-disciplinary and cover various scientific fields, in particular chemistry, physical chemistry, analytics and biology. Teams of experts have therefore been formed, and then expanded, in each discipline. The various teams are coordinated during regular working meetings held for each project. In addition, each lead scientist presents a bimonthly report on scientific advances every two weeks.

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 more than 15 years of experience in R&D management, first with Flamel Technologies and then with Adocia.

1.3.6.2 Procedures for the protection of intellectual property

• IP department and external Industrial Property consultancy

The Intellectual Property department reports to the Business Development and legal department under the responsibility of Rémi Soula, BD and Legal Director. The Intellectual Property department is under the responsibility of Walter Roger, IP Director and comprises three people at the date of this registration document.

The Intellectual Property department, in collaboration with an intellectual property consulting firm, evaluates the patentability of inventions and, if applicable, conducts studies of freedom to operate for the products intended to be utilized, in particular via a license. Patent applications and examination procedures are conducted in collaboration with this consulting firm.
Presentation of Adocia and its activities

This intellectual property firm, Cabinet Tripoz, manages the Company’s portfolio of patents.

- **Designation of inventor and remuneration**

An invention declaration form has been created to describe the invention and designate its inventor(s), specifying their respective contribution.

Besides, 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 employee-inventors are entitled to the additional compensation prescribed by the French Intellectual Property Code, and provides for payment of attractive lump-sum fixed compensation after submission of a first patent application and granting of a patent in Europe or the United States, as well as variable compensation that increases in accordance with sales generated by the relevant invention.

Mr. Gérard Soula has assigned to the company, without any financial consideration, all of the rights he held for inventions within the Company’s field of business at the date of this registration document. Assignment agreements are signed whenever required by national 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.

- **Communication and confidentiality**

It is essential for an innovation company such as Adocia to manage communication and control the confidentiality of information.

Technical communication is therefore approved by the Intellectual Property department and, if applicable, subject to contracts suitable to the situation (see chapter relating to Contracts below).

### 1.3.6.3 Patents and patent applications

- **Intellectual property protection policy**

The success of the Company depends at least in part on its ability to protect its inventions, primarily by obtaining and renewing patents in Europe, the United States and the rest of the world.

Since March 16, 2013, priority applications are only submitted in France since it is no longer necessary to apply for a US patent in order for protection to be recognized in this country. Before the new regulation took effect in the United States on March 16, 2013, priority applications were filed simultaneously in France and the United States to implement protection as rapidly as possible.

However, direct extensions in the United States are often conducted simultaneously with PCT extensions to ensure direct and rapid US procedures.

- **Offensive, alternative and defensive strategies**

An active policy is pursued to protect products under clinical development (offensive strategy) as well as products derived from alternative solutions (alternative strategy) and products corresponding to defensive solutions (defensive strategies). Patent applications are qualified as (i) protection of core business, (ii) protection of alternative solutions and (iii) defensive applications.

- **Territories**

Patent coverages are examined with respect to the importance of inventions, and three predetermined strategies are implemented by the Company concerning the choice of countries in which the national phase of PCT applications are in force (no later than 30 months after submitting 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, China, India, and possibly Brazil, Canada, Japan, Australia and/or Israel;

Strategy 3 for the core business: United States, Europe, Canada, China, Japan, India, Australia, Israel, Mexico, Brazil, Russia (or Eurasia), South Africa, Singapore and South Korea, even additional territories depending on the market

- **Patents Applications in the sole name of Adocia**

Patents applications submitted by the Company are filed in the name of the Company if their inventors are all employees, with the exception of Mr. Gérard Soula. In the case of company employees, every employment contract for staff contributing to invention contains a clause covering inventions, and all inventions legally belong to the Company as stipulated in article L.611-7 of the French Intellectual Property Code. Transfer agreements are systematically signed for each invention whenever required by government regulation.

- **Types of patent application**

There are two main types of patent:

- Patents concerning an object (also known as “composition of matter” patents) may involve polymers, composites or compositions;
- Patents concerning actions, such as utilizations or procedures.

- **Portfolio**

A review of the portfolio was carried out in 2018 and notably led to the discontinuation of certain patents granted which were no longer relevant to ongoing projects. This explains the decrease in the number of patents issued compared to the latest figures released.

To date inventions are protected by patent application filings comprising 47 distinct families. Adocia’s portfolio contains more than 200 patents and patent applications belonging to the Company, of which 157 are being examined by patent authorities. The table below indicates the number of patents granted as well as the patent applications currently underway, by territory, as of December 31, 2018:
Adocia’s portfolio is primarily composed of “composition of matter” patents. More specifically, the families involving prandial or basal insulin, amylin receptor agonists (RA) and glucagon rely on polymers, composites and/or compositions.

The FAST insulin project (BC Lispro and HinsBet) comprises 13 families of patent that include many delivered patents. It includes in particular, the WO2014076422 and WO2014076423 families currently under review for which patent applications have been submitted in Australia, Brazil, Canada, China, Eurasia, Europe, Hong Kong, Israel, India, Japan, South Korea, Mexico, Saudi Arabia, Singapore, the United States and South Africa. The WO2014076423 application led indeed to the issuance of the patents US9700599 in the United States, CN104902922 in China, EP2918804 in Europe and JP6322642 in Japan.

The patents for these families, subject to their delivery and to payment of annuities, will confer protection until 2033.

The project for the combination of basal insulin, notably glargine insulin, and prandial insulin, comprises 14 families of patents.
We can cite among these the WO2017211916 and WO201721903 applications submitted in 2017, involving new composites and new compositions combining a basal insulin, like glargine uinsulin and a prandial insulin. These families have patents pending in the following countries or regions: South Africa, Saudi Arabia, Brazil Cambodia, China, Egypt, Europe, India, Indonesia, Japan, Mexico, Eurasia, Singapore and United States. Subject to payment of annuities, the patents of this family will provide protection until 2037.

The glucagon project involves in particular the applications WO2017211917 et WO2017211917 submitted in 2017. These families have patents pending in the following countries or regions: Australia, Brazil, China, South Korea, Europe, Japan, Mexico, New-Zealand, and Singapore. Subject to payment of annuities, the patents of this family will provide protection until 2037.

ADOCIA is still developing a project involving a composition combining amylin, an agonist of amylin or an agonist of amylin receptor, in particular Pramlintide, formulated at physiological pH value. This project involves notably the application WO2018122278.

Finally, the project involving the combination of prandial insulins with GLP-1 RA includes the application WO2019020820.

It should be noted that published patent applications and patents granted can be found on the internet using free patent databases, such as Espacenet or USPair (USPTO).

- **Portfolio management**

  The portfolio is examined periodically for patent applications made for inventions that are no longer under development and that can neither be sold nor licensed. These are terminated to reduce costs. This is the case of applications concerning nanoparticles, for example.

1.3.7 Legal

1.3.7.1 Major Contracts

- **Protection of proprietary technologies**

  Before any exchange of information or material of a confidential nature with a third party, a suitable contract is drafted that systematically includes confidentiality and restriction of use clauses. A confidentiality contract is generally signed first when assessing the relevance of entering into a possible commercial relationship or collaboration. There will follow, depending on the situation, one or more contracts for transfer of equipment, service provision, consulting or collaboration, which will ensure, among other provisions, that Adocia retains full ownership of the results (related to Adocia’s proprietary technologies) arising from these contracts and of the intellectual property rights attached to these results.

- **Cooperation agreements**

  Starting in November 2007, the Company began signing cooperation agreements with various major pharmaceutical groups.

  The Company did not assign intellectual property rights to its technology with any of the agreements it signed, and no implicit license can arise from any of the cooperation agreements with its partners, as this is a prerequisite demanded by Adocia upon signing any such 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 involve evaluating BioChaperone® technology with respect to active pharmaceutical ingredients that are already marketed or are under pharmaceutical development.
Studies are conducted in either the Company’s or the partners’ laboratories, and the costs of such trials are either fully paid by the Company’s partners or shared between the partner and Adocia.

Because the Company’s partners have demanded confidentiality about the very existence of these agreements, neither the areas of cooperation nor the partners’ identities may be disclosed in this reference document.

1.3.7.2 Licenses

- License granted by Adocia to Eli Lilly

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 Lispro rapid-acting insulin analog in conjunction with BioChaperone® technology (“BioChaperone® Lispro”). The company granted Eli Lilly exclusive worldwide rights to BioChaperone® for the purpose of developing, manufacturing and marketing BioChaperone® Lispro. This agreement covered all potential indications for BioChaperone® Lispro. The license rights granted were based on the WO2008038111 and WO2010122385 families of patent applications and patents. In July 2013, Adocia and Eli Lilly decided to terminate their licensing and cooperation agreement, and Adocia recovered its rights to develop ultra-rapid insulin analogs.

On December 19, 2014, Adocia and Eli Lilly announced the signature of a licensing agreement for the development of an ultra-rapid insulin based on insulin lispro (commercial product from Eli Lilly, Humalog®) with BioChaperone® technology (“BioChaperone Lispro”).

Adocia’s and Eli Lilly’s goal was to develop BioChaperone Lispro with the goal of optimizing glucose levels during and after meals. The expected benefits of BioChaperone Lispro for patients with diabetes included greater flexibility in the timing of insulin injections, lower variability of postprandial glycemic levels, lower rates of hypoglycemia and better overall glycemic control.

Under the terms of the agreement, Lilly was responsible for future development, manufacturing, and commercialization of BioChaperone Lispro. The total upfront and milestone payments could have reached $570 million. Adocia had received an upfront payment of $50 million, and a $10 million milestone payment in December 2015.

No joint patent applications were submitted during this collaboration.

By letter dated January 26, 2017, Eli Lilly announced its decision to terminate the 2014 licensing contract. As a result, the rights that Adocia has licensed to Lilly reverted to Adocia at no cost (see Adocia press release of January 27, 2017).

- Licenses granted by Adocia to Tonghua Dongbao Pharmaceuticals Co. Ltd

April 26th, 2018, Adocia and Tonghua Dongbao Pharmaceuticals Co. Ltd Pharmaceuticals a strategic partnership, whereby Adocia granted the exclusive development and commercialization rights to Tonghua Dongbao Pharmaceuticals Co. Ltd for the fixed-ratio insulin glargine and insulinlispro combination, BioChaperone® Combo, and ultra-rapid insulin, BioChaperone® Lispro, in China and other designated Asian and middle-East countries.

Under the terms of the Licensing Agreements, Tonghua Dongbao is responsible for the future development, manufacturing, and commercialization of BioChaperone Combo and BioChaperone Lispro in China and certain other countries. Adocia received a total upfront payment of $50 million, including $40 million for BioChaperone Combo and $10 million for BioChaperone Lispro. Additionally, Adocia is entitled to receive development milestone payments up to $85 million, including $50 million for BioChaperone Combo and $35 million for BioChaperone Lispro. Finally, Adocia is expected to receive double-digit royalties on the sale of both products in the territories. Tonghua Dongbao will also reimburse some of Adocia’s expenses for research and development activities performed during the terms of the agreements.
Adocia retains the rights to develop and license these two insulin programs in worldwide markets outside of the territories covered by these agreements, including the United States, Europe and Japan. Adocia remains responsible for the development and the manufacturing of BioChaperone® pharmaceutical excipients.

Tonghua Dongbao Pharmaceutical Co., Ltd. is a China-based company with over 2,000 employees, principally engaged in the research and development, manufacture and distribution of pharmaceuticals. The Company provides biological products, traditional Chinese medicines and chemical supplements, applied in the treatment of diabetes and cardiovascular and cerebrovascular diseases, among others. The Company produces 10 different types of products with over 100 specific pharmaceutical products in production. Tonghua Dongbao Pharmaceutical Co., Ltd. main products portfolio consists, at the time of the signature of the partnership with Adocia, of recombinant human insulin crystal API, regular recombinant human insulin injection Gansulin R, isophane protamine recombinant human insulin injection Gansulin N, 30/70 mixture recombinant human insulin injection Gansulin 30R, 3 50/50 mixture recombinant human insulin injection Gansulin 50R, 40/60 mixture recombinant human insulin injection Gansulin 40R, Zhen Nao Ning capsules and Dongbao Gantai tablets, among others. Tonghua Dongbao Pharmaceutical Co., Ltd. also provides medical instruments. The Company distributes its products within domestic markets and to overseas markets.

1.3.7.3 Litigation

- Arbitrations

In October 2017, Adocia announced in a press release its filing of an arbitration claim against Eli Lilly & Co related to a research and licensing agreement signed in 2014. This proceeding concerns some $11 million and other specific compensation for changes made to the development plan during the collaboration. The arbitration court finds in favor of Adocia in first phase of arbitration against Eli Lilly in August 2018 and Adocia announced via a press release the same month that the company will separately seek interest, litigation fees and costs in addition to the damages awarded. In October 2018. The arbitration court granted Adocia fees’ interests on the amount cited above accruing from March 30, 2017.

In February 2018 Adocia announced additional arbitration claims against Eli Lilly & Company arising out of Lilly’s misappropriation and improper use of Adocia’s confidential information and discoveries as well as Lilly’s breaches of several collaboration and confidentiality agreements. Adocia is seeking monetary damages in excess of $1.3 billion (before taking into account the interests pre-and post judgment) as well as others specific relief. In this second phase of this arbitration, Lilly has filed counterclalm against Adocia seeking approximately 188 million including prejudgment interest. These counterclaims are based on an allegation that Adocia concealed its discoveries and confidential information which are at issue in Adocia’s claims. Adocia denies Lilly’s claims. Hearings were held in December 2018. Adocia expects a decision in the third quarter of 2019 on this second phase of this arbitration proceedings, as well as the reimbursement of the fees and lawyers’ fees paid as such.

- Civil Action

Eli Lilly and Company (“Lilly”) filed a complaint against Adocia in the United States District Court of the Southern District of Indiana on October 9th, 2018. Lilly’s complaint seeks a declaratory judgment that “the designations of inventorship currently appearing on [Lilly’s] United States Patent Nos. 9,901,623 and 9,993,555 are complete and correct, as required by the patent laws of the United States.” US Patent No.9,901,623 is entitled “Rapid-acting insulin compositions” and was issued February 27, 2018. US Patent No 9,993,555 is entitled “Rapid-acting insulin compositions” and was issued June 12, 2018. Lilly contends in its complaint that it filed the action because Adocia has asserted that Lilly’s patents reflect Adocia’s inventive contributions. The agenda of this proceeding is not known at date of the current reference document (please see Adocia’s Press release published on October 11th, 2018).

1.3.7.4 Insulin supply agreements

Adocia and Tonghua Dongbao Pharmaceuticals Co. Ltd announced on June 1st, 2018 an expansion of their strategic alliance with Tonghua Dongbao. “(see section 1.3.8.2 « Licences granted by Adocia to Tonghua Dongbao Co.Ltd »)
above) by signing with the Chinese company two supply agreements in insulin, under the terms of the agreements, Tonghua Dongbao Pharmaceuticals Co. Ltd will manufacture and supply insulin lispro and insulin glargine APIs to Adocia worldwide, excluding China in accordance with Adocia’s specifications and established quality standards.

Local leader on the Chinese insulin market, Tonghua Dongbao Pharmaceuticals Co. Ltd can currently produce several tons of insulin per year divided on numerous outstanding production plants. While the Chinese company commercializes already human insulin products in China and in other market, Tonghua Dongbao Pharmaceuticals Co. Ltd develop in parallel several insulin analogs. Notably, its insulin glargine is under commercial approval in China, and its insulin lispro is expected to enter Phase 3 trials in the near future. Insulin lispro from Tonghua Dongbao Pharmaceuticals Co. Ltd. is produced in the same plant as human insulin used in its commercial products; this plant has recently passed a cGMP standard audit allowing Phase 3 entry into Europe of this human insulin from Tonghua Dongbao Pharmaceuticals Co. Ltd.

### 1.3.7.5 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:

The company agreed to repay OSEO the full amount lent based on the following payment schedule:

- €130,000 for the year 2017 (€32,500 per quarter),
- €150,000 for the year 2018 (€37,500 per quarter),
- €200,000 for the year 2019, and
- €320,000 for the year 2020.

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 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 corresponding to the amounts due for 2017 and 2018 as described above. In 2017 and 2018, the Company reimbursed accordingly to the plan.

If the company fails to fulfill its obligations, OSEO would have a right to demand the repayment of the advance granted.
1.3.7.6 Coface – International business development insurance agreement of
October 1st, 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, 2021. 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.

During the period between October 1, 2013 and September 30, 2014, the Company has not committed exploration
expenditures on target markets and the contract has been canceled. Therefore, the Company entered into the
amortization period on amounts received previously, meaning €91 thousand and as provided in the contract and
listed above. By letter received on November 27, 2014, Coface declared the guarantee period extended by two years,
i.e. from October 1, 2013 to October 1, 2018.

Over the year 2018 and following the signature of the partnership with the Chinese Company Tonghua Dongbao
Pharmaceuticals Co. Ltd, the Company proceeded to reimburse the totality of the amount advanced ie €91 thousand,
according to the terms of the agreement.

1.4. Analysis and comments on activities during the year

Readers are invited to read this analysis of the Company’s financial position and results along with the financial
statements prepared under IFRS for the fiscal years ended December 31, 2017 and December 31, 2018, as well as
the notes to the consolidated financial statements prepared under IFRS and presented in section 4.1 of this
registration document and all other financial information included herein. Readers may also review the description
of the Company in section 1.2 “Presentation of Adocia and its activities.”

The consolidated financial statements prepared under IFRS are presented in section 4.1 of this registration
document. Only the corporate financial statements prepared under French GAAP have legal force and are
reproduced in the notes to this registration document along with the statutory auditors’ reports.

1.4.1. Main activities during the year

2018 was marked by the signature of a strategic alliance with the company Tonghua Dongbao Pharmaceuticals Co.
Ltd (« THDB »), Chinese leader of the production and commercialization of insulin. In April 2018, Adocia and THDB
announced the signature of two licenses to develop and commercialize BioChaperone® Lispro and BioChaperone®
Combo in China and other Asian and Middle-East territories. Under the terms of the Licensing Agreements, THDB
is responsible for the future development, manufacturing, and commercialization of BioChaperone Combo and
BioChaperone Lispro in China and certain other covered territories. Adocia received a total upfront payment of $50
million and is entitled to receive development milestone payments up to $85 million, as well as double-digit royalties on the sale of both products in the territories. Since the signature, the two companies actively worked on technology transfer to enable the manufacturing of the two products. THDB envisaged in 2019 to start a Phase 3 for BioChaperone Lispro in 2019 and a first clinical study for BioChaperone Combo at the end of 2019.

In June 2018, the partnership with THDB, was reinforced by two global supply agreements for insulin lispro and insulin glargine. Under the terms of the Supply Agreements, THDB will manufacture and supply insulin lispro and insulin glargine (APIs) to Adocia worldwide, excluding China. These agreements offer Adocia the opportunity to further develop the BioChaperone Lispro and BioChaperone Combo projects and open additional collaboration opportunities. Adocia is preparing a « bridging » clinical study to qualify the insulin lispro from THDB as a source equivalent to Lilly’s insulin lispro. This study should be the only one required by regulatory agencies to enable BioChaperone Lispro to enter in phase 3.

From a clinical perspective, in 2018 Adocia initiated a first-in-human clinical trial of BioChaperone® Pramlintide Insulin (BC Pram Ins). This trial in people with type 1 diabetes, which positive topline results were announced in September 2018, showed a significant 97% decrease in blood glucose excursion over the first two hours after the meal with BC Pram Ins compared to Humalog®. The product was well tolerated. Adocia plans to initiate a second, repeated administration trial in Q2 2019.

The development of our varied portfolio products to date revealed unique properties of the BioChaperone technology, which notably enables to significantly improve single agents and to combine multiple therapeutic proteins. In order to expand the use of this technology, Adocia announced early in 2018 that BioChaperone® would now be deployed in a selected range of injectable therapeutics across numerous therapeutic areas. Initial programs added to the portfolio include a ready-to-inject version of teduglutide for the treatment of short bowel syndrome and a fixed dose combination of glucagon and exenatide for the treatment of obesity, both in preclinical stage.

Lastly, regarding legal proceedings, the first phase of the arbitration procedure initiated by Adocia against Lilly concluded in favor of Adocia. The Arbitration Tribunal awarded Adocia USD 11.6 million, as well as interests.

Adocia’s additional claims against Lilly for a revalued amount of USD 1.3 billion and the counterclaims of Lilly for an amount of USD 188 million, remain pending, with a decision of the court expected in the third quarter of 2019.

Finally, in October 2018, Lilly filed a civil complaint against Adocia in the United States District Court of the Southern District of Indiana to seek a declaratory judgment for two of its US patents regarding ultra-rapid insulin formulation (Lilly’s United States Patent Nos. 9,901,623 and 9,993,555 entitled “Rapid-acting insulin compositions”). Lilly contends in its complaint that it filed the action because Adocia has asserted that Lilly’s patents reflect Adocia’s inventive contribution. We do not expect the matter to be resolved during this fiscal year.

1.4.2. Presentation of the financial statements

1.4.2.1. General information

The Company’s principal activity is research and development of innovative formulations of pre-approved therapeutic proteins. It has a high level of expertise in the field of insulin. The proprietary technology platform, called BioChaperone®, aims to improve the efficacy of therapeutic proteins and their ease of use for patients.

1.4.2.2. Main accounting principles

- Revenue recognition

Adocia generates revenue from collaboration and licensing agreements signed with other companies operating in its sector and from public funding of research costs (grants and research tax credit).
Research and development costs

Research and development costs are recognized as expenses on the income statement in the year in which they are incurred. Development costs are capitalized only when the conditions required by IAS 38 are met. As of the date of this registration document, these conditions had not been met and the Company therefore did not capitalize its development costs.

1.4.3. Financial position and appropriation of profit

1.4.3.1. Components of income

The table below summarizes the Company’s income statement under IFRS for the fiscal year ended December 31, 2018 and provides a comparison with fiscal year 2017.

<table>
<thead>
<tr>
<th>In (€) thousands</th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revenue (a)</td>
<td>47 389</td>
<td>19 469</td>
</tr>
<tr>
<td>Research and collaborative agreements</td>
<td>0</td>
<td>650</td>
</tr>
<tr>
<td>Licencing revenues</td>
<td>47 389</td>
<td>18 819</td>
</tr>
<tr>
<td>Other revenue (b)</td>
<td>6 541</td>
<td>7 708</td>
</tr>
<tr>
<td>Research tax credit</td>
<td>6 368</td>
<td>7 535</td>
</tr>
<tr>
<td>Grants, public financing, others</td>
<td>173</td>
<td>173</td>
</tr>
<tr>
<td>Operating revenue (a) + (b)</td>
<td>53 930</td>
<td>27 177</td>
</tr>
<tr>
<td>Research and development expenses</td>
<td>(25 760)</td>
<td>(27 074)</td>
</tr>
<tr>
<td>General and administrative expenses</td>
<td>(18 463)</td>
<td>(8 284)</td>
</tr>
<tr>
<td>Operating expenses</td>
<td>(44 223)</td>
<td>(35 358)</td>
</tr>
<tr>
<td>OPERATING INCOME (LOSS)</td>
<td>9 707</td>
<td>(8 180)</td>
</tr>
<tr>
<td>FINANCIAL INCOME (LOSS)</td>
<td>2 051</td>
<td>(335)</td>
</tr>
<tr>
<td>Tax</td>
<td>(4 144)</td>
<td>(35)</td>
</tr>
<tr>
<td>NET INCOME (LOSS)</td>
<td>7 615</td>
<td>(8 550)</td>
</tr>
<tr>
<td>Base earning per share (€)</td>
<td>1,1</td>
<td>(1,2)</td>
</tr>
<tr>
<td>Diluted earning per share (€)</td>
<td>1,0</td>
<td>(1,2)</td>
</tr>
<tr>
<td>GROUP NET PROFIT (LOSS)</td>
<td>7 615</td>
<td>(8 550)</td>
</tr>
</tbody>
</table>

Operating income

The Company’s operating income resulted from collaboration and licensing agreements and public funding of research costs. In 2018, operating income amounted to €53.9 million compared to €27.2 million in 2017 based on the following breakdown:

<table>
<thead>
<tr>
<th>In (€) thousands</th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revenue (a)</td>
<td>47 389</td>
<td>19 469</td>
</tr>
<tr>
<td>Research and collaborative agreements</td>
<td>0</td>
<td>650</td>
</tr>
<tr>
<td>Licencing revenues</td>
<td>47 389</td>
<td>18 819</td>
</tr>
<tr>
<td>Grants, public financing, others (b)</td>
<td>6 541</td>
<td>7 708</td>
</tr>
<tr>
<td>OPERATING REVENUE (a) + (b)</td>
<td>53 930</td>
<td>27 177</td>
</tr>
</tbody>
</table>
Revenue of €47.4 million in 2018 resulted up to €37.1 million from the partnership and licensing agreement signed with Tonghua Dongbao Pharmaceuticals Co. Ltd (THDB) in April 2018. The non-refundable upfront payment provided for in the contract in the amount of 50 million dollars, or €41.1 million, is partially recognized as revenue (i.e. €37.1 million) in 2018. It reflects the rights thus granted to THDB to develop, manufacture, and commercialize BioChaperone® Lispro and BioChaperone® Combo in China and other territories in Asia and the Middle-East. The remaining non-amortized amount of the initial payment will be recognized upon provision of research and development services by Adocia related to the transfer and development of the products.

By the end of December 2018, licensing revenues also included an amount of $11.6 million (€10.3 million) corresponding to a contractual milestone payment contested by Lilly, for which Adocia obtained a favorable arbitration judgement in August 2018. The payment is expected to be received in 2019.

Last year, revenue for 2017 was impacted by the end of the collaboration with Lilly which resulted in the recognition of the not-yet-amortized balance of the $50 million upfront payment received in 2014 (no cash impact as payment had been received upon contract signature in December 2014).

Other operating income includes the research tax credit in the amount of €6.4 million at December 31st, 2018 compared to €7.5 million at December 31st, 2017. This decrease by €1.1 million is in line with the reduced amount of research and development expenses recorded this year.

### Operating expenses

The table below shows a breakdown of operating expenses by function for the fiscal years ended December 31st, 2017 and December 31st, 2018:

<table>
<thead>
<tr>
<th>In (€) thousands</th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research and development expenses</td>
<td>(25,760)</td>
<td>(27,074)</td>
</tr>
<tr>
<td>General and administrative expenses</td>
<td>(18,463)</td>
<td>(8,284)</td>
</tr>
<tr>
<td><strong>OPERATING EXPENSES</strong></td>
<td><strong>(44,223)</strong></td>
<td><strong>(35,358)</strong></td>
</tr>
</tbody>
</table>

Research and development expenses mainly include payroll costs of research and development employees, subcontracting costs (including preclinical studies and clinical trials), intellectual property costs and purchases of materials (reagents and other consumables), pharmaceutical products and other raw materials. In 2018, these expenses amounted to €25.8 million compared to €27.1 million in 2017.

The activities carried out during the 2018 financial year focused mainly on the preparation of clinical studies and support for the Company’s Chinese partner for the development of the two products licensed in April 2018. In 2017, research and development, and more specifically clinical expenses were impacted by the costs of three clinical studies.

General and administrative expenses mainly include payroll costs of non-research and development employees, as well as the cost of services related to the management and business development of the Company and its subsidiary in the United States. They also include fees and expenses related to the arbitration procedure launched against Lilly. These general costs amounted to €18.5 million in 2018 compared to €8.3 million in 2017. This increase of €10.2 million is mainly due, for an amount of €8.3 million, to the legal expenses related to the current litigation proceedings and, for an amount of €1.5 million, to the increase in staff expenses, notably following the payment of performance bonuses to employees, as a result of the signature of the partnership with THDB. As a reminder, in 2017 salaries and bonuses were frozen due to the termination of the contract with Lilly.

R&D expenses represented in 2018 76.4% of the operating expenses compared to 81% in 2017, once restated for the costs related to the arbitration proceedings against Lilly.
The table below shows a breakdown of operating expenses by type of expense for the fiscal years ended December 31st, 2017 and December 31st, 2018:

<table>
<thead>
<tr>
<th>In (€) thousands</th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchases used in operations</td>
<td>(2,188)</td>
<td>(1,740)</td>
</tr>
<tr>
<td>Payroll expense</td>
<td>(13,327)</td>
<td>(10,843)</td>
</tr>
<tr>
<td>Share-based payments</td>
<td>(1,574)</td>
<td>(2,525)</td>
</tr>
<tr>
<td>External expenses</td>
<td>(25,537)</td>
<td>(19,019)</td>
</tr>
<tr>
<td>Taxes and contributions</td>
<td>(553)</td>
<td>(217)</td>
</tr>
<tr>
<td>Depreciation, amortization &amp; provisions</td>
<td>(1,044)</td>
<td>(1,013)</td>
</tr>
<tr>
<td><strong>OPERATING EXPENSES</strong></td>
<td><strong>(44,223)</strong></td>
<td><strong>(35,358)</strong></td>
</tr>
</tbody>
</table>

The cost of materials, products and supplies consumed increased in 2018 compared to 2017 up to €2.2 million, as a result of additional purchase of the raw materials needed for the manufacturing of clinical batches. This increase of €0.5 million is mostly due to the increase in raw material purchase necessary to manufacture clinical batches.

Payroll expenses totaled €13.3 million in 2018 compared to €10.8 million in 2017. Given the recruitments conducted last year, the average workforce rose from 126.1 full-time equivalents (FTE) in 2017 to 129.4 FTE in 2018, an increase of nearly 3%. The €2.5 million increase in personnel expenses mainly reflects the payment of performance bonuses to employees, as a result of the signature of the partnership with THDB.

The share-based payments item of €1.6 million in 2018 mainly includes the impact of the plans implemented in previous years. The €0.9 million decrease in this item is related to the vesting of several share-based plans in 2018. In accordance with IFRS 2, these expenses correspond to the fair value of the equity instruments granted to managers and employees. These elements had no impact on the Company’s corporate financial statements or cash position.

External charges mainly included the costs of preclinical studies, clinical trials, subcontracting expenses, intellectual property costs, professional fees and administrative expenses. These expenses amounted to €25.5 million and increased by €6.5 million in 2017. This is mainly due to the intensification of the legal fees incurred for the procedures against Lilly. Restated of these fees, external charges amounted to €15 million in 2018, versus €16.8 million in 2017.

Taxes totaled €0.6 million in 2018, versus €0.2 million in 2017.

Depreciation and amortization remained stable over both years totaling more than €1 million.

- **Net financial income/expense**

The net financial result was a profit of €2 million in 2018, compared to a loss of €0.3 million in the previous year. This is explained by the recognition of the accrued interest of €1.6 million calculated on the contractual milestone payment of $11.6 million, which cash payment is expected in 2019 after the second phase of the arbitration procedure against Lilly is concluded.

The Company’s investment policy focuses on liquidity, the absence of capital risk and, to the extent possible, guaranteed performance.

- **Corporation tax**

The 2018 tax amount recorded in the consolidated income statement for €4.1 million refers to the corporate income tax calculated on the fiscal benefit subject to a reduced tax rate of 15%. This tax will be paid in full by charging the withholding tax paid in China on the initial upfront payment.
The amount of carryforward tax losses, after allocation of the fiscal deficit subject to the standard tax rate for the 2018 financial year, was €115.5 million. This carryforward loss is not limited in time. Since the company cannot determine with sufficient reliability when it will be able to absorb its accumulated tax loss, it did not recognize a deferred tax asset for this loss.

### Net profit/loss

The net profit for 2018 totaled €7.6 million compared to a loss of €8.6 million in 2017. The net profit per share for 2018 amounts to €1.10, compared to a net loss of €1.25 per share in 2017.

#### 1.4.3.2. Balance sheet analysis

### Non-current assets

Between 2017 and 2018, non-current assets have remained stable at €9.1 million. The investments in 2018 of €0.8 million are mainly due to ongoing renovation work of the two 450 m² floors by December 31, 2018 dedicated to the analytical department (for an amount of €0.4 million), as well as the purchase of scientific and computer hardware material (for €0.3 million). These cumulative investments, added to the increase of the valuation of the liquidity agreement in the financial assets of €0.25 million, are compensated by the depreciation of the year, which amounts to €1 million.

### Current assets

Current assets amounted to €61 million at December 31, 2018 compared to €44.7 million at December 31, 2017. They consisted of the following items:

- "Cash and cash equivalents" increased from €34.8 million at December 31, 2017 to €39.8 million at December 31, 2018. The €5 million increase on the year reflects the initial upfront payment of THDB for €37.2 million ($ 45 million) net of Chinese withholding taxes, as well as a level of expenditure similar to that of last year, after restating expenses related to the legal proceedings against Lilly.

- « Other current assets » amounted to €9.8 million at December 31st, 2017 and consisted mainly of the receivable related to the research tax credit (CIR) of €7.5 million. At December 31st, 2018, this item amounted to €21 million. The €11.2 million increase is mainly due to the favorable outcome of the first phase the arbitration proceedings initiated by Adocia against Lilly. The Arbitration Tribunal ordered Lilly to pay the disputed milestone payment of $11.6 million, or €10.3 million, plus interests (accrued end of December for $1.6 million). The payment of this total receivable of €11.9 million at the end of December 2018 is expected in 2019. The research tax credit amounts to €6.4 million at the end of 2018.

### Current and non-current liabilities

Liabilities consisted mainly of four items presented on the balance sheet according to their maturity:

- “Trade payables” under current liabilities in the amount of €7.5 million compared to €4.9 million at end-December 2017, which reflect the intense activity at the end of the year 2018 and the lawyers’ fees incurred in connection with the proceedings against Lilly.

- “Financial debt” totaling €7.1 million at end-December 2018, decreasing by €0.5 million compared to the previous year. This decrease related mainly to the repayment of the loans taken out to finance the building. The short-term portion, shown under "Current financial liabilities", totaled €2.2 million at end-December 2018 compared to €1.8 million a year earlier.

- “Long-term provisions” mainly comprise provisions for retirement benefits, which totaled €2.8 million for fiscal year 2018 versus €2.2 million for fiscal year 2017.

- The “other liabilities” item for 2018 mainly includes tax and social security liabilities which amounted to €2.7 million, an increase by €0.6 million from the previous year given the increase of the accrual for paid
vacation and the value-added contribution (CVAE) tax. In 2018, other liabilities also included €4 million in deferred revenue related to the agreement signed with THDB in 2018.

### 1.4.4. Cash, financing and equity

Readers are invited to review notes 9 and 10 to the consolidated financial statements prepared under IFRS for the fiscal years ended December 31, 2017 and December 31, 2018, which are presented in section 4.1.6 and Chapter 5 of this registration document.

#### 1.4.4.1. Debt financing

As of the date of this registration document, the Company received non-interest-bearing repayable aid for its research from Bpifrance and COFACE, for a total amount of €4.1 million. At December 31, 2018, the amount still owed on these advances was €0.5 million. The details of each of the repayable advances received and the repayment terms are provided in section 1.3.7 of this registration document.

The Company also uses other types of financing to finance the purchase of laboratory equipment and a company car. As of December 31, 2018, short-term future obligations under these finance leases totaled €0.4 million.

In 2016, the Company took out a loan to finance the purchase of the building that it has occupied since its creation as well as adjoining parking. At the end of 2018, the principal balance was €4.9 million.

Finally, in 2017 the Company funded part of the legal costs incurred in the arbitration against Lilly. This financing, obtained from two banks, took the form of two lines of credit, each in an amount of $1.5 million each. At December 31, 2018, one of the two cash lines was renewed and Adocia’s financial debts were impacted by €1.3 million ($1.5 million).

At end-December 2018, debt totaled €7.1 million, with a portion due in less than one year of €2.2 million.

#### 1.4.4.2. Cash flows

<table>
<thead>
<tr>
<th>In (€) thousands, Consolidated financial statements, IAS/IFRS</th>
<th>FY 2018 (12 months)</th>
<th>FY 2017 (12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net cash flow generated by operating activities</td>
<td>6 313</td>
<td>(22 227)</td>
</tr>
<tr>
<td>Net cash flow in connection with investment transactions</td>
<td>(1 034)</td>
<td>(1 685)</td>
</tr>
<tr>
<td>Net cash flow in connection with financing transactions</td>
<td>(216)</td>
<td>653</td>
</tr>
<tr>
<td><strong>Changes in net cash</strong></td>
<td><strong>5 063</strong></td>
<td><strong>(23 259)</strong></td>
</tr>
<tr>
<td>Cash and cash equivalents at the start of the year</td>
<td>34 778</td>
<td>58 037</td>
</tr>
<tr>
<td>Cash and cash equivalents at year-end</td>
<td>39 841</td>
<td>34 778</td>
</tr>
</tbody>
</table>

- **Net cash flow from operations**

For fiscal year 2018, net cash inflows related to operations amounted to €6.3 million compared to a net cash outflow of €22.2 million in the previous year.

Net cash flow includes the cash proceeds from THDB’s initial payment of €37.2 million (or $45 million), net of Chinese withholding tax.

- **Net cash flow from investments**

Cash consumption related to investment transactions was €1 million, compared to €1.7 million in the previous year.
Presentation of Adocia and its activities

In 2018, the Company acquired equipment and made some renovation for an amount of €0.8 million. It also increased by €0.25 million the resources made available under the liquidity contract entrusted to Kepler Cheuvreux.

- **Net cash flow from financing transactions**

In 2018, net cash flow from financing transactions resulted primarily from the repayment of the two lines of credit obtained in 2017 to finance the legal costs incurred for legal proceedings against Lilly, as well as the renewal in December 2018 of one of its two lines. At the same time, the Company continued to repay its mortgages as well as its conditioned advances, according to the planned deadlines.

1.4.4.3. **Funding sources needed in the future**

With nearly €40 million in cash and cash equivalents at December 31, 2018, the Company believes that it has the necessary resources to finance its operating expenses for at least the next 12 months from the date of this registration document.

Including financial debt, net cash at the end of 2018 was €37.2 million. This level of cash enables the Company to fund its planned clinical development (see section 1.3.2 of this registration document) and the development of its new programs.

The Company believes that it is able to make its next repayments of the loans and the Bpifrance repayable advances, which are estimated at €2.2 million for 2018 being precised that no reimbursements are expected within Bpifrance (see note 10 to the Company's consolidated financial statements prepared under IFRS in section 4.1 of this registration document).

1.4.5. **Growth prospects, outlook and significant events after the close of the fiscal year**

1.4.5.1. **Trend information**

See section 1.3 of this registration document which describes the epidemiological data for the pathologies targeted by the BioChaperone® technology platform, and, for certain pathologies, market trends and size.

1.4.5.2. **Profit forecasts and estimates**

The Company does not plan to make profit forecasts or estimates.

1.4.5.3. **Significant change in the financial or trading position**

None.

1.5. **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.
In addition, the Company may be subject to other risks that, as of the date of this presentation, are unknown to the Company or which the Company deems immaterial at this time, and which may have a material adverse impact on the Company, its business, financial position, income or outlook.

In each section below, the risk factors are presented in order of decreasing importance, according to the Company’s assessment as at the date of this Registration Document. The occurrence of new facts, either internal to the Company or external, may change this order of importance in the future.

1.5.1. Risks associated with implementation of the Company’s strategy

1.5.1.1. The Company is dependent on its BioChaperone® technology platform.

The Company does not plan to develop or market therapeutic products directly. The Company’s main strategy is to develop innovative formulations for various therapeutic proteins based on its BioChaperone® technology, and then to license use thereof to major players in the pharmaceutical, biotechnology and medical devices industries for the development and marketing of therapeutic products.

Research programs to identify new product candidates require substantial technical, financial and human resources. Research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development that would be attractive to potential partners, for a number of reasons, including:

- The research methodology used may not be successful in identifying potential product candidates; or
- Product candidates may, on further study or through clinical trials, show inadequate efficacy, harmful side effects, undifferentiated features or other characteristics suggesting that they are unlikely to be effective or safe products.

If the Company is unable to develop suitable innovative formulations for various therapeutic proteins based on its BioChaperone® technology through its research programs or otherwise, the Company might have difficulty finding partners and its medium and long-term business, financial position, income, expansion and outlook would be materially adversely affected.

1.5.1.2. In order to carry out its medium-term strategy, the Company must enter into agreements with partners.

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, material and financial resources necessary to develop, manufacture and market therapeutic products using its technology.

As part of its strategy, when proof of concept has been obtained for humans or animals, the Company intends to license products derived from its BioChaperone® technology to industrial partners in the pharmaceutical, biotechnology or medical device markets who have the human, material and financial resources necessary to conduct and successfully complete the clinical trials required by law, apply for market authorization, and produce and market the products. Accordingly, the Company plans to sign licensing and collaboration agreements under 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, once commercialized.

However, the research and results of clinical trials that the Company carries out itself may fail to yield product candidates or may fail to yield candidates that are sufficiently safe, efficacious and innovative to attract major players
in the pharmaceutical, biotechnology and medical devices industries to sign licensing and collaboration agreements for the Company's products and technologies.

In addition, other factors including general market demand for particular product candidates or therapeutic areas, market competition or other reasons, the Company may be unable to attract partners for future licenses and/or collaborations and/or the terms of those licensing and collaboration agreements the Company enters into may not be favorable to the Company.

If the Company is not successful in its efforts to enter into licensing and collaboration agreements, the Company may not have sufficient funds to further develop its product candidates internally. In addition, the inability to enter into licensing and collaboration agreements could delay or preclude the development, manufacture and/or commercialization of the relevant product candidate or any other product candidates and could have a material adverse effect on the Company's financial condition and results of operations, as revenues from product candidate licensing arrangements could be delayed or never materialize. If so, the Company may elect not to commercialize or further develop the product candidate.

1.5.1.3. The commercialization of the Company's product candidates is often dependent on the actions of the Company's partners, which are largely outside of the Company's control.

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 the Company's technology.

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

The success of our partnership agreements will depend on the efforts and activities of the Company's current and potential partners, who may have significant discretion in determining how to pursue planned activities and the quality and nature of the efforts and resources that they will apply to the partnership agreements, and who otherwise may be unable to complete the development and commercialization of the Company's product candidates.

The Company cannot be certain that it will be able to initiate and maintain partnerships, that any partnerships will be scientifically and/or commercially successful or that the Company will receive revenues from any of these agreements. For example, in December 2011, the Company entered into a first licensing and collaboration agreement with Eli Lilly for the development of a formulation of a rapid-acting insulin analog. In 2013, the Company and Eli Lilly agreed to terminate such an agreement. In 2014, given the clinical results, Eli Lilly signed a new licensing agreement with Adocia for the formulation of an ultra-rapid insulin lispro analog, BC Lispro. In January 2017, Eli Lilly announced its decision to terminate this collaboration.

Factors that may affect the success of the Company's collaborations include the following:

- 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 or prevent altogether approval of potential products incorporating the Company's technology, which is an indispensable stage for the success of its commercial policy;
- 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, or decide to prioritize internal development of products in markets that compete with the Company's product candidates, and which would therefore compete with the Company's business (see the section below on risks associated with competition);
current or future partners could limit or terminate their relationships with the Company, which could lead to additional costs, delays, and difficulties in the development of, or in obtaining approval by regulatory authorities for, or successfully commercializing, our product candidates which could have a material adverse impact on the Company’s business, financial position, income, expansion and outlook. Limitation or termination of an agreement could make it difficult for the Company to attract new partners or adversely affect its reputation in the business and financial communities, cause the Company to lose expertise and 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.

Furthermore, the Company’s current revenues in 2018 depended in large part on the licensing and collaboration agreement signed with the Chinese Company Tonghua Dongbao Pharmaceuticals Co. Ltd. Upon signature in April 2018 of these two licensing and collaborative agreements focused on the development of an ultra-rapid insulin, known as BioChaperone Lispro and a combination of a basal and rapid insulin named BioChaperone Combo, Adocia received an upfront payment of $50 million. According to the terms of the agreement, there had been potential for future payments of up to $85 million if the product reached certain development and regulatory milestones, (ii) sales royalties (for more information on this partner, please refer to section 1.3.7.2 “licenses granted by Adocia to Tonghua Dongbao Co Ltd”).

The Company cannot guarantee that collaboration with a partner will meet the development and regulatory milestones that would enable it to receive the anticipated revenues. Thus, when Eli Lilly decided to terminate the contract in January 2017, the Company faced a difficult situation forcing it to review its development plan. Any decision by a future partner to discontinue its agreement with the Company could have a material adverse effect on its business, operational results and prospects.

If the Company does not realize the anticipated benefits from its partners, its business, results of operations, and prospects would be materially adversely affected.

1.5.2. Risks associated with the Company’s business

1.5.2.1. Research programs and clinical studies are lengthy, time consuming, expensive and have uncertain outcomes.

Research programs are designed to identify new product candidates and require substantial technical, financial and human resources. Only a small minority of all research programs result in product candidates, and completion of preclinical studies does not guarantee that we will initiate additional studies or trials for our product candidates. If a product candidate passes the preclinical stage, the Company must then develop and design clinical trials to test specific characteristics of the candidate. In order to carry out clinical trials, the Company must first obtain appropriate authorizations to conduct clinical trials in the countries where the Company will seek market authorization. The Company cannot predict the time that will be necessary for regulatory authorities to review the trial protocol and approve the files submitted to them. For example, for its phase 3 clinical trials for the treatment of diabetic foot ulcers conducted in India, the Company submitted the authorization request to the Drug Controller General of India (Indian drug regulation body) in September 2012. However, processing of this request was delayed by the internal restructuring of the Indian regulatory agency, and the Company was only granted final authorization in August 2014.

The completion of clinical trials will depend on various factors, such as the therapeutic indication in question, the size of the population affected, clinical trial design, qualification and initialization of clinical trial sites, availability of the investigational product, the proximity of patients to clinical test sites, the eligibility criteria for trials, recruitment rates and competition for the recruitment of patients, and compliance with and changes in 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, and inability to meet prespecified primary endpoints or side effects. Even if the Company obtains positive results from preclinical or early clinical studies, the Company may not achieve success in future studies. Furthermore, 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 innovative therapeutic protein formulations that the Company currently provides and intends in the future to provide its current and future industrial partners for incorporation into their own products may also not prove to be sufficiently effective and/or have a sufficient safety profile to justify marketing them.

The inability of the Company and/or its partners to successfully complete the necessary clinical trials, including obtaining positive results, and meet certain other requirements for regulatory approval, could cause the development of the Company’s research programs and technologies to be delayed or abandoned. As a result, the Company may never realize revenues from certain product candidates, despite significant investments.

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.

1.5.2.2. The products developed based on the Company’s current or future technologies may take significant time to gain regulatory approval and reach the marketing stage, if at all.

The technologies developed by the Company have not yet led to the marketing of products. The Company and its partners must obtain regulatory approval for each product candidate before marketing or selling any of them. 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.

The Company’s product candidates must undergo preclinical trials on animals and clinical trials in humans in order to be approved by the regulatory authorities with jurisdiction before they may be placed on the market. Obtaining marketing authorization requires compliance with strict rules imposed by the regulatory authorities, as well as providing the authorities with extensive preclinical and clinical data and supporting information about the new product and for each indication, such as its toxicity, dosage, quality, effectiveness and safety. The approval process is lengthy, time consuming, expensive and has uncertain outcomes.

Factors that can impact the approval process include: failure of the Company’s and its partners’ product candidates to meet a regulatory agency’s requirements for safety, efficacy and quality, disagreements over interpretations of results of clinical trials, unforeseen safety issues or side effects, failure of trials to be conducted with internationally recognized requirements for good laboratory practice and good clinical practice, disapproval of manufacturing processes or facilities of third-party manufacturers with which the Company and its partners contract for clinical and manufacturing supplies, and changes in governmental regulations or regulatory delays.

Regulators can refuse marketing approval or can require the Company or the Company’s partners to repeat previous clinical studies or conduct further clinical studies. A pre-approval inspection of manufacturing facilities by regulatory authorities may need to be completed before marketing approval can be obtained, and such facilities will be subject to periodic inspections that could prevent or delay marketing approval or require the expenditure of financial or other resources to address.

Moreover, both the approval process and the requirements governing the conduct of clinical trials, product manufacturing, safety profiles and other criteria vary significantly from country to country and the fact that the regulatory authorities in one country grant approval does not guarantee that approval will be obtained in other countries.
If a partner of the Company is unable to obtain marketing authorization for one or more products incorporating its technologies, or succeeds only after delays, this could have a material adverse effect on the Company’s ability to generate revenues.

Delays in obtaining regulatory approvals may:
- adversely affect the successful commercialization of any product that the Company or its partners develop;
- impose costly procedures on the Company or its partners;
- diminish any competitive advantages in the marketplace that the Company or its partners may attain; and
- adversely affect the Company’s receipt of revenues or royalties.

As a result, it may take several years before products are available to end users, if at all, primarily due to the time periods necessary to conduct clinical trials, develop products and obtain marketing authorization.

Even if marketing authorization is obtained, there is a risk that the approved indication is narrower than originally sought and/or contains restrictions regarding its use such as those set out in black box warnings, and there is no guarantee that the authorization will not be subsequently suspended, for example in the event of non-compliance with manufacturing rules or if undesirable side effects are discovered. All of these risks may have a material effect on the ability of the Company and its partners to generate revenues.

1.5.2.3. Even if the Company and its partners’ product candidates obtain regulatory approval, they may not gain market acceptance.

Even if the Company’s and its partners’ product candidates obtain regulatory approval, they may not gain market acceptance by the relevant medical community. 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 or delays thereof;
- their acceptance by the relevant medical community; and/or
- the intensity of sales efforts deployed by the Company and/or its partners.

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. If the Company and its partners are unsuccessful in commercializing the product because of lack of market acceptance or resources employed for marketing or other post-commercialization problems, the Company and its partners will have spent valuable time and development and financial resources on research programs that ultimately do not yield commercially viable products. As a result, the Company’s business, results of operations and prospects could be materially adversely affected.

1.5.2.4. There is significant competition in the Biotechnology, pharmaceutical and medical devices industries.

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 markets in which the Company and its current and future partners compete and intend to compete are undergoing, and are expected to continue undergoing, rapid and significant technological changes. New therapeutic products or technologies developed by the Company’s and its current and future partners’ competitors may be more effective, safer and/or less expensive than those that the Company or its partners have developed,
which could render the Company’s current or future product candidates and/or technologies non-competitive, obsolete or non-economical.

The Company’s competitors may have:

- significantly greater financial, technical and human resources than the Company has at every stage of the discovery, development, manufacturing and commercialization process;
- more extensive experience in preclinical testing, conducting clinical studies, obtaining regulatory approvals, commercializing drugs, challenging patents and in manufacturing and marketing pharmaceutical products;
- products that have been approved or are in late stages of development;
- for products of similar efficacy, more favorable recommendations or decisions in relation to reimbursement or pricing of their products;
- stronger patent protection;
- more innovative technologies or delivery devices; and/or
- collaborative arrangements in the Company’s target markets with leading companies and research institutions.

The Company’s and its current or future partners’ competitors may be more successful in developing and commercializing their products than the Company, which could materially adversely affect the medium- and long-term business, financial position, income, expansion and outlook of the Company.

1.5.3. Risks associated with the Company’s organization

1.5.3.1. The Company could lose key employees and be unable to attract new qualified personnel.

To a large extent, the Company’s success depends on the involvement and expertise of its managers and expert scientific staff, in particular its three founders, Gérard Soula, Olivier Soula and Rémi Soula.

The Company has taken out a “key person” insurance policy covering its chairman and founder Gérard Soula (see section 1.5.7 of this registration document, “Insurance and risk coverage”).

His departure or the departure of Olivier Soula and/or Rémi Soula or other key employees of the Company could cause:

- a loss of know-how 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 cause slowdowns in the business and ultimately compromise the Company’s ability to achieve its objectives.

Furthermore, in light of the Company’s current development, the Company is in the process of expanding its workforce and actively recruiting 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. Because the Company faces significant competition in recruiting and retaining personnel, 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.
1.5.3.2. **Company’s inability to manage internal growth**

In connection with its development, the Company is in the process of recruiting additional staff and expanding its operating capacity significantly, which could make high demands on its internal resources.

In this respect, the Company will notably 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.

In addition, the Company is in the process of significantly expanding its research and development facilities, including renovating and equipping these facilities. Unexpected issues related to the Company’s expansion could divert management attention from other business concerns or be potentially disruptive to employees.

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.

1.5.3.3. **As part of its growth and development, the Company and its partners will need to find new supply sources for certain of the proteins it uses in its product candidates.**

In connection with the progression of the Company’s pipeline and the initiation of later stage clinical trials for BC Lispro U100, BC Combo and other product candidates, the Company will need to purchase greater quantities of the specific proteins required to develop its formulations to meet the needs of larger clinical trials. The Company may be unable to find suppliers able to supply the appropriate quantities and qualities of proteins at a competitive price, which could delay the start or completion of clinical trials.

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

As a result, the Company may not 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 inability of the Company or its partners to obtain, on financially acceptable terms, or at all, one or more specific proteins of sufficient quality necessary for the development of its projects could have a material adverse impact on the Company’s business, income, financial position, expansion and outlook.

1.5.3.4. **The Company relies on third parties to conduct clinical trials on its product candidates.**

The Company relies on specialized healthcare institutions, including clinical research organizations and clinical investigators to conduct clinical trials of its product candidates, which are necessary to obtaining proof of concept in order to license the Company’s technologies. Although the Company relies on these parties for high quality execution of the Company’s clinical trials, the Company is unable to control all aspects of their activities.

If these third parties do not carry out their contractual duties or obligations or meet expected deadlines, if the third parties need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to failure
to adhere to the Company’s clinical protocols or good clinical practices or for other reasons, the Company’s current or planned clinical studies may be extended, delayed or terminated.

Any extension, delay or termination of any of the clinical trials would have a significant negative impact on the Company’s business and would compromise the Company’s ability to license or commercialize its product candidates. 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.

1.5.4. Regulatory and legal risks

1.5.4.1. Risks associated with obtaining regulatory approvals

The Company has only limited experience in filing and pursuing applications necessary to obtain regulatory approval or authorization. It also cannot ensure that its product candidates will be approved or licensed for marketing, even in circumstances where the Company is collaborating with a partner who has more experience in seeking market authorization. The process of applying for regulatory approval is expensive, often takes many years and can vary substantially based upon the type, complexity and novelty of the product candidates involved.

If any of the Company’s product candidates are not approved, this could have a material adverse effect on the Company’s business, results of operations and prospects and the value of the Company’s shares.

1.5.4.2. Risks associated with an increasingly restrictive regulatory environment for the pharmaceutical industry

One of the most significant challenges faced by a growth company like Adocia is to succeed, with the assistance of its partners, in developing 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 or restrictions regarding use such as those set out in black box warnings for products incorporating the Company’s technologies; and
- significant delays in obtaining marketing authorization for products incorporating the Company’s technologies and, consequently, in the generation of revenue for the Company.
1.5.4.3. Risks associated with uncertain protection of the Company’s patents and other intellectual property rights

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 be successful in preventing unlawful use of the Company’s products or technologies.

The patents and patent applications that the Company has filed and that aim to protect its technologies are recent and many are still being examined by patent authorities. 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 means commonly used in the industry (such as filing additional results to expand one or more patent claims) to extend the protection of its technologies beyond application periods, although it cannot guarantee the results thereof.

The outcome of patent applications for biotechnology and pharmaceutical products are generally very uncertain, raising complex legal and scientific questions. The standards applied by patent offices to grant patents in different countries, or to define the subject and scope of admissible applications, are not always applied in a predictable or uniform manner, and may be amended without warning. Neither the Company nor its partners can be assured that the Company was the first to claim a given invention among its current patent applications, nor that it or its partners were the first to submit applications to protect these inventions. The Company may therefore encounter difficulties in gaining approval for some of its current or future patent or trademark applications currently under examination or that may be examined in the future.

In addition, the Company regularly files trademarks. These trademarks have been registered or are currently undergoing examination. When the Company 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, such as being subject to revocation for non-use, and no affidavits of use are currently required to maintain them.

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.

In addition, the Company may also in-license certain technologies, such as the DriveIn® technology which it has since abandoned. The patents licensed to the Company could be challenged, discovered to have been issued on the basis of insufficient and/or incorrect documentation or disclosure, or held to be unenforceable.

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.

If the Company fails to obtain and maintain intellectual property protection of its products or product candidates and protection of its trade secrets, the Company could lose its competitive advantage, and the increased competition the Company may face could materially adversely affect its business, results of operations and prospects.
1.5.4.4. Risks associated with the inability to protect its intellectual property rights

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, particularly 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. Through contractual provisions, in particular confidentiality clauses, the Company 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;
- its competitors have not already developed a technology or products similar to its own;
- the scope of the protection afforded by patents and trademarks is sufficient to protect it 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.

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 establish the validity and scope of its intellectual property rights, this could have material adverse impact on the Company’s income and financial position and may not provide the protection sought.

Thus, the Company is currently engaged in legal proceedings against its former partner Eli Lilly in order to defend its rights following the appropriation and misuse by Lilly of confidential information and discoveries belonging to Adocia, as well as Lilly’s breach of several collaboration and confidentiality agreements.

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 not be as well protected.

1.5.4.5. Risks associated with license holders that may affect the Company’s relations with its current or potential licensees

The Company may infringe or violate the intellectual property rights of others with technologies, product candidates or products that the Company or its partners seek to use, target or develop and commercialize. These third parties could bring claims against the Company or the Company’s collaborative partners, which could cause the Company to incur substantial expense, and if successful, could require the payment of substantial damages. The Company or its partners could be forced to cease or delay research, development, manufacturing or sales of the product or product candidate or technology that is the subject of the suit.
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.

The Company’s domain names could also be the subject of Uniform Dispute Resolution Policy (UDRP) proceedings or an infringement action brought by a third party claiming prior trademark rights. Therefore, the Company cannot guarantee with certainty that its products do not infringe patents or trademarks owned by third parties.

The Company can also not guarantee that there are no trade secrets or know-how owned by third parties that may provide the grounds for a misuse action against the Company.

1.5.4.6. Risks associated with liability arising from products

The Company’s business exposes it to potential liability, in particular 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, even when 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 healthcare or research professionals), the regulatory authorities, distributors or any other third party that uses or markets products incorporating its technologies.

Product liability claims may be expensive to defend and may result in judgments against the Company that are material. Although the Company has taken out specific insurance policies to cover the resulting financial risk (see section 1.5.7 of the registration document, “Insurance and risk coverage”), and believes that this coverage is appropriate for its business and stage of development, it cannot be certain that the insurance policies will be sufficient to cover all claims made against it. Product liability insurance is expensive, difficult to obtain, and may not be available in the future on acceptable terms. However, any such claims, regardless of merit, could be time-consuming and expensive to defend, could divert management’s attention and resources, and could materially adversely affect the Company’s reputation, business, results of operations and prospects.

1.5.4.7. Risks associated with litigation and claims

From time to time, the Company may become subject to litigation and claims or become otherwise involved in litigation, arbitration proceedings or similar disputes. In addition, the Company regularly includes indemnification provisions in its contractual arrangements and, from time to time, may be subject to claims by its contractual counterparties or third parties with respect to these obligations. The Company has no reason to believe that the Company’s contracting partners, or other interested parties in its agreements, would raise any claims against the Company. However, any such claims, regardless of merit, could be time consuming and expensive to defend, could divert management’s attention and resources, and could materially adversely affect the Company’s business, results of operations and prospects.

1.5.4.8. Risks associated with evolving reimbursement and drug pricing policies

The process of setting the sale price of drugs and their reimbursement rate begins when marketing authorization has been granted.

The ability of the Company’s partners to achieve acceptable levels of reimbursement for drug treatments by governmental authorities, private health insurers and other organizations will have an effect on its ability to successfully commercialize its product candidates. 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.

The price, as set by governmental authorities, private health insurers and other organizations, 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, the Company to earn profits on the sale of the corresponding products.

If reimbursement is not available or is available only at limited levels, the Company’s partners may not be able to successfully commercialize its product candidates and may not be able to obtain a satisfactory financial return on products that the Company may develop. 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.

1.5.4.9. **Risks associated with health, safety of use of hazardous substance, technical facilities and the environment**

Research and development activities in the biology 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.

1.5.5. **Financial risks**

1.5.5.1. **History of operating losses – Risks associated with projected losses**

The Company has posted operating losses every year since its creation in 2005. As of December 31, 2018, its cumulative net losses presented under IFRS rules (including losses carried forward) were €41.3 million.

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.
To become profitable, the Company must sign successful license and collaborative agreements and/or successfully develop and obtain regulatory approval for its product candidates. The Company may never generate significant revenues and, even if it does, it may never achieve profitability.

However, the signature of an important agreement with a licensing and collaborative partner could have an immediate effect on profitability for a given fiscal year.

In addition, as a result of recent changes to French tax law, the amount of operating losses a company may carry forward in a given fiscal year is now limited to €1 million plus 50% of the income before tax per fiscal year. As a result, the Company could become profitable more quickly than prior to such changes, particularly in a situation where the Company enters into one or more major agreements with a licensing and collaborative partner.

Nevertheless, to become and remain profitable, the Company must succeed in developing and commercializing products with significant market potential. This will require the Company to be successful in developing its current product candidates, some of which are only in the preliminary stages of development, signing agreements with partners, obtaining regulatory approval and marketing, manufacturing and selling the products. The Company may never succeed in these activities and may never generate revenues that are significant or large enough to achieve profitability. Even if the Company does achieve profitability, the Company may not be able to sustain or increase profitability in the long term. The Company’s failure to become and remain profitable may cause the market price of its shares to decrease and could impair the Company’s ability to raise capital, expand its business, diversify its product offerings or continue its operations.

1.5.5.2. Uncertain capital resources and additional financing

In the future, the Company will continue to have significant financing needs in order to develop its technologies and pursue its strategy. 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 licensing agreements with industrial partners;
- the costs of keeping up 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® technological platform 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.
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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.

### 1.5.5.3. Risk of dilution

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, 2018 is 7.3% 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.

### 1.5.5.4. Risks associated with access to public subsidies and to the research tax credit

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 may request additional grants or advances in the future.

As of December 31, 2018, and since its creation in 2005, the Company has received the following financial assistance:

<table>
<thead>
<tr>
<th>In (€) thousands</th>
<th>Amount granted and cashed in</th>
<th>Amount reimbursed</th>
<th>Amount granted as a subvention</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSEO repayable advances</td>
<td>3 470</td>
<td>1 900</td>
<td>1 050</td>
</tr>
<tr>
<td>OSEO FEDER subvention</td>
<td>605</td>
<td></td>
<td>605</td>
</tr>
<tr>
<td>COFACE repayable advances</td>
<td>91</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td><strong>TOTAL ADVANCES</strong></td>
<td><strong>4 166</strong></td>
<td><strong>1 991</strong></td>
<td><strong>1 655</strong></td>
</tr>
</tbody>
</table>

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 adversely impact its business, financial position, income, expansion and outlook.

### 1.5.5.5. Risks associated with access to public subsidies and to 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.
In 2018 the Company received a total reimbursement of €7.6 million under the research tax credit for expenditures generated in fiscal year 2017.

For fiscal year 2018, the Company recorded an amount of €6.5 million under the research tax credit that appears in its receivables, for which it will seek reimbursement in 2019.

With respect to 2018 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 a material adverse impact on the Company’s income, financial position and outlook.

1.5.6. Market risks

1.5.6.1. Liquidity risk

Historically, the company has financed its growth primarily by increasing its equity through capital increases. For the acquisition of the building completed in February 2016, the Company took out bank loans. However, it is not exposed to liquidity risks from the application of early repayment clauses in bank loans.

The Company’s cash and cash equivalents totaled €35 million as of December 31, 2017 and almost €40 million as of December 31, 2018.

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. With integration of its financial debt and loans in the amount of €7.1 million at end-December 2018, net cash flow for this period was €32.7 million. This level of cash enables the Company to fund its planned clinical development (see section .1.3 of this registration document) and the development of its new programs.

In particular, the Company believes that it is able to make its next repayments of its loans and Bpifrance repayable advances, being precised that no reimbursement are expected for 2019 (see note 10 to the Company’s consolidated financial statements prepared under IFRS in chapter 4.1 of this registration document).

The company supports the development of the projects licensed to Tonghua Dongbao and pursues its research and development activities while nevertheless focusing its expenses on projects and priority activities. The recovery of damages awarded under the first part of the arbitration proceeding against Lilly ($11.6 million plus interest) is expected in 2019, following the conclusion of the second part of the arbitration. Pending the cash receipt of this amount, the possibility of an advanced payment of the research tax credit allows the Company to finance the defined operational plan and thus to meet its financial commitments for at least the next 12 months. Therefore, the going concern assumption has been retained.

1.5.6.2. 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, because its expenditures are also largely denominated in euros.

However, as a result of the agreement signed with Tonghua Dongbao Pharmaceuticals Co. Ltd in April 2018, a major part of the Company’s revenues, such as the upfront payment received in connection with that agreement, were denominated in US dollars. As a result, the Company was exposed to risk in relation to fluctuations in the euro-US dollar exchange rate.

If the Company signs further licensing and collaboration agreements with US pharmaceutical companies, it may be exposed to additional euro-US dollar exchange rate risks.
The Company cannot rule out that significant growth in its business may create greater exposure to exchange rate risk. In such case, the Company will consider adopting a new policy appropriate to hedging such risk such as currency hedging transactions and the purchase of currency forwards.

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.

1.5.6.3. Interest rate risk

In 2015 the Company took out a loan from two banks to finance the acquisition of the building in which its research center and headquarters are located. These loan agreements were negotiated at a fixed rate for a 12-year term.

The Company is exposed to changes in interest rates in the course of managing its cash and cash equivalents. The Company’s cash and cash equivalents totaled €35 million as of December 31, 2017 and almost €40 million as of December 31, 2018. 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.

1.5.6.4. Equity risk

None.

1.5.6.5. The price of the Company’s shares is subject to significant volatility.

The price of the Company’s shares is subject to significant volatility. For example, on December 31, 2017 the Company’s share price traded at €14.35, compared with €16.54 on December 31, 2018. The average daily trading volume of 36,265 shares traded per day in 2017 decreased to 19,615 shares traded per day in 2018. The public float remained steady in 2018 and was around 60% at the end of December 2018.

As of April 9th, 2019, shares traded at €14.14 with an average volume of 13,329 shares traded since the beginning of the year.

In addition to the occurrence of the risks described herein, the market price of the Company’s shares 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;
- announcements regarding results of the Company’s clinical trials or other scientific developments;
- 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;

1.5.7. Insurance and risk coverage

The company has adopted a policy to cover the main risks to which it is exposed, when possible, 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 remained stable in the fiscal years ended on December 31, 2017 and 2018.

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;
- a “business liability” policy, which covers risks in connection with business operations for all damage, including bodily injury;
- 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.

For all the policies, the Company and the insurer determine together the maximum coverage in adequacy with the specificities of the Company and in line with the practices of companies in a similar field of activity.

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 in particular 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 to 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.

1.5.8. Extraordinary events and disputes

Except as noted below, during the 12-month period preceding the filing date of this registration 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 date of this registration document, the company is not threatened with any such proceedings.

To the Company’s knowledge, no exceptional event arose during the same period that would generate additional risk or additional unplanned costs.

However, it must be noted that in October 2017, Adocia announced in a press release its filing of an arbitration claim against Eli Lilly & Co related to a research and licensing agreement signed in 2014 and terminated in January
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2017 at the initiative of Eli Lilly & Company. In August 2018, the first phase of the arbitration procedure initiated by Adocia against Lilly concluded in favor of Adocia. The Arbitration Tribunal awarded Adocia $11.6 million, as well as interests.

The arbitration proceeding is continuing, in particular related to Adocia’s additional claims against Lilly, filed in February 2018, for a revalued amount of USD 1.3 billion and the counterclaims of Lilly for an amount of USD 188 million, remain pending, with a decision of the court expected in the third quarter of 2019.

Finally, in October 2018, Lilly filed a civil complaint against Adocia in the United States District Court of the Southern District of Indiana to seek a declaratory judgment for two of its US patents regarding ultra-rapid insulin formulation (Lilly’s United States Patent Nos. 9,901,623 and 9,993,555 entitled “Rapid-acting insulin compositions”). Lilly contends in its complaint that it filed the action because Adocia has asserted that Lilly’s patents reflect Adocia’s inventive contribution. Adocia does not expect the matter to be resolved during this fiscal year.