



## PRESS RELEASE

## Adocia Reports Positive Preliminary Results from Dose Response Clinical Study of Ultra-fast acting BioChaperone<sup>®</sup> Lispro U100 in Patients with Type 1 Diabetes

- BioChaperone Lispro U100 shows a proportional dose-exposure and a linear dose-response when tested at 0.1; 0.2 and 0.4 U/kg
- Study confirms BioChaperone Lispro U100 is significantly faster than Humalog<sup>®</sup> in type 1 diabetic patients, as was observed in the previous clinical trial
- BioChaperone Lispro U100 combines an ultra-fast profile across the therapeutic dose range with an excellent local tolerance.

**Lyon, France, Sept 09, 2014** - Adocia (Euronext Paris: FR0011184241 - ADOC) announces today positive preliminary results from a Phase IIa dose-response clinical trial evaluating its innovative ultra-fast formulation of insulin lispro (BioChaperone Lispro U100) tested at three doses, relative to Eli Lilly's Humalog<sup>®</sup> commercial insulin (insulin lispro U100). Adocia's formulation incorporates proprietary BioChaperone<sup>®</sup> technology which enables accelerated absorption of prandial insulins.

This dose response study confirms that BioChaperone Lispro U100 more closely mimics the endogenous insulin secretion observed in healthy individuals in response to a meal than Humalog, at all tested doses. BioChaperone Lispro U100 has now been tested in 73 patients (for a total of 149 injections) and was very well tolerated.

Gerard Soula, chairman and CEO of Adocia, commented on the results, "The present study supports the best-in-class potential of BioChaperone Lispro U100 among prandial insulins. Based on the expected superior medical benefit of ultra-fast insulins for patients, we believe that BioChaperone Lispro U100 could efficiently compete on the \$5B prandial insulin analogs market. Moreover, the minimal additional cost of the BioChaperone technology, which should permit to keep the price of the end-product unchanged, will probably be a key success factor considering the public policies to control healthcare expenses."

"We are also actively developing an ultra-fast concentrated formulation of BioChaperone Lispro, a potential first-in-class product, to reduce injection volumes, especially for severely insulin-resistant type 2 diabetic patients." added Mr. Soula.

**Clinical results confirm the ultra-fast action of BioChaperone Lispro U100 and show a dose-response effect**

In this double-blind, randomized, four-period cross-over study, the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of BioChaperone Lispro at three doses were compared to those of Humalog at a single dose. 37 patients with type 1 diabetes received three increasing doses of BioChaperone Lispro (0.1 U/kg, 0.2 U/kg and 0.4 U/kg ) and one dose of Humalog (0.2 U/kg) under automated euglycemic clamp conditions (ClampArt<sup>®</sup>, target blood glucose (BG) 100 mg/dL, clamp duration 12 hours post-dosing).

All BioChaperone Lispro dosages were well tolerated and did not induce any local reaction, while Humalog was associated to an injection site erythema in one patient.

In pharmacokinetics, BioChaperone Lispro showed a significantly faster rate of insulin lispro absorption than Humalog with an increase in the early insulin exposure of 136% at the same dose ( $AUC_{\text{lispro}_0-30\text{min}}$   $25 \pm 10$  vs.  $12 \pm 7$  h\*mU/L;  $p < 0.001$ ). The time to peak insulin lispro concentration was significantly reduced (median  $T_{\text{max}}$  40 vs. 60 min;  $p = 0.001$ ). BioChaperone Lispro was also cleared from the blood significantly earlier than Humalog, reflected in the time to half-maximum insulin levels after  $T_{\text{max}}$  (late  $T_{50\% \text{max}}$  =  $132 \pm 41$  vs.  $163 \pm 49$  min,  $p < 0.001$ ).

The acceleration of insulin lispro absorption with BioChaperone translated into a significant acceleration of its metabolic effect. The early metabolic effect was increased by more than 70% relative to Humalog during the first hour after administration ( $AUC_{\text{GIR}_0-1\text{h}}$  =  $207 \pm 87$  vs.  $123 \pm 58$  mg/kg;  $p < 0.0001$ ).

Finally, the total insulin exposure and potency of insulin lispro were similar for both formulations.

In a comparable clinical setting, BioChaperone Lispro had already shown superior PK/PD profiles vs. Humalog. The reproducibility of this second clinical study confirms the robustness of the product performance.

The primary objective of this study was to investigate the dose-exposure and the dose-response relationships of BioChaperone Lispro at 0.1, 0.2 and 0.4 U/kg.

A dose proportionality relationship was demonstrated for the total insulin exposure and the maximum insulin lispro concentration ( $AUC_{0-\text{last}}$  = 112, 213 and 452 h\*mU/L and  $C_{\text{max}}$  = 55, 100 and 191 mU/L for 0.1, 0.2 and 0.4 U/kg respectively).

A linear dose response relationship was demonstrated for the total metabolic effect and the maximum glucose infusion rate ( $AUC_{\text{GIR}_0-\text{last}}$  = 726, 1357 and 2422 mg/kg and  $\text{GIR}_{\text{max}}$  = 4.8, 7.4 and 10.2 mg/kg/min for 0.1, 0.2 and 0.4 U/kg respectively).

The ultra-fast absorption of insulin lispro for all doses of BioChaperone Lispro is confirmed by constant time-related parameters, such as time to early maximal observed insulin lispro concentration (early  $T_{50\% \text{max}}$  =  $15 \pm 5$ ,  $15 \pm 5$  and  $15 \pm 5$  min at 0.1, 0.2 and 0.4 U/kg respectively).

"This solid clinical evidence confirms that BioChaperone Lispro U100 is a compelling ultra-fast-acting insulin across the usual therapeutic dose range," said Olivier Soula, Deputy General Manager and R&D Director at Adocia, "We are now confident that the clinical development path is straightforward, as the product combines a high level of performance with a solid safety and stability profile. The key next step is to establish the medical benefit, which we intend to do with a meal study in Type 1 diabetics using insulin pumps beginning in Q1 2015."

## Next events

Adocia will be present at the 50th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Vienna, Austria from the 15-19th September 2014, to present two posters on Phase IIa clinical data previously obtained with BioChaperone Lispro and BioChaperone Glargine Lispro Combo.

## About diabetes

Diabetes is a chronic condition in which the person has high blood glucose (hyperglycemia), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. Chronic hyperglycemia contributes to disease progression and results in macrovascular and microvascular complications. Diabetes, which today affects more than 382 million individuals worldwide, is forecasted to grow to 592 million individuals by 2035, an average increase of 55%, and an increase of as much as 70% in emerging countries. (Source: International Diabetes Federation, 2013).

## About prandial insulins

Prandial insulins include regular human insulin and fast-acting insulin analogs. The main objective of prandial insulins is to control the rapid rise in glycaemia associated with digesting a meal. Available prandial insulins act with a delay of 15 minutes (insulin analogs) to 30 minutes (regular human insulin) after injection, which fails to replicate the immediate secretion of insulin observed in healthy individuals during a meal. This delay makes it extremely hard for patients to correctly dose insulin relative to the actual meal and results in an unsatisfactory glycemic control (i.e. hyper- and hypoglycemia). Hyperglycemia results from a delay in insulin response compared to glucose entry in the blood flow following a meal. Chronic hyperglycemia is correlated with vascular complications in diabetic patients and represents a major health issue. Conversely, hypoglycemia results from an excess of insulin relative to blood glucose concentration. Severe hypoglycemia can be life-threatening.

The goal of ultra-fast insulin is to accelerate prandial insulin action, to facilitate dosage at the time of, or after, the meal and reduce the risk of both hyperglycemia and hypoglycemia.

## About BioChaperone Lispro U100

BioChaperone Lispro is an ultra-fast formulation of insulin analog lispro (Eli Lilly's Humalog®) incorporating Adocia's proprietary BioChaperone® technology. Ultra-fast BioChaperone Lispro aims to accelerate the action of insulin lispro, thus improving prandial glycemic control for insulin-dependent diabetics. Indeed, the earlier onset and higher early bioavailability of BioChaperone Lispro compared to Humalog has the potential to reduce the incidence of hyperglycemic events, while its shorter exposure may also limit the incidence of hypoglycemic events, by allowing dosing at the time of the meal. In a previous Phase IIa clinical trial on 36 Type 1 diabetic patients, BioChaperone Lispro showed a significant acceleration of its onset of action compared to insulin lispro. (<http://www.adocia.fr/WP/wp-content/uploads/2014/04/140409AdociaUltraFastLisproPhase2aClinicalresultsENVF.pdf>)

## About Adocia

### **To be a global leader in the innovative delivery of insulins and therapeutic proteins**

Adocia is a clinical-stage biotechnology company that specializes in the development of innovative formulations of already-approved therapeutic proteins. It has a particularly strong expertise in the field of insulins. Adocia's proprietary BioChaperone® technological platform is designed to enhance the effectiveness and safety of therapeutic proteins and their ease of use for patients.

Adocia has successfully completed two Phase I and IIa studies of a fast-acting human insulin formulation (HinsBet), one Phase I and two Phase IIa studies of an ultra-fast-acting insulin lispro (BioChaperone Lispro U100) and a Phase I/II of a unique combination of insulin glargine, the gold-standard of basal insulin and insulin lispro, a fast-acting insulin analog (BioChaperone Combo).

A Phase IIa study of HinsBet is ongoing and a dose-escalation Phase IIa study of BioChaperone Combo is scheduled for the fourth quarter 2014. The company is also preparing a first clinical study of a new ultra-fast concentrated insulin formulation based on insulin lispro for 2015.

Adocia also completed one Phase I/II clinical study of its product based on PDGF-BB for treating diabetic foot ulcer (BC PDGF-BB). A Phase III clinical study was launched in India in August 2014.

Adocia has extended its activities to the formulation of monoclonal antibodies, which are gold-standard biologics for the treatment of various chronic pathologies (cancer, inflammation, etc.). Adocia is engaged in collaborative programs with two major pharmaceutical companies in this field.

### **Fighting cancer with targeted treatments**

DriveIn<sup>®</sup> is a nanotechnology which is remarkably efficient in delivering active compounds into cancer cells. This new platform constitutes an exceptional opportunity to enter the oncology market by improving the efficacy of both already approved treatments and novel proprietary molecules.

### **“Innovative medicine for everyone, everywhere”**

Adocia's therapeutic innovations aim at providing solutions in a profoundly changing global pharmaceutical and economic context, characterized by (i) an increased prevalence and impact of the targeted pathologies, (ii) a growing and ageing population, (iii) a need to control public health expenditures and (iv) an increasing demand from emerging countries.

Adocia is listed on the regulated market of Euronext Paris (ISIN: FR0011184241; Reuters/Bloomberg ticker: ADOC, ADOC.PA, ADOC.FP) and is included in the Next Biotech index.

American Depositary Receipts representing Adocia common stock are traded on the US OTC market under the ticker symbol ADOCY.

For more information, visit [www.adocia.com](http://www.adocia.com)

### **Safe Harbor**

This press release contains certain forward-looking statements concerning Adocia and its business. Such forward-looking statements are based on assumptions that Adocia considers to be reasonable. However, there can be no assurance that the estimates contained in such forward-looking statements will be verified, which estimates are subject to numerous risks including the risks set forth in the 'Risk Factors' section of the Reference Document registered by the Autorite des marches financiers on April 24, 2014 under number R.14-020 (a copy of which is available on [www.adocia.com](http://www.adocia.com)) and to the development of economic conditions, financial markets and the markets in which Adocia operates. The forward-looking statements contained in this press release are also subject to risks not yet known to Adocia or not currently considered material by Adocia. The occurrence of all or part of such risks could cause actual results, financial conditions, performance or achievements of Adocia to be materially different from such forward-looking statements.

This press release and the information contained herein do not constitute an offer to sell or the solicitation of an offer to buy Adocia shares in any jurisdiction.

### **Contact**

Gerard Soula - [contactinvestisseurs@adocia.com](mailto:contactinvestisseurs@adocia.com)  
Chairman and CEO of Adocia  
Tel.: +33 4 72 610 610

### **Press Relations**

#### **ALIZE RP**

Caroline Carmagnol  
[caroline@alizerp.com](mailto:caroline@alizerp.com)  
[adocia@alizerp.com](mailto:adocia@alizerp.com)  
Tel.: +33 170 225 390

