



## PRESS RELEASE

## Adocia reports positive results from phase IIa clinical study of fast-acting human insulin, HinsBet®

- HinsBet is significantly faster than human insulin in type 1 diabetic patients; onset of action is 70 percent earlier and early metabolic effect is doubled;
- HinsBet's fast action is similar to that of Humalog in the first hour which is critical for glycemic control;
- A concentrated formulation of HinsBet at 500 IU/ml is under development to answer the needs of the growing population of severely resistant diabetic patients.

**Lyon, France, February 05, 2015** - Adocia (Euronext Paris: FR0011184241 - ADOC) today announced positive results from a Phase IIa clinical trial evaluating its innovative fast-acting formulation of recombinant human insulin, HinsBet, in comparison to Eli Lilly's commercial products, Humalog® (insulin lispro) and Humulin® (recombinant human insulin). Adocia's HinsBet formulation incorporates proprietary BioChaperone® technology which enables accelerated absorption of prandial insulins. Annual revenues for Humulin and Humalog, both off-patent, are USD 1.4 B and USD 2.8 B<sup>1</sup> respectively.

The present study met its primary endpoint, measuring the increase of recombinant human insulin bioavailability during the first hour for HinsBet as compared to Humulin. The main objective for prandial insulins is to mimic physiological response to a meal with an absorption of subcutaneous insulin as fast as possible. Therefore, the effect of prandial insulins in the first hour is critical. These clinical results show that HinsBet has an early effect equivalent to that of a fast-acting insulin analog, Humalog, and twice superior to that of regular recombinant human insulin, Humulin.

"We are extremely pleased with the performance of this optimized formulation of HinsBet in type 1 diabetic patients as it shows that our product is superior to regular human insulin and has an efficacy identical to Humalog in the first hour," comments Olivier Soula, R&D director and deputy general manager. "This new result demonstrates once more the value of the BioChaperone technology to improve the performance of approved insulins. Thanks to our innovative products portfolio, we are in a position to play an important role in the field of insulin therapy. Now, our priority is to bring these innovations to patients in the most efficient and rapid manner".

---

<sup>1</sup> Eli Lilly's press release on full-year 2014 results dated January 30, 2015.

## Clinical results support the fast action of HinsBet

In this double-blind crossover study, the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of HinsBet were compared to those of Humulin and Humalog. Thirty-six patients with type 1 diabetes received single 0.2 U/kg doses of HinsBet, Humulin and Humalog under automated euglycemic clamp conditions (ClampArt<sup>®</sup>, target blood glucose (BG) 100 mg/dL, clamp duration ten hours post-dosing).

All three formulations were well tolerated and did not induce any local reaction.

HinsBet had a significantly faster rate of absorption than Humulin with an increase in the early insulin exposure of 70% (primary endpoint,  $AUC_{ins\_0-1h}$   $26.0 \pm 14.3$  vs.  $15.5 \pm 9.7$  h\*mU/L;  $p < 0.0001$ ).

The acceleration of human insulin absorption with BioChaperone translated into a significant acceleration of its action. Indeed, the metabolic effect is triggered significantly earlier for HinsBet than for Humulin with a 70% shorter onset of action ( $T_{onset} = 28 \pm 10$  vs.  $49 \pm 20$  min;  $p < 0,0001$ ). Moreover, the metabolic effect of HinsBet is more than twice the one of Humulin in the first hour post-administration ( $AUC_{GIR\_0-1h} = 111 \pm 63$  vs.  $46 \pm 52$  mg/kg;  $p < 0,0001$ ).

Finally, the total insulin exposure and potency of recombinant human insulin was similar for both HinsBet and Humulin with no significant difference ( $AUC_{ins\_0-last} = 158 \pm 47$  vs.  $152 \pm 33$  h\*mU/L and  $AUC_{GIR\_0-last} = 1294 \pm 611$  vs.  $1256 \pm 613$  h\*mU/L).

In comparison to Humalog, HinsBet demonstrated a similar absorption rate to Humalog with no significant difference in early exposure ( $AUC_{ins\_0-30min}$   $10.7 \pm 6.3$  vs.  $11.5 \pm 9.6$  h\*mU/L). This similar absorption also translated into a similar early metabolic effect between HinsBet and Humalog ( $AUC_{GIR\_0-1h} = 111 \pm 63$  vs.  $130 \pm 80$  mg/kg).

## HinsBet U500, a new opportunity

Some people with type 2 diabetes are severely insulin-resistant and their treatment can require insulin daily doses that are more than two to three times higher than standard doses. It is difficult for these patients to use popular formulations of insulin analogs at 100 IU/ml, such as Humalog, since the volumes to be administered are too large.

The main insulin treatment option for highly insulin resistant patients is Humulin U500 (Eli Lilly), a human insulin formulation at 500 UI/ml, i.e. five times more concentrated than standard commercial products. This product has rapidly growing U.S. revenues that, in 2014, are expected to total more than \$300 million. The growth of Humulin U500 market is driven by ongoing expansion in the population of insulin-resistant patients as well as product price increases.

Although Humulin U500 reduces the total volume of insulin, its action profile is much slower than U100 formulations. Hence, there is an unmet need for a concentrated formulation of recombinant human insulin with a faster action profile.

Adocia develops HinsBet U500 with the objective to reach a faster action profile. This program is currently under development.

« The results we have just obtained reinforce the potential for HinsBet, on one hand, for patients with a high sensitivity to insulin analog price as formerly envisaged, and on the other hand, potentially addressing unmet needs in the treatment of severely insulin resistant patients » comments Gérard Soula, Chairman and CEO of Adocia. « Hence, HinsBet opens two different market opportunities, the first one in emerging countries, the other one for western countries. HinsBet may be a compelling solution for a large number of diabetic patients to both improve their insulin treatment and make it more accessible. »

### 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 glycemia associated with meal digestion. Available prandial insulins act are required to be injected 15 minutes (insulin analogs) to 30 minutes (regular human insulin) before mealtime. This delay makes it extremely hard for patients to correctly dose insulin relative to the actual meal and usually results in an unsatisfactory glycemic control (i.e. hyper- and hypoglycemia).

Hyperglycemia results from a delayed exogenous insulin absorption compared to the increase of meal-related glycemia. 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 and is a significant cost burden to health systems.

BioChaperone enables acceleration of prandial insulin action profiles, allowing administration at a more appropriate time relative to the meal and potentially improve glycemic control.

### About HinsBet

HinsBet is a fast-acting formulation of recombinant human insulin incorporating Adocia's proprietary BioChaperone<sup>®</sup> technology. HinsBet aims to accelerate the action of recombinant human insulin to reach an insulin analog-like performance, thus improving prandial glycemic control for insulin-dependent diabetics. Indeed, the earlier onset and higher early bioavailability of HinsBet compared to Humulin has the potential to improve glycemic control, while taking advantage of the long safety and efficacy track-record of human insulin, as well as its lower cost of production compared to insulin analogs.

### 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<sup>®</sup> technological platform is designed to enhance the effectiveness and safety of therapeutic proteins and their ease of use for patients.

In December 2014, ADOCIA signed a partnership with the company Eli Lilly for the development and commercialization of its new formulation of insulin lispro, BioChaperone Lispro, previously tested successfully in two phase Ib/IIa studies.

ADOCIA will continue to develop its fast-acting human insulin formulation internally. ADOCIA is also actively continuing the development of its BioChaperone Combo, a unique combination of insulin glargine, the gold-standard of basal insulin and insulin lispro, a fast-acting insulin analog. A dose-response clinical study (Phase IIa) is scheduled for Q1 2015.

In August 2014, ADOCIA also launched a phase III clinical study in India on its product based on PDGF-BB for treatment of the diabetic foot ulcer (BioChaperone PDGF-BB).

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***

Drive/n<sup>®</sup> is a nanotechnology which is intended to significantly improve delivery of active compounds into cancer cells. This new proprietary 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 to provide 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)

### **Contact ADOCIA**

G rard 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 1 44 54 36 61

### **Disclaimer**

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 French *Autorit  des march s financiers* (Financial Markets Authority) on April 24, 2014 under number R14-020 (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 therein do not constitute an offer to sell, nor the solicitation of an offer to purchase or subscribe for, ADOCIA shares in any country.