



PRESS RELEASE

Adocia announces positive topline results for the first clinical study of ADO09, a new co-formulation of pramlintide and a prandial insulin analog, in people with type 1 diabetes

- ADO09 is the first co-formulation of pramlintide and the rapid-acting A21G human insulin analog, the metabolite of insulin glargine
- ADO09 showed a significant 85% decrease in blood glucose excursion over the first two hours after a meal compared to Humalog®
- ADO09 showed similar glucose control over the first two hours after a meal compared to separate injections of Symlin® and Humulin®
- All treatments were well tolerated

Lyon, France, April 9th, 2019 – 6:00 pm CET - Adocia (Euronext Paris: FR0011184241 – ADOC) the biopharmaceutical company focused on the treatment of diabetes and other metabolic diseases with innovative formulations of approved proteins, announces today positive topline pharmacodynamic and safety results from the first Phase 1 study of ADO09, a ready-to-use, pH 4, co-formulation at fixed ratio of pramlintide, the only FDA-approved analog of amylin, and A21G human insulin analog (“A21G human insulin”), a rapid-acting insulin that is known to be the main circulating metabolite of insulin glargine (Lantus®, Sanofi). A21G human insulin is considered to be safe, as millions of people using insulin glargine are routinely exposed to it¹. ADO09 is an innovative formulation for which Adocia has filed an international patent application.

ADO09 is intended to improve post-prandial glucose control and long-term outcomes for people requiring prandial insulin treatment by enabling the synergistic combination of two complementary hormones: the amylin-analog pramlintide and prandial insulin. Indeed, in a person without diabetes, insulin and amylin are co-secreted and act synergistically to control glycemic excursions after a meal.

“The positive results of this study support our conviction that a fixed-ratio co-formulation of pramlintide with prandial insulin has the potential to significantly improve the lives of people with diabetes by delivering superior postprandial glycemic control and decreasing glycemic variability.” said Dr. Olivier Soula, Adocia’s Deputy General Manager and Director of R&D *“Our intense efforts to advance such a combination led us to this alternate approach, distinct from our first candidate enabled by BioChaperone and formulated at pH 7. The foundation of ADO09 is the use of A21G human insulin, which, like pramlintide, is stable at pH 4, in order to better mimic the therapeutic benefit of the separate injection of pramlintide and human insulin.”*

In December 2018, Adocia announced positive first-in-human clinical data for BioChaperone® Pramlintide Insulin (BC Pram Ins), a neutral pH co-formulation of pramlintide and human insulin based on Adocia's proprietary BioChaperone® technology.

"Today we show that ADO09 offers the same synergistic benefits, measured by prandial glucose excursion, as the co-administration of pramlintide and human insulin, in a single product that could be injected at mealtime. At this stage, based on positive clinical results which better mirror those of the separate injections and a straightforward development path, we have decided to prioritize ADO09." continues Dr. Olivier Soula. *"We will now move quickly into a Phase 2 clinical trial."*

Adocia expects to launch a Phase 1/2, outpatient, 3-week trial of ADO09 during this quarter. Consequently, the timelines of this key program remain unchanged compared to what was originally announced with BC Pram Ins.

The present study was a randomized, double-blind, active comparator-controlled, three-period cross-over study, which enrolled 24 participants with type 1 diabetes. Subjects were randomly allocated to a sequence of three treatments, administered immediately before 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 ADO09 (containing 7.5 U insulin and 45 µg pramlintide), compared to the separate and simultaneous injections of human insulin (7.5 U, Humulin®, Eli Lilly) and pramlintide (45 µg, Symlin®, AstraZeneca), and to an injection of rapid-acting insulin analog lispro (7.5 U, Humalog®, Eli Lilly).

"The first clinical results obtained with ADO09 are highly encouraging, as they are very similar to the results obtained with a co-administration of human insulin and pramlintide. I thus expect this co-formulation to deliver a similar medical benefit to the one found for pramlintide when given in a separate injection with prandial insulin, still the only FDA-approved adjunctive treatment for people with type 1 diabetes." said Prof. Robert Ratner, Professor of Medicine, Georgetown University School of Medicine, Washington DC. *"I believe this combination has the potential to finally deliver on the promise of pramlintide for a large number of patients, by addressing the significant unmet need for tighter post-prandial control and lower glycemic variability without the burden associated with another product and a higher number of injections."*

Treatment with ADO09 resulted in a statistically significant 85% reduction of blood glucose excursions over the first two hours after the meal compared to Humalog® (Mean(±SD) DeltaAUC_{Blood_Glucose 0_2h} = 18 (40) mg*h/dL vs. 119 (56) mg*h/dL; p<0.0001) and comparable postprandial glycemic control to that of the separate injections of Humulin and Symlin (Mean(±SD) DeltaAUC_{Blood_Glucose 0_2h} = 26 (49) mg*h/dL, n.s.).

Additionally, oral acetaminophen used as a marker of gastric emptying demonstrated that ADO09 and Symlin® + Humulin® separate injections resulted in similarly slower gastric emptying versus Humalog®. The slowing of gastric emptying towards a physiological is a known pharmacological effect of pramlintide and plays an important role in reducing post-prandial blood glucose excursions.

All treatments were well tolerated. The overall number of hypoglycemic events during dosing visits was similar between ADO09 (n=2), Symlin® + Humulin® (n=2) and Humalog® (n=0). There were no signals of gastrointestinal side-effects known to occur with Symlin® in either of the pramlintide-treated groups.

Additional endpoints from this trial, such as the effect of the ADO09 formulation on endogenous glucagon secretion and the pharmacokinetic profiles of insulins and pramlintide, will be published separately.

Results of this trial have been submitted for publication at a major diabetes conference later this year.

Adocia was the sponsor of this study, which was performed by Profil Neuss in Germany.

About ADO09

In people without diabetes, insulin and amylin are hormones co-secreted by pancreatic beta cells and act in synergy to control blood glucose. While insulin controls glucose disposal, amylin modulates glucose appearance in the blood by suppressing liver glycogenolysis through glucagon inhibition and by slowing gastric emptying. Amylin also decreases food intake by inducing satiety. As diabetes progresses, and beta cell mass declines, the secretion of both insulin and amylin is diminished and, eventually, absent.

Adocia's proprietary ADO09 formulation enables the fixed-ratio combination of the FDA-approved amylin analogue pramlintide and A21G human insulin analog ("A21G human insulin"), at pH 4. A21G human insulin is the main metabolite of FDA-approved insulin glargine¹. A21G human insulin has pharmacokinetic and pharmacodynamic profiles similar to that of human insulin. Through the use of glargine, millions of people with diabetes worldwide have been exposed to A21G human insulin, which is considered to be safe².

Pramlintide is approved in the USA for both type 1 and type 2 diabetes as an adjunct therapy to mealtime insulin treatment. The Phase 3 trials leading to pramlintide approval showed that, when added to an existing insulin regimen, pramlintide significantly improves post-prandial glucose control by flattening postprandial glucose excursions. After 6 months of use, pramlintide as an adjunct to insulin therapy resulted in improved HbA1c, reduced prandial insulin consumption, and resulted in weight loss compared to the use of insulin alone in both people with type 1³ and with type 2⁴ diabetes. Like amylin, pramlintide delays the timing and reduces the magnitude of postprandial blood glucose spikes. As intensified insulin therapy requires multiple daily injections and frequent glucose monitoring, however, the addition of daily mealtime injections of pramlintide has proved a challenge to patient adherence, compliance, and persistency.

By combining two synergistic agents, ADO09 is designed to deliver superior postprandial glycemic control for people with diabetes without the burden of separate administration of two different products.

About Adocia

Adocia is a clinical-stage biotechnology company that specializes in the development of innovative formulations of already-approved therapeutic proteins and peptides for the treatment of diabetes and other metabolic diseases. In the diabetes field, Adocia's portfolio of injectable treatments is among the largest and most differentiated of the industry, featuring seven clinical-stage products. Additionally, Adocia expanded its portfolio to include the development of treatments of obesity and short bowel syndrome.

The proprietary BioChaperone® technological platform is designed to enhance the effectiveness and/or safety of therapeutic proteins while making them easier for patients to use. Adocia customizes BioChaperone to each protein for a given application. Adocia's clinical pipeline includes six novel insulin formulations for the treatment of diabetes: two ultra-rapid formulations of insulin analog lispro (BioChaperone® Lispro U100 and U200), a combination of basal insulin glargine and rapid-acting insulin lispro (BioChaperone® Combo), a rapid-acting formulation of human insulin (HinsBet® U100), and two combinations of a prandial insulin with amylin analog pramlintide (BioChaperone® Pramlintide Insulin and ADO09). It also includes an aqueous formulation of human glucagon (BioChaperone® Glucagon) for the treatment of hypoglycemia. Adocia preclinical pipeline includes combinations of insulin glargine with GLP-1 receptor agonists (BioChaperone®

¹ Bolli *et al.* Diabetes Care. 2012 Dec; 35(12): 2626–2630. & Lucidi *et al.* Diabetes Care. 2012 Dec; 35(12): 2647–2649; Lantus® label, Section 12.3.

² Lantus® label, Section 12.3.

³ Whitehouse F, *et al.* Diabetes Care. 2002;25(4):724-730; Ratner RE, *et al.* Diabet Med. 2004;21(11):1204-1212.

⁴ Hollander PA, *et al.* Diabetes Care. 2003;26(3):784-790.

Glargine GLP-1) for the treatment of diabetes, a ready-to-use combination of glucagon and a GLP-1 receptor agonist (BioChaperone® Glucagon GLP1) for the treatment of obesity and a ready-to-use aqueous formulation of teduglutide (BioChaperone® Teduglutide) for the treatment of short bowel syndrome.

In 2018, Adocia and Chinese insulin leader Tonghua Dongbao entered into a strategic alliance. In April 2018, Adocia granted Tonghua Dongbao licenses to develop and commercialize BioChaperone Lispro and BioChaperone Combo in China and other Asian and Middle-Eastern territories. The licensing included 50 million dollars upfront and up to 85 million dollars development milestones, plus double-digit royalties on sales. In June 2018, Tonghua Dongbao agreed to manufacture and supply active pharmaceutical ingredients insulin lispro and insulin glargine to Adocia globally, excluding China, to support Adocia's portfolio development in these territories.

Adocia aims to deliver “Innovative medicine for everyone, everywhere.”

To learn more about Adocia, please visit us at www.adocia.com



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For more information please contact:

<p>Adocia Gérard Soula Chairman and CEO contactinvestisseurs@adocia.com Ph.: +33 4 72 610 610</p>	<p>Adocia Press Relations Europe MC Services AG Raimund Gabriel adocia@mc-services.eu Ph.: +49 89 210 228 0</p>	<p>Adocia Investor Relations USA The Ruth Group Tram Bui tbui@theruthgroup.com Ph.: +1 646 536 7035</p>
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