SYNOPSIS

Name of Sponsor: Olivier Soula, Adocia SAS, Lyon, France	Individual Trial Table referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: n.a.	Volume:	
Name of Active Ingredient: BioChaperone® rhInsulin	Page:	

Title of study: A Phase IIa, double-blinded, randomized trial comparing the pharmacokinetics, pharmacodynamics and safety of BioChaperone® rhInsulin to fast-acting insulin analog in patients with Type 1 diabetes mellitus

Principal investigator: Prof. Thomas Forst, MD, Parcusstraße 8, 55116 Mainz, Germany

Study center: ikfe GmbH, Clinic, Parcusstraße 8, 55116 Mainz, Germany

Publication (reference): not applicable

Studied period:	**Phase of development:**
First patient enrolled: June 07, 2011 Last patient completed: July 26, 2011	Phase IIa

Objectives:

The primary objective was to assess the non-inferiority of BioChaperone® rhInsulin (BCI) in comparison to insulin Aspart (IAS) with regard to the onset of absorption after three consecutive injections of each product.

Secondary objectives were to compare the pharmacokinetic and pharmacodynamic profiles of BioChaperone® rhInsulin to insulin Aspart by the mean of several variables.

Methodology: This phase IIa clinical trial was designed as a single-center, prospective, double blind, randomized crossover manual euglycemic clamp study.

Number of patients (planned and analyzed): It was planned to randomize 20 male and female patients with type 1 diabetes mellitus. 20 patients finished the study and 18 patients were included in the statistical analysis.

Diagnosis and main criteria for inclusion: Male and female patients with type 1 diabetes mellitus with a body mass index between 18 and 29 kg/m^2, an HbA1c <8.5% and an age between 18 and 50 years could be included.

Test product, dose and mode of administration, batch number:

In a crossover design, all patients received three consecutive injections of both study medications

Study medication A: Subcutaneous injections of BioChaperone® rhInsulin 100 IU/mL at a fixed dose of 12 IU. Batch number: BC3 001/10 (DC 10143).

Reference therapy, dose and mode of administration, batch number:

Study medication B: Subcutaneous injections of NovoRapid® 100 IU/mL at a fixed dose of 12 IU. Batch number: AS60040.

Duration of treatment: The average duration of trial participation for patients completing the study was estimated to be approximately eight weeks and the duration of the total trial to be three months. The entire study lasted 50 days and each sequence of injection was inferior to 4 weeks.

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Criteria for evaluation:
Efficacy:

The primary efficacy variable was the mean time to reach half-maximal insulin concentration ($TINS_{0.5max}$) following three consecutive doses of 12 IU BCI in comparison to three consecutive doses of 12 IU IAS.

Pharmacokinetic secondary efficacy variables were: time to reach maximal insulin concentration ($TINS_{max}$), maximal insulin concentration (INS_{max}), time to reach half-maximal insulin concentration after T_{max} ($TINS_{-0.5max}$), $AUC\text{-}INS_{(0\text{-}1h)}$, $AUC\text{-}INS_{(0\text{-}3h)}$ and $AUC\text{-}INS_{(0\text{-}6h)}$ and the variability of these parameters.

Additional pharmacodynamic efficacy variables were: maximal glucose infusion rate (GIR_{max}) as determined by the euglycemic glucose clamp technique, time to maximal GIR ($TGIR_{max}$), time to half-maximal GIR before and after T_{max} ($TGIR_{0.5max,}$ $TGIR_{-0.5max)}$, $AUC\text{-}GIR_{(0\text{-}3h)}$ and $AUC\text{-}GIR_{(0\text{-}6h)}$, time to reach baseline GIR and variability of all pharmacodynamic variables.

Safety:

Safety and tolerability were assessed by monitoring the frequency of adverse events, injection site reaction(s), clinical examination and laboratory safety parameters (hepatic and renal parameters, lipids, and blood cell count) of all patients.

Statistical methods:

Standard descriptive summary statistics were calculated for continuous variables (i.e. arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values). Categorical data were presented in frequency tables using counts and percentages. To test differences for statistical significance, Student's one-sided paired t-test was conducted to confirm non-inferiority of BCI vs. IAS. Due to the shape of the time course of insulin levels, INS_{max} (and derived kinetic values) were calculated with two methods i) the "three points plateau method" and ii) the actually measured maximum values. The latter method was also used to calculate GIR_{max}. The variables Time to reach half-maximal levels of GIR and INS before ($TGIR_{0.5\ max}$, $TINS_{0.5max}$) and after ($TGIR_{-0.5\ max}$, $TINS_{0.5max}$) the maximal level were calculated by linear interpolation. The area under the curve (AUC) was calculated according to the trapezoidal rule for GIR and insulin. Three analysis sets (safety analysis set (SAS), full analysis set (FAS), and per protocol set (PPS)) were planned for evaluation. The FAS and PPS were identical and data were therefore evaluated for two analysis sets (FAS/PPS and SAS).

Summary - Conclusions:

Efficacy results:

The primary efficacy variable was the time required to reach half-maximal plasma insulin level ($TINS_{0.5max}$). Regardless of the mode of calculation of INS_{max} ("three points plateau method", "actually measured maximum"), BCI administration resulted in a statistically significant faster achievement of $TINS_{0.5max}$ than IAS administration (14.7 min vs. 26.4 min with the "three points plateau method", p = 0.000; 17.3 min vs. 27.6 min with actually measured maximum, p = 0.000).
Results of the pharmacokinetic variables were:

- the time to reach maximum insulin level $TINS_{max}$ differed in dependence of the mode of calcu-

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lation: whereas the "three points plateau method" yielded $TINS_{max}$ faster after administration of BCI (BCI: 33.3 min, IAS: 50.7 min; p = 0.000), it was the opposite when the actually measured INS_{max} was used for calculation (BCI: 114.9 min, IAS: 64.2 min; p = 0.000);

- the maximum insulin level INS_{max} was significantly lower after BCI vs. IAS treatment regardless whether the "three points plateau method" (BCI: 357 pmol/L, IAS: 764 pmol/L; p = 0.000) or the actually measured maximum value (BCI: 442 pmol/L, IAS: 805 pmol/L; p = 0.000) was used for calculation;
- more time was required to reach half-maximal plasma insulin level after INS_{max} ($TINS_{-0.5max}$) following BCI vs. IAS administration using both the "three points plateau method" (BCI: 309 min, IAS: 182 min; p = 0.000) and the actually measured maximum values (BCI: 305 min, IAS: 182 min; p = 0.000). $TINS_{-0.5max}$ was not reached during the clamp period in a number of patients, especially those treated with BCI.
- Although the AUC values were lower following BCI administration, the difference of AUC between IAS and BCI decreased with increasing time of the clamp procedure: $AUC\text{-}INS_{(0\text{-}1\ h)}$ (BCI: 16393 min·pmol/L, IAS: 26891 min·pmol/L; IAS vs. BCI +64%), $AUC\text{-}INS_{(0\text{-}3\ h)}$ (BCI: 62132 min·pmol/L, IAS: 94769 min·pmol/L; IAS vs. BCI +53%) and AUC- $INS_{(0\text{-}6\ h)}$ (BCI: 115004 min·pmol/L, IAS: 132134 min·pmol/L; IAS vs. BCI +15%).

The following results were obtained for the pharmacodynamic variables:

- the maximum glucose infusion rate ($GIR_{max)}$ was statistically significantly lower after BCI vs. IAS administration (BCI: 7.1 mg/min/kg, IAS: 8.7 mg/min/kg; p = 0.000);
- the time to reach maximum GIR ($TGIR_{max)}$ calculated with the actually measured GIR_{max} was statistically significant longer after BCI injection (BCI: 193 min, IAS: 118 min; p = 0.000);
- the time to reach initial half-maximal GIR ($TGIR_{0.5max}$) was identical for both insulins (BCI: 53.0 min, IAS: 52.8 min; p = 0.980);
- the half-maximal GIR after GIR_{max} ($TGIR_{-0.5max}$) was reached faster after BCI administration than after IAS injection (BCI: 250 min, IAS: 273 min; p = 0.361);
- the total levels of glucose infusion rates were statistically significantly higher after treatment with IAS than after BCI injection during both the first three hours ($AUC\text{-}GIR_{(0\text{-}3\ h)}$; BCI: 676 min·mg/ml/kg, IAS: 911 min·mg/ml/kg; p = 0.000) and the entire duration of the clamp procedure ($AUC\text{-}GIR_{(0\text{-}6\ h)}$; BCI: 1654 min·mg/ml/kg, IAS: 1865 min·mg/ml/kg; p = 0.003).
- Time to reach baseline GIR could not be calculated.

The inter- and intra-patient variability of results for pharmacodynamic variables was predominantly higher ($TGIR_{0.5max}$, $TGIR_{-0.5max}$, $AUC\text{-}GIR_{(0\text{-}3\ h)}$, $AUC\text{-}GIR_{(0\text{-}6\ h)}$) after BCI treatment. For GIR_{max} an increased intra-patient variability was assessed upon BCI administration and the inter-patient variability of this parameter shows a trend towards a higher variability, too. The results regarding $TGIR_{max}$ were diverse with a trend towards a reduced inter-patient variability and an increased intra-patient variability following BCI administration.

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Safety results:

A total of 26 adverse events was reported in this study, the majority of which occurred during the clamp procedures (15 after IAS administration, 9 after BCI administration). None of AEs recorded was indexed as serious.
The majority of AEs was 'metabolism and nutrition disorders', 'nervous system disorders' and 'administration site conditions' as coded by system organ class. Relatedness to study drug was not excluded for six AEs (causality assessment: 1x "certain" after IAS injection, 2x "probable/likely" after BCI injection, 2x "possible" immediately after BCI injection and 5 days after BCI injection).
Hypoglycemic events occurred more often after IAS injection (6 of 8 hypoglycemic events).
More injection site reactions were observed after BCI administration (2x 'warming', 2x 'burning pain', 1x 'redness') vs. IAS injection (1x 'redness').

Conclusion:

The injection of BioChaperone® rhInsulin results in a statistically significant faster achievement of the half-maximal plasma insulin level ($TINS_{0.5max}$) than the injection of NovoRapid® (Insulin Aspart). In addition, the Maximal insulin concentration (INS_{max}) as well as the pharmacokinetic variables AUC-$INS_{(0\text{-}1\ h)}$, AUC-$INS_{(0\text{-}3\ h)}$, AUC-$INS_{(0\text{-}6\ h)}$ were considerably lower after BCI injection.

Inter- and intra-patient variability of pharmacodynamic secondary variables was predominantly higher after BCI treatment, whereas no tendency regarding variability of pharmacokinetic parameters was seen for either study medication.

A higher number of adverse events was observed after IAS administration but more injection site reactions were reported after BCI injection. However, both study drugs were well-tolerated and did not lead to serious or unexpected adverse events.

The onset-of-absorption of BioChaperone® rhInsulin is non-inferior to the onset-of-absorption of the reference treatment NovoRapid® (insulin Aspart).

BioChaperone® rhInsulin is as well tolerated as marketed insulin both at systemic and local levels after 60 injections in type-1 diabetes patients.

Date of the report: April 13, 2012