Better Postprandial Glucose (PPG) Control with BioChaperone® Combo (BC Combo) than with Lispro Mix25 (LMx) or separate Glargine & Lispro (G+L) Administrations in Subjects with Type 2 Diabetes (T2DM)

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Abstract

BC Combo is a co-formulation of prandial insulin lispro (25%) and basal insulin glargine (75%) with a rapid "prandial" insulin component and prolonged flat "basal" component compared to LisproMix (LMx). In this study the effects of BC Combo on PPG vs. LMx and Glargine + Lantus (G+L) were investigated. Thirty-nine T2DM subjects (mean ± SD age 60.8 ± 7.5 years and HbA1c 8.0 ± 0.6 %) received the three insulin combinations immediately before a standardised solid meal test (MMT, 20% protein 30% fat 50% carbohydrates) in a double-blind, double-dummy, randomised crossover design. The individual insulin dose was the same for each visit day (mean 0.62 U/kg). BC Combo improved early PPG compared to LMx (reduction $\Delta AUC_{BG\_0\text{-}2h}$ of 18%, p=0.0009) and G+L (reduction $\Delta AUC_{BG\_0\text{-}2h}$ of 10%, p=0.0450) (primary endpoint). The proportion of subjects experiencing symptomatic hypoglycaemic events (plasma glucose <70 mg/mL) over 24h was lower with BC Combo (15.8%) vs. LMx (32.4%) and G+L (21.6%). The total insulin PK profile of BC Combo showed a faster time to insulin peak and a lower exposure in the late prandial phase (2-6 h) than LMx and G+L. In conclusion, BC Combo demonstrated superior PPG control in T2DM subjects with fewer subjects experiencing symptomatic hypoglycaemia compared to both LMx and separate G+L.

Introduction & Background

- Use of premix insulin formulations like LisproMix (LMx) allows simultaneous administration of short-acting and long-acting insulin in one injection which might increase treatment compliance and improve overall glycaemic control in patients with type 2 diabetes.
- So far, it has been impossible to design a premix insulin with insulin glargine as basal component due to the reduced solubility of insulin glargine at neutral pH and the impossibility to mix it with prandial insulin.
- BioChaperone® Combo (BC Combo) is an innovative insulin formulation with a BioChaperone® excipient, combining the already approved insulin analogues lispro (25%) as fast-acting component and glargine (75%) as basal component.

Aims of the study

- To compare postprandial glucose (PPG) excursions after a standardised meal between BC Combo and LMx in patients with T2DM.
- To compare postprandial glucose (PPG) excursions after a standardised meal between BC Combo and simultaneous separate injections of glargine and lispro (G+L) in patients with T2DM.
- To assess the pharmacokinetic (PK) exposure of BC Combo, LMx and G+L after administration of a subcutaneous dose.
- To investigate safety and tolerability of BC Combo.

Methods

- Two-centre, randomised, double-blind, double-dummy, 3-treatment, 3-period crossover phase 1 trial.
- Male or female subjects aged 18 to 70 years (both inclusive) with T2DM ≥12 months, HbA1c between 7 and 9.5% (both inclusive), a body mass index (BMI) between 20 and 40 kg/m² (both inclusive), treated with once daily injections with insulin glargine U-100 or insulin glargine U-300 for at least 3 months prior to screening with a total insulin dose <1.2 U/kg/day and a dose of insulin glargine ≥0.2 U/kg/day were allowed to participate in the trial after having given written informed consent.
- In random order, BC Combo, LMx or G+L were administered over 3 days, separated by a wash-out phase of 5-21 days. PPG excursions and PK were assessed over 6 hours after insulin administrations immediately before standardised solid meals (610 kcal, 50% carbohydrates, 30% fat, 20% protein) on Day 2 and Day 3 of each treatment period
- Prior to the test meals, blood glucose (BG) was stabilised at 110 mg/dl ± 10% with i.v. infusion of insulin glulisine or glucose. These infusions were stopped no later than 30 min before insulin dosing.
- BG levels were monitored at 4-30 minute intervals in the first 5 hours with a final sample taken at 6 hours post-dose.

Statistical Analysis

- For normally or log-normally distributed endpoints, the difference in means between treatments was analysed in a mixed effect linear model with untransformed (ΔBG_{max}, BG_{min} and $AUC_{Tot,0\text{-}30min}$) or log-transformed endpoints as response variable, treatment, trial centre, period and sequence as fixed effects and subject within sequence as a random effect. If the trial centre effect was not significant, the analyses were done without trial centre as factor.
- Other PK and PD endpoints, and time in hypoglycaemia and in target range were analysed using the Wilcoxon Signed Rank Test.
- Comparison of the number of hypoglycaemic events between the treatments was performed by frequency analyses using Fisher's Exact Test.
- A two-sided significance level of 5% was used.

Disposition of subjects

- Out of 56 subjects screened, 17 were screen failures, 39 were randomised & exposed (Full analysis set), and 36 completed.

Baseline characteristics of the study population

- All subjects were white with 9 (23.1%) females and 30 (76.9%) males.
- The mean age was 60.8 ± 7.5 years (mean ± SD) with a diabetes duration of 13.4 ± 5.4 years. The BMI was of 31.4 ± 4.1 kg/m². HbA1c at screening was 8.0 ± 0.64%.
- All subjects used once daily injection with insulin glargine, either alone or in combination with insulin lispro (n=9) or insulin glulisine (n=8).

Results

Pharmacokinetics

- BC Combo showed an earlier onset of appearance (Early $t_{0.5max}$) and higher early PK exposure in the first hour compared with LMx and G+L (Fig. 1a & Table 2).
- BC Combo reached similar maximum concentrations but significantly earlier than both LMx and G+L.
- After reaching t_{max}, PK-profiles declined more rapidly with BC Combo than with LMx with lower exposure from 2 to 6 hours indicating a faster transition from prandial to basal insulin exposure.
- Total exposure over 6 hours was lower with BC Combo than with LMx or G+L, but as expected PK-exposure was ongoing with all three insulins at the end of the test meal period.

Pharmacodynamics

- BG profiles correlated well with PK profiles.
- BC Combo significantly reduced mean maximum postprandial blood glucose concentrations and the postprandial glucose excursions over the first 2 hours compared with LMx and G+L (Fig. 1b & Table 1).
- Mean PPG excursions decreased below baseline with all insulins in the late postprandial phase, but more slowly with BC Combo than with LMx and G+L resulting in lower minimum BG with LMx and G+L.
- The total area under the BG concentrations curve was similar between the insulins.

Safety

- All insulins were well-tolerated and no differences in Adverse Event rate and local tolerability were seen.
- Hypoglycaemia (defined as plasma glucose <70 mg/mL) occurred most often during the meal test period (93 out of 99 events). No event was serious or of severe intensity and all subjects recovered.
- The number of hypoglycaemic events during the test meal period was significantly lower with BC Combo versus LMx (p=0.0028) and tended to be lower versus G+L. Likewise, the number of patients experiencing hypoglycaemia and hypoglycaemia rate were lowest for BC Combo, Table 3).
- Subjects spent significantly (p=0.0384) more time in the pre-defined target range (BG 72-162 mg/dL) and numerically less time in hypoglycaemia after dosing with BC Combo compared with LMx (p=0.1433) (Table 3).

Table 1: Blood glucose parameters (LS-Mean)

Parameter	LS Means BC Combo (n=38)	LS Means LMx (n=37)	p value	LS Means BC Combo (n=38)	LS Means G+L (n=37)	p value
Early prandial phase (0-2h)						
$\Delta AUC_{BG\_0\text{-}1h}$ [mg.h/dL]	35.150	43.488	**0.0004**	35.144	41.137	**0.0020**
$\Delta AUC_{BG\_0\text{-}2h}$ [mg.h/dL]*	108.177	131.551	**0.0009**	108.396	120.266	**0.0450**
ΔBG_{1h} [mg/dL]	68.0	84.2	**0.0006**	68.0	78.4	**0.0055**
ΔBG_{max} [mg/dL]	79.4	93.6	**0.0139**	79.4	85.5	0.2346
Late prandial phase (2-6h)						
$\Delta AUC_{BG\_2\text{-}6h}$ [mg.h/dL]	99.846	76.727	0.0928	101.192	69.031	0.0506
ΔBG_{6h} [mg/dL]	-22.8	-33.1	**0.0154**	-22.7	-26.6	0.2592
ΔBG_{min} [mg/dL]	-27.8	-37.4	**0.0017**	-27.6	-31.9	0.0628
BG_{min} [mg/dL]	79.8	70.1	**0.0007**	80.1	75.2	**0.0412**
Total prandial phase (0-6h)						
$\Delta AUC_{BG,0\text{-}6h}$ [mg h/dL]	208.044	208.442	0.9819	209.585	189.329	0.3015

*primary endpoint, p<0.05 in bold
(Δ)AUC_{BG} : (incremental) area under the blood glucose curve, $\Delta BG_{max/min}$: maximal/minimal blood glucose excursion, BG_{min}: minimum blood glucose concentration, ΔBG_{1h} : blood glucose excursion 1h after the start of the meal

Figure 1: Mean PK (a) and BG (b) profiles

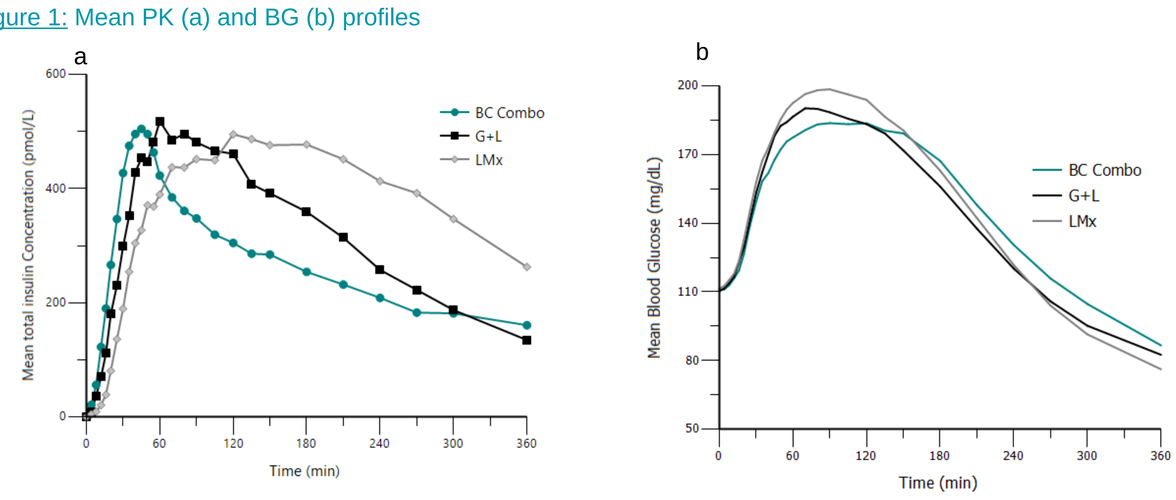

Table 2: Pharmacokinetic parameters (LS-Mean)

Parameter	LS Means BC Combo (n=38)	LS Means LMx (n=37)	p value	LS Means BC Combo (n=38)	LS Means G+L (n=37)	p value
$AUC_{0\text{-}30min}$ [pmol.h/L]	92.6	28.8	**<.0001**	92.5	57.8	**0.0007**
$AUC_{0\text{-}1h}$ [pmol.h/L]	281.9	149.3	**<.0001**	283.7	218.8	**0.0022**
$AUC_{2\text{-}6h}$ [pmol.h/L]	745.1	1312.4	**<.0001**	746.5	858.3	0.0789
$AUC_{0\text{-}6h}$ [pmol.h/L]	1351.7	1878.8	**<.0001**	1356.8	1559.6	**0.0069**
C_{max} [pmol/L]	500.9	495.3	0.8537	515.5	533.4	0.5538
t_{max} [h]	0.722	2.228	**<.0001**	0.731	1.239	**<.0001**
Early $t_{0.5max}$ [h]	0.351	0.667	**<.0001**	0.351	0.511	**<.0001**

p<0.05 in bold

Table 3: Incidences of hypoglycaemic episodes and time spent in hypoglycaemia and in target range during meal test

Parameter	BC Combo (n=38)	LMx (n=37)	G+L (n=37)
	N (%) / E		
Overall	15 (39.5) / 24	21 (56.8) / 46	19 (51.4) / 29
Overall – meal test	14 (36.8) / 22	20 (54.1) / 43	19 (51.4) / 28
N = number of subjects, % = percentage of subjects, E = number of events			
Parameter	**Mean (SD)**		
Time in Hypoglycaemia	17.9 (34.06)	26.5 (42.83)	21.2 (37.73)
Time in Target Range	201.9 (64.93)	183.1 (55.41)	195.7 (70.95)
Unit: min Hypoglycaemia: BG <63 mg/dL Target range: BG 72-162 mg/dL. Ranges derived from serial blood sampling up to 6 hours after the test meal.			

Conclusions

- BC Combo showed a faster rise in insulin concentrations and a higher early insulin exposure than both Humalog Mix and separate injections of glargine and lispro resulting in improved postprandial control in the first two hours after a test meal.
- Late PK-exposure from 2 to 6 hours was lower with BC Combo which reduced the decline of BG concentrations below baseline and the rate of postprandial hypoglycaemia compared to LMx.

This study was sponsored by Adocia and performed by Profil.
NCT trial number: NCT02915250
Presented at the 12th International Conference on Advanced Technologies & Treatments for Diabetes, February 20 – 23, 2019, Berlin, Germany
ATT19-0194