Ultra-Rapid BioChaperone® Lispro Improves Post-Prandial Blood Glucose Control vs. Humalog® in a 14-day Treatment Study in Subjects with Type 2 Diabetes

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Abstract

BioChaperone Lispro (BC Lispro) is an ultra-rapid insulin lispro formulation designed to better mimic the physiological timing of prandial insulin action. We investigated safety and post-prandial blood glucose (PPG) control with BC Lispro and Humalog® (LIS) in a double blind randomized crossover study in 51 T2DM participants treated with multiple daily injections [mean±SD age: 62±9 yrs; BMI: 30.5±4.1 kg/m²; HbA1c: 7.1±0.8%]. Participants used individualized doses of BC Lispro or Humalog® as prandial insulin immediately before meals with unchanged basal regimens during two 14-day outpatient periods. PPG and pharmacokinetics were assessed during individualized solid mixed meal tests (MMTs) (50% carbs, 30% fat, 20% proteins) on days 1, 2, 13 and 14. BC Lispro and Humalog® were well tolerated with no injection site reactions, similar overall hypoglycemic events and comparable outpatient glycemia based on SMPG. Daily prandial insulin doses were ~10% lower with BC Lispro than with Humalog®. BC Lispro showed a significantly faster absorption than Humalog® with faster-in and faster-out characteristics underlined by significant reduction of early- and late-time-to-half-maximal insulin lispro blood concentrations by -21% (p<0.0001) and -11% (p<0.013) respectively. These characteristics were maintained after 14 days of use. BC Lispro resulted in a significantly improved PPG control with >20% reductions in the first 2 hours when all MMTs were analyzed, mainly driven by differences on days 13-14. In conclusion, BC Lispro was well-tolerated over 14 days of MDI treatment and significantly improved PPG control vs. Humalog® in subjects with T2DM.

Introduction & Background

- Rapid analogs are not able to match the speed of physiological post-meal insulin secretion seen in healthy individuals and ultra-rapid acting formulations should result in tighter post-prandial blood glucose control.
- BioChaperone® Lispro is an-ultra-rapid insulin lispro formulation based on the BioChaperone® technology of polymers and oligomers derived from natural molecules. BC Lispro contains the BioChaperone BC222 and citrate to accelerate the absorption of insulin lispro
- Previous clinical trials in T1DM subjects demonstrated:
  - A faster absorption of insulin lispro with BC Lispro compared to Humalog® (2.68-fold higher $AUC_{0\text{-}30min}$) with similar total exposure at a dose of 0.2 U/kg[a]
  - A reduction of 61% in incremental $AUC_{BG\_0\text{-}2h}$ vs. LIS after a liquid meal test[a]
  - A proportional dose-exposure relationship in the range 0.1 – 0.4 U/kg[b]

Objective of the study

- To compare the post-prandial glucose (PPG) response to an individualized solid mixed meal after bolus administration of BC Lispro or LIS immediately before the meal in participants with T2DM.
- To compare PK profiles of BC Lispro and LIS.
- To investigate safety and tolerability of BC Lispro.

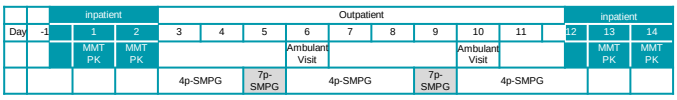
Methods

- Randomized, bi-centric, double-blind, comparator-controlled, two-period 14-day crossover phase 1 trial in participants with T2DM.
- Participants self-administered individualized bolus doses of BC Lispro or LIS for 14 days with random allocation to treatment sequence. Participants were not supposed to change basal insulin except for safety reasons.
- Each period consisted of 14 inpatient and outpatient days (Fig.1). Patients arrived at the clinic in the evening of days -1 and 12, and received a standardized dinner. In the morning of days 1, 2, 13 and 14, an individualized mixed meal was served and covered by an individualized dose of BC Lispro or LIS. BG was adjusted to 126 mg/dL ± 10% prior to the meal using intravenous infusions of insulin or glucose.
- Blood samples for PK assessments were collected at pre-specified timepoints during MMT procedures. Free immunoreactive insulin lispro concentrations were measured with a validated assay.
- In the afternoon of day 2, the participants left the clinical site for an outpatient period until day 12, with ambulant safety visits on days 6 and 10.
- Participants performed 4-point SMPGs on outpatients days and 7-point SMPGs on days 5 & 9.

Statistical Analysis

- The difference in means between BC Lispro and LIS was analyzed in a mixed-effect linear model with log-transformed endpoints of day 1/2 (mean of day 1 & 2) and day 13/14 (mean of day 13 & 14) as response variable, treatment, period, sequence, day (1/2 and 13/14) and treatment*day (as interaction) as fixed effects and subject within sequence as a random effect (trial center effect was not significant).
- For the endpoints analyzed using an additive model (not log-transformed endpoints), treatment ratios and 95% confidence intervals were calculated by Fieller's method.
- Statistical tests between treatments were two-sided and were performed at the 5% level of significance.

Figure 1: Design of each 14-day period



Baseline characteristics of the study population

Parameter	Mean ± SD	Parameter	Mean ± SD
Race	White n=50 American Indian or Alaska Native n=1	Diagnosis of T2DM (years)	15.8 ± 7.5
Sex	Male n=42 (82.4%) Female n= 9 (17.6%)	Age (years)	61.9 ± 9.1
Weight (kg)	92.4 ± 15.7	Waist circum. (cm)	106.7 ± 11.1
Height (cm)	174 ± 8	HbA_{1c} (%)	7.1 ± 0.8
BMI (kg/m^2)	30.5 ± 4.1	eGFR ($mL/min/1.73m^2$)	86.4 ± 13.4
Type of basal insulin	Isophane insulin (n=18) Insulin glargine (n=14)		Insulin detemir (n=10) insulin degludec (n=1)

67 subjects screened, 16 screening failures, 51 randomized & exposed, 49 completers.
Full analysis set n=51

Results

Pharmacokinetics

- BC Lispro PK profiles were characterized by a left shift vs. LIS with a "faster-in/faster-out" phenomenon as indicated by an earlier time to early half maximal insulin lispro concentration, a greater early insulin lispro exposure over the first three hours and an earlier time to late half maximum insulin lispro concentration (Fig 2a, Table 2).
- Insulin lispro was absorbed faster with BC Lispro than LIS on days 1-2. The faster PK of BC Lispro was maintained at days 13-14, after up to two weeks of self-administration (Table 2).

Pharmacodynamics

- Composite analysis across all meal test days demonstrated a significant reduction in incremental PPG exposure (~20%) for up to 3 hours after dosing with BC Lispro compared with LIS, as indicated by a reduction in maximum glucose excursions and glucose excursions at one hour. The differences in glycemic excursions were more pronounced and significant on days 13 and 14.(Fig. 2b, & Table 2).
- 7-point SMPG profiles did not demonstrate any clear difference between treatments.
- Basal insulin doses remained constant whereas daily prandial insulin doses were up to 10% lower with BC Lispro.

Safety

- 19 adverse events (AE) occurred in 14 participants with BC Lispro vs. 28 AEs in 16 participants with LIS.
- One serious adverse event (acute coronary syndrome in a 71-year-old patient) occurred in the washout period after BC Lispro and was judged to be unlikely related to investigational drug.
- One mild injection site induration occurred with BC Lispro vs. 2 injection site redness and 1 injection site edema with LIS.
- There was no evidence for increased risk of hypoglycaemia (plasma glucose<70 mg/dL or hypoglycaemic symptoms) with BC222 insulin lispro (Fig. 3 and table 3).

Table 2: Pharmacokinetic and blood glucose parameters (LSM)

	Parameter	Treatment	Days 1-2	Means Days 13-14	all days	p value BC Lispro vs LIS all days
PK parameters	$AUC_{LIS\_0\text{-}30min}$ (pmol*h/L)	BC Lispro	91	103	99	<0.0001
		LIS	50	64*	58	
	$AUC_{LIS\_0\text{-}2h}$ (pmol*h/L)	BC Lispro	763	783	778	<0.0001
		LIS	666	682	679	
	$AUC_{LIS\_0\text{-}3h}$ (pmol*h/L)	BC Lispro	1055	1068	1067	0.0027
		LIS	980	987	988	
	$AUC_{LIS\_2\text{-}6h}$ (pmol*h/L)	BC Lispro	613	594	606	0.0018
		LIS	688	637*	666	
	$AUC_{LIS\_0\text{-}last}$ (pmol*h/L)	BC Lispro	1400	1399	1404	0.0619
		LIS	1375	1322	1352	
	Early T0.5max (h)	BC Lispro	0.372	0.348	0.365	<0.0001
		LIS	0.469	0.416*	0.448	
Blood glucose parameters	$\Delta AUC_{BG\_0\text{-}1h}$ (mg*h/dL)	BC Lispro	17.7	15.6	16.7	0.0025
		LIS	20.4	22.3	21.4	
	$\Delta AUC_{BG\_0\text{-}2h}$ (mg*h/dL)	BC Lispro	47.7	39.7	43.6	0.0041
		LIS	50.3	62.0*	56.1	
	$\Delta AUC_{BG\_0\text{-}6h}$ (mg*h/dL)	BC Lispro	63.3	49.0	55.9	0.3816
		LIS	54.5	77.2	67.3	
	ΔBGmax (mg/dL)	BC Lispro	51.0	51.0	51.0	0.0107
		LIS	56.1	61.2	58.6	
	ΔBG1h (mg/dL)	BC Lispro	35.0	29.0	32.0	0.0018
		LIS	37.6	43.2	40.5	

* indicates a significant difference within treatment between day 1-2 and day 13-14
AUC_{LIS} : area under the serum lispro concentration curve
Early T0.5max : Time to half-maximal observed serum lispro concentration
ΔAUC_{BG} : incremental area under the blood glucose curve
ΔBGmax : maximal blood glucose excursion
ΔBG1h : blood glucose excursion 1h after the meal start

Figure 2: Mixed meal test mean±SE PK (a) and BG (b) profiles for all tests days.

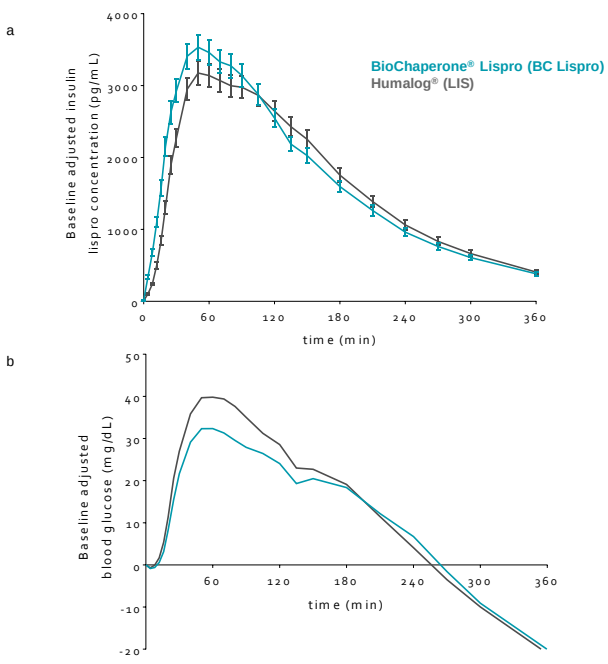


Figure 3: Cumulative number of hypoglycemic events during meal tests

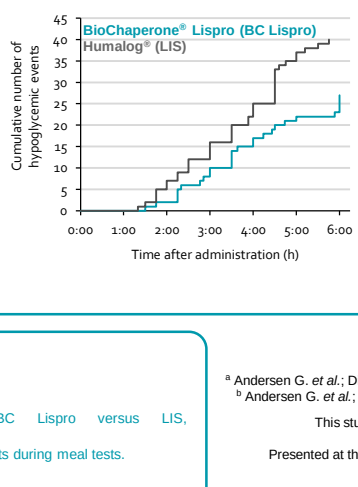


Table 3: Number of hypoglycemic events and number of subjects with hypoglycemia

	BC Lispro	LIS
6 hours post-meal test (Day 1, 2, 13, 14)	27 / 13	40 / 14
24 hours inpatient (Day 1, 2, 13, 14)	35 / 17	47 / 16
All outpatient days	33 / 18	19 / 13
Number of events / number of subjects		

Conclusions

- BC Lispro exhibits an accelerated insulin lispro absorption profile compared with LIS.
- The ultra-rapid PK properties of BC Lispro were sustained in a basal-bolus insulin regimen over 14 days.
- These PK properties led to significant reductions in PPG excursions with BC Lispro versus LIS, more pronounced and significant on days 13 and 14.
- This reduction in glycemic excursions was achieved without an increase in number of hypoglycemic events during meal tests.
- In outpatient days, similar SMPG profiles were obtained, with numerically lower doses of BC Lispro.
- The treatment with BC Lispro over 14 days was safe and well tolerated.

References:

[a] Andersen G. *et al.*; Diabetes, 2016 June; volume 65, supplement 1 294-OR
[b] Andersen G. *et al.*; Diabetes, 2015 June; volume 64, supplement 1 979-P

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