Ultra-Rapid BioChaperone Insulin Lispro (BC LIS): Linear Dose-Response and Faster Absorption than Insulin Lispro (LIS)

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Abstract

Background and aims: This double-blind, randomised, four period crossover study investigated the dose-response relationship of BC LIS, a novel ultra-rapid insulin lispro formulation.
Materials and methods: Thirty-eight male patients with type 1 diabetes received single doses of 0.1, 0.2 and 0.4 U/kg of BC LIS and 0.2 U/kg of LIS under automated euglycemic clamp conditions (ClampArt®, clamp duration 12h post-dosing).
Results: Mean baseline adjusted insulin (INS) profiles are given in the Figure 1. Ultra-rapid properties of BC LIS were confirmed with significantly greater early exposure and higher glucose infusion rates (GIR) in the first hour post-dosing than LIS at 0.2 U/kg ($AUC_{INS(0-1h)}$ 71 vs. 48 h*mU/L, $AUC_{GIR(0-1h)}$ 205 vs. 122 mg/kg, all comparisons p <0.001). Late effect was significantly lower for BC LIS ($AUC_{GIR(3-8h)}$ 357 vs. 446 mg/kg, p=0.0115). Dose-proportionality was established for early and total exposure of BC LIS ($AUC_{INS(0-12h)}$ 102 vs 205 vs 444 h*mU/kg, 0.1 vs 0.2 vs 0.4 U/kg) and dose-linearity for pharmacodynamics ($AUC_{GIR(0-12h)}$ 726, 1357 and 2422 mg/kg for 0.1, 0.2 and 0.4 U/kg). BC LIS was well tolerated; no injection site reactions were observed.
Conclusion: BC LIS shows dose-linear absorption and action at clinically relevant doses of up to 0.4 U/kg in subjects with type 1 diabetes. Because of its ultra-rapid action BC LIS has the potential to improve postprandial glucose control.

Introduction

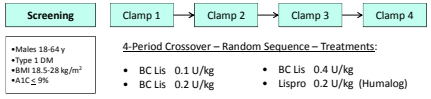
- Current prandial insulin analogues do not act fast enough to fully match the kinetics of the physiological post-meal insulin secretion.
- BioChaperone is a library of excipients derived from naturally occurring molecules designed to enhance the effectiveness and safety of therapeutic proteins and their ease of use for patients.
- BioChaperone Insulin Lispro (BC LIS) has been developed as a second generation of prandial insulin analog lispro aimed at further improving the pharmacokinetic (PK) and glucodynamic properties of currently marketed insulins and insulin analogues.

Objective: Characterize BC LIS dose-response and compare time-action profile versus equivalent dose of LIS (Humalog) in patients with type I diabetes.

Methods

- This was a randomized, single-center, double-blind, four-way crossover euglycemic clamp study in male subjects with type I diabetes.
- Euglycemic Clamp Schedule - 4 test days each included 12-hour euglycemic clamps after administration of BC LIS at a dose of 0.1, 0.2 or 0.4 U/kg or LIS at 0.2 U/kg in random order.
- Pharmacokinetics of insulin were determined with an immunoradiometric sandwich assay
- Pharmacodynamics of insulin were assessed based on Glucose infusion rates (GIR).

Study Schematic



4-Period Crossover – Random Sequence – Treatments:

- BC Lis 0.1 U/kg
- BC Lis 0.2 U/kg
- BC Lis 0.4 U/kg
- Lispro 0.2 U/kg (Humalog)

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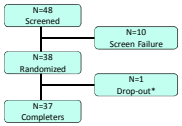
Subject Disposition & Demographics

Table 1: Subject Disposition and Demographics



*1 subject withdrew consent

Parameter	Mean (SD)
Age (years)	47 (11.7)
Height (m)	1.80 (0.05)
Weight (kg)	80 (7.8)
BMI (kg/m²)	24.7 (1.9)
Diabetes duration (years)	23 (12.2)
HbA1c (%)	7.5 (0.8)
C-Peptide (nmol/L)	0.05 (0.05)

Statistical analysis

- Dose-response/exposure relationships of BC LIS were assessed using a regression model with the log-transformed endpoint as response variable and log-dose as independent variable.
- Dose linearity of PD endpoints were assessed using a regression model with the untransformed endpoint as response and dose and dose*dose as independent variable.
- Dose-response differences of BC LIS and treatment differences between BC LIS and LIS were analyzed using a linear mixed effect model with treatment, period and sequence as fixed effects and subjects within sequence as random effect.

Safety Results

- No serious or other significant adverse events occurred.
- One mild injection site reaction (mild erythema) occurred after dosing with LIS 0.2 U/kg.
- There were 14 mild (71%) or moderate (29%) adverse events rated as possibly related to study drug (10 with BC LIS and 4 with LIS). All subjects fully recovered from the adverse events.
- BC LIS was well tolerated with safety profile not different relative to LIS.

PKPD Results

Table 2: PK/PD Parameters

	BC LIS 0.1 U/kg	BC LIS 0.2 U/kg	BC LIS 0.4 U/kg	LIS 0.2 U/kg	p-value
Pharmacokinetic (PK) parameters, based on baseline adjusted total insulin (Ins) concentrations					
$C_{max\ Ins}$ [mU/L]*	52 (16)	99 (35)	190 (53)	90 (28)	0.0404
$t_{max\ Ins}$ [min]¹	40 (12; 105)	40 (25; 105)	45 (25; 120)	60 (25; 105)	< 0.0001
Early $t_{0.5max\ Ins}$ [min]*	14 (7; 28)	14 (8; 27)	15 (6; 32)	27 (12; 43)	< 0.0001
$AUC_{Ins(0-1h)}$ [h*mU/L]*	35 (16; 54)	70 (27; 119)	139 (55; 229)	48 (18; 84)	< 0.0001
$AUC_{Ins(0-12h)}$ [h*mU/L]¹	96 (40; 200)	195 (123; 449)	430 (322; 851)	201 (142; 504)	0.4039
Pharmacodynamic (PD) parameters, based on glucose infusion rates (GIR)					
GIR_{max} [mg/kg/min]*	4.8 (1.9)	7.4 (2.7)	10.2 (2.5)	6.6 (2.3)	0.0661
$t_{GIR\ max}$ [min]¹	83 (42; 169)	86 (55; 200)	109 (65; 221)	117 (71;225)	0.0005
Early $t_{0.5max\ GIR}$ [min]*	30 (11; 45)	32 (16, 63)	31 (23; 49)	42 (24; 81)	< 0.0001
$AUC_{GIR\ 0-30min}$ [mg/kg]¹	18 (0; 80)	42 (0; 94)	60 (8; 121)	0 (0; 63)	< 0.0001
$AUC_{GIR\ 0-1h}$ [mg/kg]*	137 (62)	205 (88)	296 (99)	123 (58)	< 0.0001
$AUC_{GIR\ 0-3h}$ [mg/kg]*	577 (199)	952 (350)	1411 (346)	821 (288)	0.0090
$AUC_{GIR\ 3-8h}$ [mg/kg]*	155 (97)	394 (206)	996 (337)	482 (239)	0.0115
$AUC_{GIR\ 0-12h}$ [mg/kg]*	734 (231)	1353 (443)	2424 (521)	1307 (374)	0.4461

* Values are mean ± SD, p-values are based on LS-Mean Difference for the comparison between 0.2 U/kg BC LIS and LIS.
¹ Values are median (min; max), p-values are based on the Wilcoxon-Signed Rank Test for the comparison between 0.2 U/kg BC LIS and LIS.

Figure 1: Differences in early insulin exposure between BC LIS and LIS (PK)

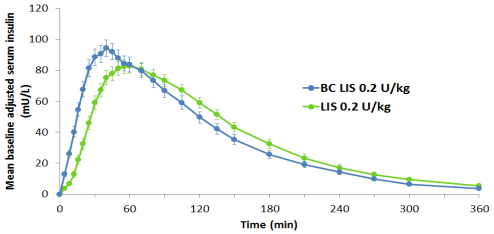
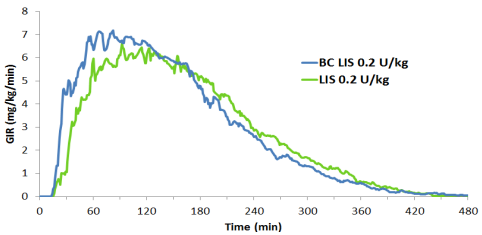


Figure 2: Differences in early metabolic effect between BC LIS and LIS (PD)



- BC LIS displayed an ultra-rapid absorption of insulin with a total exposure similar to LIS.
- Total glucodynamic effect was similar for BC LIS and LIS over the entire clamp interval ($AUC_{GIR(0-12)}$).
- Onset of action was significantly earlier for BC LIS than for LIS (defined as time from dosing until decrease in blood glucose by 5 mg/dl).
- Early glucodynamic effect was significantly stronger for BC LIS than for LIS both over 30 minutes, 1 hour and up to 3 hours post-dose.
- The glucodynamic effect in the late part of the GIR profile (3-8 hours post-dose) was significantly lower for BC LIS compared to LIS.
- BC LIS had a shorter duration of action than LIS as indicated by a significantly shorter time to late half maximum GIR (3.78 vs. 4.07 hours; p= 0.0004).
- Total exposure ($AUC_{LIS(0-12)}$) and maximum insulin concentration (C_{max}) increased proportionaly with increasing the dose of BC LIS.
- Dose-proportionality was established for BC LIS (all $AUCs_{BC\ LIS}$ and Cmax) as showed in the superimposed dose normalized profiles (Figure 3 inset).
- Dose-linearity was shown for pharmacodynamics (all $AUCs_{GIR}$ and GIR_{max}).

Figure 3: BC LIS proportional dose exposure (PK)

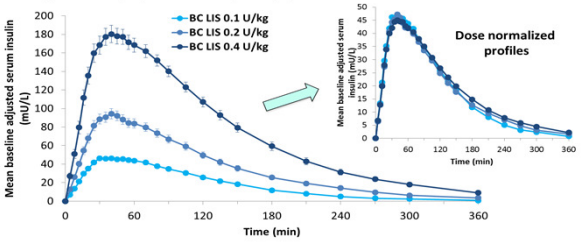
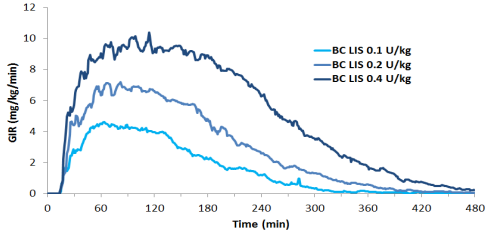


Figure 4: BC LIS linear dose response (PD)



Conclusions

- BC LIS showed a proportional dose-exposure relationship and a linear dose-response relationship across the dose-range of 0.1, 0.2 and 0.4 U/kg.
- BC LIS is an ultra-rapid insulin compared to Humalog as demonstrated both in PK and PD.
- Trial results confirm that BC LIS – in comparison to LIS – more closely mimics the prandial insulin secretion pattern. Therefore BC LIS has the potential to achieve a better postprandial glucose control.
- BC LIS is currently tested in a meal tolerance study in subjects with type I diabetes.

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