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ORIGINAL ARTICLE

Ultra-rapid BioChaperone Lispro improves postprandial blood glucose excursions vs insulin lispro in a 14-day crossover treatment study in people with type 1 diabetes

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Aim: To investigate the safety and efficacy of BioChaperone Lispo (BCLIS), an ultra-rapid formulation of insulin lispro (LIS) in people with type 1 diabetes.

Materials and Methods: In this randomized, double-blind study, participants self-administered individualized bolus doses of BCLIS or LIS during two 14-day periods in a crossover fashion. Postprandial blood glucose (BG) was assessed after individualized solid mixed meal tests (MMTs) (50% carbohydrate, 29% fat, 21% protein), with additional randomization for the sequence of timing of insulin administration, immediately (t0), 15 minutes before (t − 15) and 15 minutes after (t + 15) meal start on days 1, 2 and 3, and with t0 administration on day 14. Pharmacokinetic (PK) variables were assessed for t0 MMTs. Participants also used individualized BCLIS or LIS doses immediately before meals during two 10-day outpatient periods with an unchanged basal insulin regimen.

Results: Overall, 35 participants completed both treatment periods. In MMTs with t0 administration, the higher early postprandial PK exposure of BCLIS led to significant reductions in 1- to 2-hour postprandial BG excursions by 30% to 40% vs LIS and the accelerated absorption and action of BCLIS persisted over 14 days. There was no difference in glucose excursion over the full 360-minute postprandial period. Postprandial BG control was similar between BCLIS injected at t + 15 and LIS injected at t0. BCLIS was shown to have safety and tolerability similar to LIS. No injection site reactions occurred with BCLIS.

Conclusions: BCLIS was well tolerated and safe over 14 days of treatment and significantly improved postprandial BG vs LIS when administered at mealtime.

KEYWORDS

antidiabetic drug, insulin analogues, insulin therapy, pharmacokinetics, phase I-II study, type 1 diabetes

1 | INTRODUCTION

Rapid-acting insulin analogues are the current standard to control postprandial blood glucose (BG) excursions; however, they are not able to match the speed of physiological post-meal insulin secretion seen in healthy individuals, and faster-acting insulins are expected to result in tighter postprandial BG control and less hypoglycaemia.[1]

BioChaperone Lispro (BCLIS) is an ultra-rapid insulin lispro formulation which contains the novel excipient BioChaperone BC222 (an oligosaccharide modified with natural molecules) and citrate to accelerate the absorption of insulin lispro after subcutaneous administration. It is expected to offer people with diabetes the possibility of managing their BG levels with a higher degree of precision. This is achieved by a faster increase then decrease of hypoglycemic effect than with most commonly used rapid-acting insulin analogues. Previous clinical trials in people with type 1 diabetes (T1DM) demonstrated faster absorption of insulin lispro with BCLIS formulation than with commercial insulin lispro formulation (LIS; Humalog [Eli Lilly &

Chronology of a treatment period														
	Inpatient			Outpatient (self-monitored BG)										Inpatient
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	MMT t=−15/0/+15 PK if t=0	MMT t=−15/0/+15 PK if t=0	MMT t=−15/0/+15 PK if t=0				Ambulant visit							MMT t=0 PK

FIGURE 1 Design of each 14-day treatment period. MMT, mixed meal test; PK, pharmacokinetic assessment

Company]; 2.68-fold higher area under the curve $[AUC]_{Insulin\ 0\text{-}30\ minutes}$), with similar total exposure at a dose of 0.2 U/kg and a reduction of 61% in incremental area under the blood glucose concentration-time curve from 0 to 2 hours after a meal ($\Delta AUC_{BG\ 0\text{-}2\ hour}$) vs LIS after a liquid meal test.[2] In addition, a proportional dose-exposure relationship was shown in the range of 0.1 to 0.4 U/kg.[3]

In the present study, we investigated the pharmacodynamic (PD) and pharmacokinetic (PK) characteristics, safety and tolerability of BCLIS by comparing the postprandial BG response to individualized solid mixed meal tests (MMTs) with BCLIS or LIS injected before, at, or after a meal in people with T1DM.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a randomized, single-centre, double-blind, active comparator-controlled, multiple-daily-dose, two-period 14-day cross-over phase I trial in 36 people with T1DM. The design of each 14-day treatment period is shown in Figure 1.

The trial was approved by the local ethics committee and health authorities in accordance with Good Clinical Practice Guidelines (International Conference on Harmonization) and the Declaration of Helsinki. All participants gave written informed consent prior to initiation of any study-related activity. This study was registered at clinicaltrials.gov (NCT02528396).

2.2 | Participants

Men and women aged 18-64 years (both inclusive) with T1DM for ≥12 months, glycated haemoglobin (HbA1c) concentration ≤75 mmol/mol, fasting C-peptide level ≤0.30 nmol/L, body mass index (BMI) between 18.5 and 28.0 kg/m^2 (both inclusive), and on stable insulin regimens with multiple daily insulin injections for at least 12 months prior to inclusion, with a total insulin dose <1.2 (I)U/kg/d, were enrolled at Profil, Neuss, Germany. People with clinically relevant diseases, a history of ketoacidosis, recurrent severe hypoglycaemia and hypoglycaemia unawareness were excluded.

2.3 | Treatments

Participants self-administered individualized bolus doses of BCLIS or LIS for 14 days, followed by a washout period lasting 1-14 days to mitigate any carryover effects from the previous period, and then crossed over to the other treatment with random allocation to treatment sequences. Participants were instructed not to change their basal insulin regimen unless medically required.

2.4 | Assessments

Participants arrived at the clinic in the evening of days −1 and 13, and received a standardized dinner. In the morning of days 1, 2, 3 and 14, after BG had been adjusted to 7.0 mmol/L ± 10% prior to the meal with intravenous glucose or insulin, a solid mixed meal with a size individualized for BMI and gender, identical on all study days, was served. The meal content consisted of 21% protein, 29% fat and 50% carbohydrates. An individualized dose of BCLIS or LIS, based on the participant's usual insulin-to-carbohydrate ratio and the carbohydrate content of the meal, was administered. For each participant, the individualized dose of insulin was the same for BCLIS and LIS and for all MMTs. Randomization also determined the sequence of time of insulin administration on days 1, 2 and 3 at −15, 0 or +15 minutes relative to the meal start at t0. Insulin on day 14 was administered at t0. Blood was sampled before the meal, which was ingested within 15 minutes, and frequently thereafter up to 360 minutes. The MMT glucose endpoints were measured using the Super GL glucose analyser (Dr Müller Gerätebau GmbH, Freital, Germany). Hypoglycaemia was defined as a BG value <3.5 mmol/L (plasma equivalent 3.9 mmol/L).

The PK measurements of insulin lispro concentrations were carried out on the 2 days with insulin administration at t0. Insulin lispro concentrations in serum were measured using a validated enzyme-linked immunosorbent assay specific for insulin lispro, by Charles River Laboratories, Senneville, Canada. The lower limit of quantification of the method was 50 pg/mL for insulin lispro.

During the outpatient period from day 3 to day 13, participants injected themselves with their individualized dose of BCLIS or LIS and their regimen of basal insulin. The participants recorded each injected dose of bolus or basal insulin, their meals, and any adverse event, including hypoglycaemic episodes, in a diary. In addition, the participants had to perform and document at least 4 self-monitored BG measurements per day (before breakfast, before lunch, before dinner and at bedtime). During dosing visits, injection sites were marked and assessed for spontaneous pain, pain on palpation, itching, redness, oedema and induration/infiltration. Each was scored 0 (none), 1 (mild), 2 (moderate) or 3 (severe). This assessment was also done after 1 week of treatment and at the final follow-up.

2.5 | Statistical methods

The sample size calculation was based on the primary endpoint $\Delta AUC_{BG\ 0\text{-}2\ hour}$. Assuming a 19% reduction in the primary endpoint

with BCLIS compared with LIS, a 30% standard deviation of within-participant difference in response, there was ~90% power to detect a statistically significant difference with 30 completers.

The full analysis set was defined according to the intention-to-treat principle and included all randomized participants. Participants contributed to the evaluation "as randomized". The safety analysis set included all participants receiving at least 1 dose of the investigational product or its comparator. Participants in the safety analysis set contributed to the evaluation "as treated". Analyses of PK/PD endpoints were based on the full analysis set and analyses of the safety endpoints were based on the safety analysis set.

Phoenix WinNonlin (version 7.0, Certara, Princeton, New Jersey) was employed for all PK calculations, and the SAS System for Windows (version 9.4, SAS Institute Inc., Cary, North Carolina) statistical software for all other statistical calculations and all analyses. AUCs were calculated based on the linear trapezoidal rule and actual time points for measurements for specified time intervals, where t = 0 minutes is defined as the time of meal administration.

The primary PD endpoint was $\Delta AUC_{BG\ 0\text{-}2\ hour}$, with administration at t0 on days 1 to 3; the primary PK endpoint was area under the serum insulin lispro concentration-time curve from 0 to 30 minutes after bolus dose ($AUC_{lis\ 0\text{-}30\ minutes}$) on days 1 to 3. All other endpoints presented were secondary and predefined in the statistical analysis plan, unless indicated otherwise.

The difference in means between BCLIS and LIS on either day 1, 2 or 3 was analysed in a mixed-effect linear model, with log-transformed endpoints as response variable, treatment, dose-meal interval, their interaction, period, sequence and day (1-3) as fixed effects and participant within sequence as a random effect. Least squares (LS) means for each treatment, as well as treatment ratios and 95% confidence intervals (CIs), were estimated.

The difference in means between either day 1, 2 or 3 and day 14 after bolus administration of BCLIS or LIS immediately before the meal was analysed in a mixed-effect linear model, with the log-transformed endpoint as response variable, treatment, day time point (day 1-3 or day 14), their interaction, period and sequence as fixed effects and participant within sequence as a random effect. LS means for each treatment, as well as treatment ratios and 90% CIs, were estimated.

In case of negative values, endpoints were analysed on the linear scale. For these endpoints, treatment ratios and 90% or 95% CIs were calculated using Fieller's method. Variables that were neither normally nor log-normally distributed were analysed using the Wilcoxon signed-rank test based on a 2-sided α level of 5%. Hodges-Lehmann estimates and 95% CIs were calculated for these variables.

A post hoc analysis was carried out to compare LS means between BCLIS and LIS on day 14, using a similar mixed-effect linear model without dose-meal interval effect.

3 | RESULTS

3.1 | Participant disposition and characteristics

Of 40 participants screened, 36 were randomized and exposed to a trial insulin. Twenty-five of the participants were men (69.4%). The mean participant age was 45.4 ± 12.2 years, mean BMI was 24.3 ± 2.6 kg/m^2, mean diabetes duration was 19.9 ± 12.3 years, mean HbA1c was 55 ± 5 mmol/mol and C-peptide level was below the limit of quantification (interquartile range below limit of quantification −0.14 nmol/L). A total of 15 participants were on glargine U-100 (4 of these injecting twice daily), 14 were on insulin detemir (10 injecting twice daily), 1 was on insulin degludec once daily and 6 were on NPH twice daily.

A total of 35 participants completed the trial; 1 participant dropped out because of an adverse event deemed unlikely to be related to treatment before completion of the first treatment period (BCLIS).

3.2 | BG profiles

With administration immediately before meal start on days 1 to 3, glycaemic excursions were significantly lower (31%; $P = 0.0237$) in the first 2 hours after dosing with BCLIS compared with LIS (Figure 2A and Table 1), whereas there was no difference over the full 6-hour postprandial period (Figure 2B and Table 1). Postprandial BG excursions improved over the 14 days of treatment with both BCLIS and LIS, but the difference in the first 2 hours in favour of BCLIS was maintained (Figure 3A and B and Table 1). While no significant differences were seen with administrations 15 minutes before meal start (ΔAUC_{BG} 0-2 hour 1.8 vs 2.4 mmol h/L, LS means ratio 0.76, 95% CI 0.33-1.62; $P = 0.3959$ [Figure 4A]), lower glycaemic excursions were seen with BCLIS vs LIS when comparing administration times 15 minutes after meal start (ΔAUC_{BG} 0-2 hour 5.8 vs 7.3 mmol h/L, LS means ratio 0.80, 95% CI 0.61-0.99; $P = 0.0338$ [Figure 4B and Table 2]). $\Delta AUC_{BG\ 0\text{-}2\ hour}$ on days 1 to 3 was similar between BCLIS injected 15 minutes after meal intake and LIS injected immediately before meal intake (5.8 vs 5.0 mmol h/L, LS means ratio 1.16, 95% CI 0.82-1.50; $P = 0.2251$).

3.3 | Pharmacokinetics

BCLIS was absorbed faster than LIS on days 1 to 3 (Figure 2C and D and Table 1) and this difference was maintained until day 14 (Figure 3C and D and Table 1). The primary PK endpoint $AUC_{lis\ 0\text{-}30\ minutes}$ was 74% higher with BCLIS than with LIS on days 1 to 3 ($P < 0.0001$; Table 1). In addition, both early and late time to reach half maximal serum insulin lispro concentration $T_{0.5\ max}$ were reached earlier with BCLIS, indicating a "faster in and out" PK profile (Table 1). Finally, exposure to insulin lispro was similar for BCLIS and LIS.

There was no difference in any PK endpoints between days 1, 2 or 3 and day 14 within treatment with BCLIS.

3.4 | Insulin use during the trial

The mean total basal insulin doses per day were similar for BCLIS and LIS on outpatient days (24.6 vs 24.2 U) and inpatient days (22.9 vs 22.4 U). The mean total bolus insulin doses per day were also similar in the two treatment groups on outpatient days (22.3 vs 22.6 U) and inpatient days (20.8 vs 19.9 U).

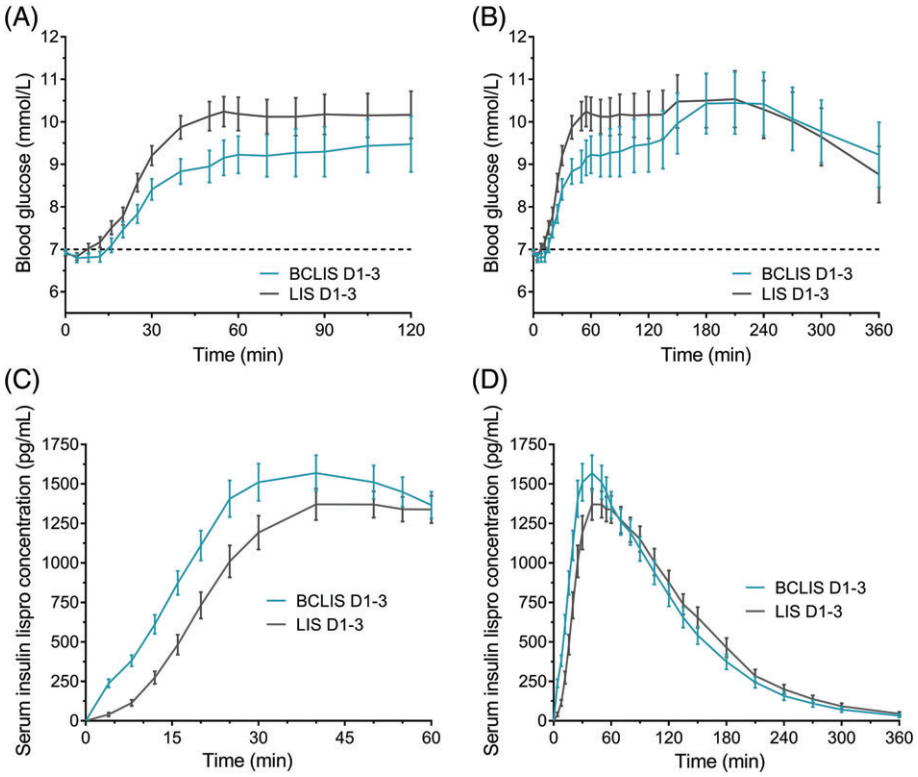

FIGURE 2 Mean ± SEM blood glucose profiles over the first 2 hours A, and over the 6-hour MMT procedure B, and pharmacokinetic profiles over the first hour C, and 6 hours D, with insulin injections immediately pre-meal for days 1 to 3. BCLIS, BioChaperone Lispro; LIS, insulin lispro

3.5 | Safety

A total of 17 adverse events were recorded during the trial, 16 of which were thought to be unrelated to the trial products. One event, a rash at the injection site starting 1 hour after injection, was assessed as possibly related to LIS. One serious adverse event, a psychogenic pseudoseizure, occurred during treatment with BCLIS and resulted in discontinuation of trial participation for that individual. A relationship with the trial product was assessed to be unlikely, although a BG measurement in the acute phase was not available.

During MMTs, a similar number of hypoglycaemic events occurred with BCLIS (27 events in 10 participants: 3 after administration at t − 15, 20 after administration at t0 [done on days 0 and 14] and 4 after administration at t + 15) and LIS (31 events in 12 participants: 5 after administration at t − 15, 21 after administration at t0 [done at days 0 and 14] and 5 after administration at t + 15).

During the outpatient period, hypoglycaemia was reported by 31 participants (156 episodes) after BCLIS and 32 participants (178 episodes) after LIS (P = 0.84). No episodes of severe hypoglycaemia were reported during the study.

TABLE 1 Blood glucose values and pharmacokinetic characteristics after injection of BioChaperone Lispro or insulin lispro at t0

Endpoint	BCLIS Day 1-3	LIS Day 1-3	Ratio (95% CI) BCLIS/LIS	*P*	BCLIS Day 14	LIS Day 14	Ratio (95% CI) BCLIS/LIS	*P*
BG endpoints								
$\Delta AUC_{BG\ 0\text{-}2\ h}$, mmol*h/L	3.5	5.0	0.69 (0.47;0.90)	0.0237	2.0[a]	3.5[a]	0.58 (0.25;0.91)	0.0204
$\Delta AUC_{BG\ 0\text{-}1\ h}$, mmol*h/L	1.1	1.8	0.60 (0.41;0.80)	0.0059	0.7[a]	1.4[a]	0.52 (0.29;0.80)	0.0019
$\Delta AUC_{BG\ 0\text{-}6\ h}$, mmol*h/L	15.5	17.2	0.90 (0.66;1.14)	0.4744	10.0[a]	11.3[a]	0.88 (0.42;1.56)	0.6174
BG 1 h, mmol/L	8.8	9.9	0.89 (0.81;0.98)	0.0223	7.8[a]	8.9[a]	0.89 (0.81;0.98)	0.0150
Pharmacokinetic endpoints								
$AUC_{lis\ 0\text{-}30\ min}$, pg*h/mL	348.5	200.0	1.74 (1.40;2.17)	<0.0001	361.8	244.6[a]	1.47 (1.19;1.81)	0.0008
$AUC_{lis\ 0\text{-}1\ h}$, pg*h/mL	1007.3	830.9	1.21 (1.04;1.42)	0.0181	1073.7	936.0	1.14 (1.00;1.31)	0.0538
$AUC_{lis\ 2\text{-}6\ h}$, pg*h/mL	571.3	950.8	0.60 (0.31;1.15)	0.1195	691.7	819.1	0.85 (0.67;1.07)	0.1568
$AUC_{lis\ 0\text{-}6\ h}$, pg*h/mL	2792.6	2961.1	0.94 (0.79;1.12)	0.4930	2900.8	2889.4	1.00 (0.87;1.16)	0.9563
Early $t_{0.5\ max}$, min	15.5	21.9	0.71 (0.64;0.79)	<0.0001	15.7	20.6	0.76 (0.65;0.88)	0.0008
Late $t_{0.5\ max}$, min	113.9	129.5	0.88 (0.78;1.00)	0.0471	111.5	117.9[a]	0.95 (0.86;1.04)	0.2404

Abbreviations: AUC, area under the curve; BCLIS, BioChaperone Lispro; CI, confidence interval; LIS, insulin lispro. Data are least squares means.

[a] Indicates a significant difference within treatment between days 1 and 2 and day 14 (P < 0.1).

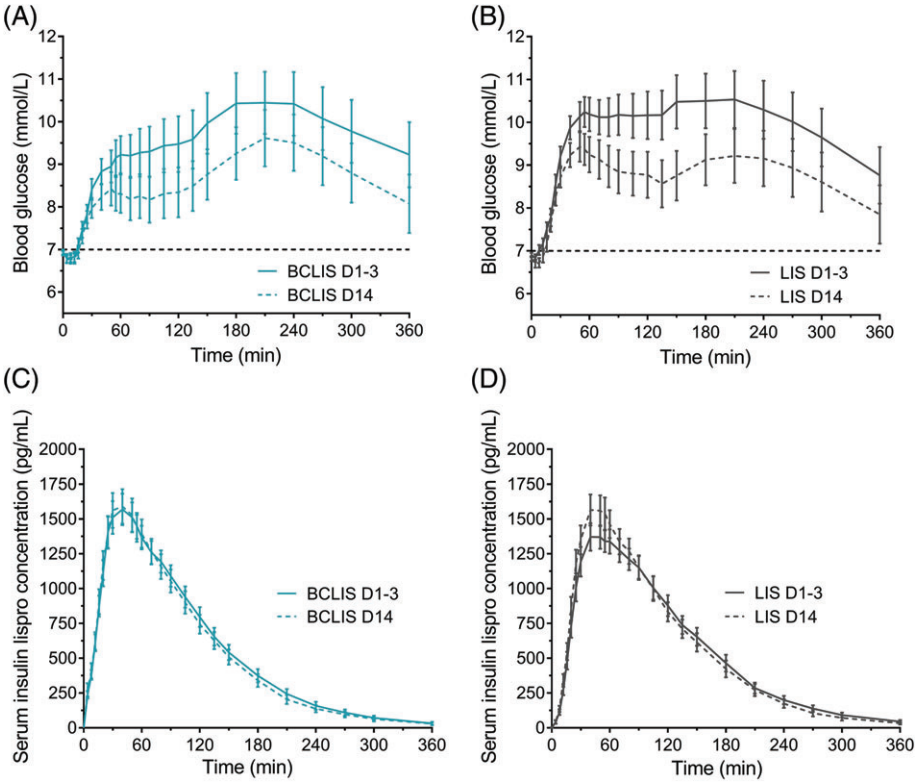

FIGURE 3 Mean ± SEM blood glucose profiles (A,B) and PK-profiles (C,D) on days 1 to 3 and day 14 with insulin injections immediately premeal, A, and C, BioChaperone Lispro (BCLIS) and B, and D, insulin lispro (LIS)

4 | DISCUSSION

The present study demonstrated a 31% improvement in early postprandial BG excursions after a mixed meal, the primary endpoint, with BCLIS compared with LIS at t0. This is explained by the faster absorption of insulin lispro with the BCLIS formulation than with LIS. This difference was maintained over a 14-day period. The improved early postprandial BG excursion was also seen with administration after the meal, but not with administration 15 minutes before the meal. No safety concerns were raised for BCLIS.

In general, dosing at the start of the meal seems preferred from the patient perspective. The ultra-rapid profile of BCLIS allows for such timing of administration, without compromising efficacy, even as compared with the administration of LIS 15 minutes before the meal. Dosing of insulin before the meal could be an alternative for some patients, but is associated with an initial decline in BG levels which may result in premeal hypoglycaemia.[4] Dosing after the meal always seems to result in larger postprandial BG excursions; however, when this is unavoidable, such as when the amount of food taken is unpredictable, postmeal dosing of an ultra-rapid insulin analogue formulation seems to limit postprandial BG excursions compared with a conventional rapid-acting analogue. BCLIS may, therefore, offer flexibility of the timing of injection with limited impact on the postprandial BG control vs LIS.

Limitations of this research include the need for standardized identical meals taken with each insulin formulation in order to limit

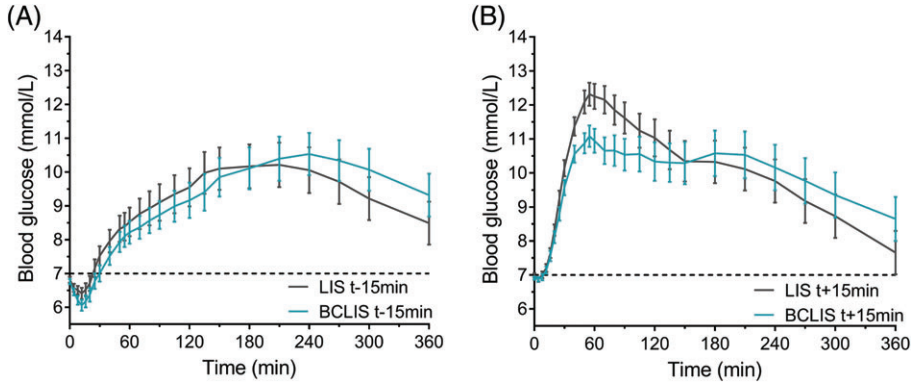

FIGURE 4 Mean ± SEM blood glucose profiles with insulin injections A,15 minutes before and B, 15 minutes after meal start on days 1 to 3

TABLE 2 Blood glucose values after injection of BioChaperone Lispro or insulin lispro at t − 15 min and t + 15 min

Endpoint (unit)	BCLIS t−15	LIS t−15	Ratio (95%CI) BCLIS/LIS	*P*	BCLIS t + 15	LIS t + 15	Ratio (95% CI) BCLIS/LIS	*P*
BG endpoints								
$\Delta AUC_{BG\ 0\text{-}2\ h}$, mmol*h/L	1.8	2.4	0.76 (0.33;1.62)	0.3959	5.8	7.3	0.80 (0.61;0.99)	0.0338
$\Delta AUC_{BG\ 0\text{-}1\ h}$, mmol*h/L	0.1	0.4	0.25 (−1.39;7.31)	0.2672	2.2	2.7	0.80 (0.62;0.98)	0.0391
$\Delta AUC_{BG\ 0\text{-}6\ h}$, mmol*h/L	14.0	13.7	1.03 (0.74;1.44)	0.8815	17.9	17.2	1.04 (0.67;1.42)	0.7684
BG 1 h, mmol/L	8.0	8.1	0.98 (0.89;1.08)	0.6870	10.8	12.1	0.89 (0.81;0.99)	0.0271

Abbreviations: AUC, area under the curve; BCLIS, BioChaperone Lispro; CI, confidence interval; LIS, insulin lispro. Data are least squares means. For the t −15 mins comparison, all but the $\Delta AUC_{BG\ 0\text{-}2\ h}$ endpoint were calculated post hoc.

variability in view of the relatively low patient numbers. Larger phase III trials are required to investigate the clinical value of this new ultra-rapid acting insulin in conditions closer to real-life. An improvement in glucose control over the 14 days of this study was seen with both insulins, probably reflecting a study effect.

In conclusion, the present study showed improved early PK and PD properties of BCLIS vs LIS, with the potential to reduce the risk of daytime postprandial hypoglycaemia and offering patients flexibility of the insulin administration time. The results of this trial justify further development of BCLIS.

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Conflict of interest

G.A., D.L and J.H.D. are employees of Profil. In addition, J.H.D is a member of advisory panels for Novo Nordisk and Sanofi, and has received speaker honoraria from Novo Nordisk. G.M., A.R., C.S., B.A., M.G. and O.S. are employees and shareholders of Adocia. T.H. is shareholder of Profil, which received research funds from Adocia, AstraZeneca, Becton-Dickinson, Biocon, Boehringer Ingelheim, Dance Biopharm, Eli Lilly, Grünenthal, Gulf Pharmaceutical Industries, Johnson & Johnson, Marvel, MedImmune, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi, Senseonics and Zealand Pharma. In addition, he is a member of advisory panels for Novo Nordisk and received speaker honoraria and travel grants from Eli Lilly, Mylan and Novo Nordisk.

Author contributions

G.A. and D.L. contributed to the study design, conduct/data collection and writing of the manuscript. G.M., A.R., M.G. and T.H. contributed to the study design, data analysis and writing of the manuscript. J.H.D. and C.S. contributed to the data analysis and writing of the manuscript. B.A. and O.S. contributed to the study design and writing of the manuscript.

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