Ultra-Rapid TDB0206 Injection (BioChaperone Lispro, BCLIS) Improves Postprandial And Daily Glucose Control Vs. Lispro (LIS) In Chinese People With Type 2 Diabetes (T2D)

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Abstract

BCLIS is an ultra-rapid insulin lispro formulation designed to more closely match physiological insulin secretion. This open-label multicenter phase 3 trial evaluated the efficacy and safety of BCLIS compared to LIS in people with T2D in China.

After an 8-week run-in period on LIS and glargine, 1040 subjects with T2D were randomized 3/2 to 26 weeks of treatment on glargine + 3 boluses of either BCLIS or LIS. Metformin was continued during the trial.

Non inferiority was confirmed for the primary endpoint for BCLIS with an estimated treatment difference in HbA1c change from baseline to week 26 of -0.07% [95% CI -0.18; 0.03] and superiority for BCLIs over LIS in subgroups of people using metformin or with baseline HbA1c below 8.5%

BCLIS was also superior to LIS in controlling 1- and 2-h meal test PPGE at week 26. Significantly more patients achieved A1C target of <7% with BCLIS (49.8% vs. 43.8%, p=0.03). Mean 10-pt SMBG was significantly reduced for BCLIS vs. LIS by -0.44 mmol/L [95% CI -0.67; -0.21] with significant reductions at each meal. There were no significant treatment differences in severe or overall hypoglycemia rates and in incidence of overall treatment-emergent adverse events.

This large phase 3 clinical trial shows that BCLIS improves postprandial glucose control compared to LIS in Chinese subjects withT2D.

Introduction & Background

- Rapid-acting insulin analogs are the current standard in controlling post-prandial glucose excursions.
- Rapid-acting analogs, however, are not able to match the speed of physiological post-meal insulin secretion seen in healthy individuals. Faster-acting insulins should result in even tighter post-prandial blood glucose control.
- THDB0206 (BioChaperone® Lispro, BCLIS) is an-ultra-rapid insulin lispro formulation containing the novel excipient BC222 and citrate.

Aims of the study

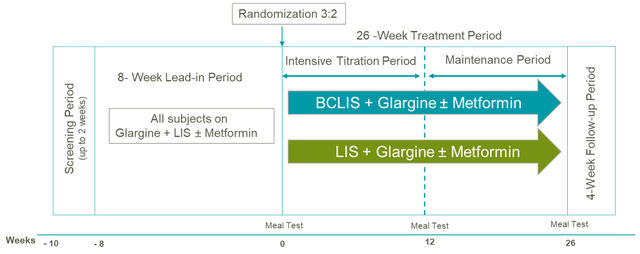
- To evaluate the efficacy and safety of THDB0206 (BCLIS) administered at mealtime, versus mealtime insulin lispro (LIS), both in combination with insulin glargine, in Chinese people with type 2 diabetes (T2D).

Figure 1: Schematic overview of the chronological structure of the trial

Key Inclusion Criteria:
- People with T2D ≥6 months
- Male of female aged 18 to 75
- Stable insulin treatment ≥3 m either on basal + ≥ 1 bolus/day or on premix ≥2/day with or without oral antidiabetic treatment
- HbA1c between 7% and 11% inclusive
- BMI between 18 and 35 kg/m² included

Primary endpoint:
- HbA1c change from baseline 26 weeks after randomization

Key secondary endpoints:
- 1-h Post Prandial Glucose Excursion after a meal test at week 26
- 2-h Post Prandial Glucose Excursion after a meal test at week 26



Methods

Design

- THDB0206L02 was a phase 3, 26-week, multicenter, randomized, treat-to-target open trial (Figure 1). Trial design, inclusion criteria, primary endpoint and key secondary endpoints are described in Figure 1.
- At the start of the run-in period, subjects were switched from their existing insulin treatment to basal insulin glargine and bolus insulin lispro (LIS). People on metformin continued their treatment but all other oral antidiabetic medications were stopped. During the run-in, insulin glargine was titrated by the investigator on a weekly basis to the pre-breakfast glycemic target of 4.4–6.1 mmol/L (80–110 mg/dL); LIS dose was not adjusted unless for safety reasons.
- During the treatment period, bolus insulin was titrated to a pre-prandial plasma glucose between 4.4–6.1 mmol/L (80–110 mg/dL), a bedtime plasma glucose between 5.0 and 7.2 mmol/L and a post prandial plasma glucose ≤7.8 mmol/L. Bolus adjustments were performed using a predefined algorithm. Glargine dose was kept stable unless for safety reasons.
- Postprandial plasma glucose (PPG) was assessed in a standardized mixed meal test (MMT, 100 g of carbohydrates). Glucose profiles were further evaluated using self-measured blood glucose (SMBG) measurements.

Statistical Analysis

- Confirmatory hypotheses were tested using a hierarchical fixed-sequence procedure ([1] Change from baseline in HbA1c, non-inferiority; [2] 1-h PPG increment at week26, superiority; [3] 2-h PPG increment at week 26, superiority.
- Efficacy endpoints were analyzed using either a mixed model for repeated measures (MMRM) with all available post-baseline observations under the missing-at-random (MAR) assumption, or an analysis of variance model.
- The number of treatment-emergent severe or blood glucose (BG)-confirmed hypoglycemic episodes was analyzed using a negative binomial regression model. All PD endpoints were derived from baseline-corrected data and AUCs were calculated based on the linear trapezoidal rule for specified time intervals.

Results

Study Population

- Out of 1040 randomized subjects, 1038 were exposed to treatment (either BCLIS or LIS). 977 (93.94%) completed the trial in treatment with similar levels of treatment discontinuation between both arms.
- Baseline characteristics were similar between treatment arms (Table 1).

Table 1: Baseline characteristics of the study population

Parameter	BCLIS (N=623)	LIS (N=415)
Age, years	59.0 ± 8.65	59.2 ± 9.43
Gender, n(%) male	340 (54.57)	221 (53.25)
Body weight (kg)	69.95 ±11.202	70.57 ±11.599
BMI (kg/m²)	25.71 ± 3.063	25.98 ± 3.105
Duration of diabetes, years	13.53 ± 7.154	13.91 ± 7.373
Baseline HbA1c (%)	7.70 ± 0.807	7.72 ± 0.815
Baseline FPG, mmol/L	7.17 ± 1.751	7.23 ± 1.838
Treatment Completion Rate, n(%)	581 (92.96)	396 (95.42)

Data are presented as mean ± SD unless specified.

Glycemic Control

- The observed change in HbA1c during the run-in and treatment periods for both treatment arms is illustrated in Figure 2.
  - Non-inferiority of the HbA1c change from baseline for BCLIS vs. LIS was confirmed using a pre-specified margin of 0.4% (Figure 2A).
  - Superiority for BCLIS was seen for prespecified subgroups of subjects either using metformin or with HbA1c<8.5% at randomization (Figure 2B).
  - Significantly more patients achieved HbA1c target of <7% (49.8% vs. 43.8%, p=0.03) and more reached the ≤6.5% target (31.4% vs. 26.8%, p=0.07 NS).
- BCLIS was superior to LIS to control meal test post prandial excursions at 1-h and 2-h (Figure 3).

Figure 2: A) HbA1c during the trial ,
B) Subgroup analyses of HbA1c change from baseline

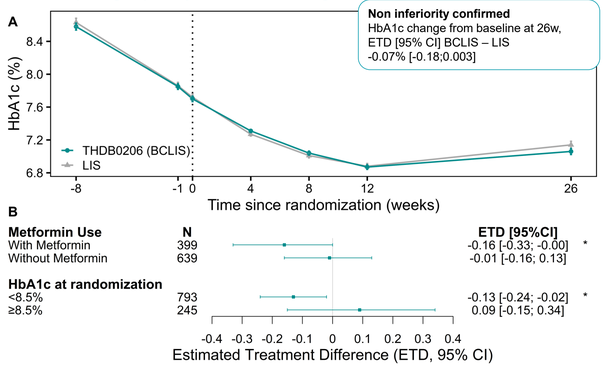
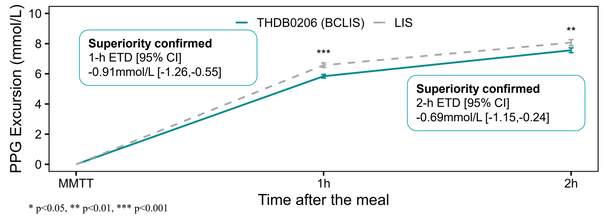


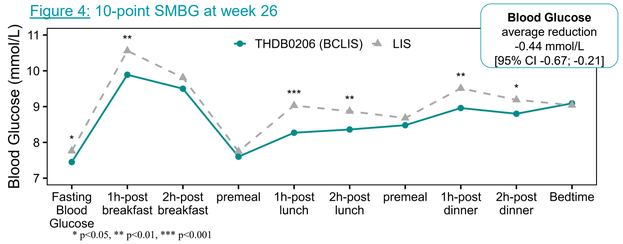
Figure 3: Meal test : Postprandial excursions at W26 (mean ± SE)



* p<0.05, ** p<0.01, *** p<0.001

- Observed mean 10-pt SMBG profiles at week 26 are presented in Figure 4.
  - Mean SMBG was significantly reduced for BCLIS vs. LIS by -0.44 mmol/L (95% CI [-0.67; -0.21]; p<0.001) with significant reductions at each meal.
- The change in 1,5-anhydroglucitol was also significantly different between BCLIS and LIS by 1.04 mg/L (95% CI [0.41;1.68]; p=0.035).

Figure 4: 10-point SMBG at week 26



* p<0.05, ** p<0.01, *** p<0.001

- There was no statistical difference in the change in body weight between treatment groups (+1.45 vs +1.41 kg, BCLIS vs LIS)
- Mean daily bolus insulin dose increased in both treatment groups, with similar doses for both treatment arms during the whole study up to week 26 (0.568 vs 0.561 U/kg/day at week 26 for BCLIS and LIS respectively).

Safety

- The overall rates of treatment-emergent severe or nocturnal hypoglycemia for BCLIS and LIS were comparable (Figure 5).
  - Rates were also comparable between treatment arms during the first four hours after a meal. There was, however, a significant difference favoring LIS observed during the 0-2 h period after the start of the meal (Figure 5) reflecting the faster insulin absorption of BCLIS.
- Injection site reactions were low and similar between both treatments (N =5 (0.8%) vs 2(0.48%) BCLIS vs LIS).
- About 65% of subjects in each treatment arm experienced treatment emergent adverse events (AEs), with rates of 3.4 and 3.8 events/patient-year of exposure (PYE) and serious AE rates of 0.21 and 0.23 events/PYE for BCLIS and LIS, respectively. Most common events were upper respiratory tract infections, hyperuricemia, and COVID-19.

Figure 5: Hypoglycemia rates during 26 weeks of treatment

Conclusions:

In comparison with insulin lispro, ultra-rapid THDB0206 (BCLIS) shows improved glycemic control in Chinese people with T2D with a similar good safety profile:

- Non inferiority in HbA1c for the whole population and superiority in people using metformin or with HbA1c below 8.5%
- Superior glucose control (SMBG), particularly post-prandially (SMBG/MMT)

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