Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Evaluation of Pharmacokinetics and Safety of the Biosimilar (B01711) and Insulin Degludec/Insulin Aspart (IDegAsp, Ryzodeg) in Healthy Chinese Adults in a Randomized, Open-Label, Single-Dose, Crossover, Phase I Study

Hui Liu[1,2], Haiyan Cao[3], Ting Li[4], Xinlei Chen[1], Hongling Yu[1], Jingfang Sun[3], Yerong Yu[1]

[1]Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, Chengdu, Sichuan, People's Republic of China; [2]Clinical Trial Center, West China Hospital of Sichuan University, Chengdu, Sichuan, People's Republic of China; [3]Hui Sheng Bio-pharmaceutical Co., Ltd., Tonghua, Jilin, People's Republic of China; [4]Health Management Center, General Practice Medical Center, West China Hospital of Sichuan University, Chengdu, Sichuan, People's Republic of China

Correspondence: Yerong Yu, Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, Guoxue Lane No. 37, Wuhou District, Chengdu, Sichuan, People's Republic of China, Email yerongyu@scu.edu.cn

Objective: B01711 is a biosimilar of insulin degludec/insulin aspart (IDegAsp 70/30). This randomized, open-label, single-dose, crossover, phase I study aimed to evaluate the pharmacokinetics (PK) and safety of B01711 compared to its original product (Ryzodeg) in healthy Chinese volunteers.

Methods: The study was conducted between April and August 2022, this study included 32 participants (22 males and 10 females) who received subcutaneous injections of both B01711 and Ryzodeg, with a ≥14-day washout period between treatments. All participants completed the study without any dropouts. Blood samples were collected at pre-defined intervals for PK analysis.

Results: The primary PK parameters included the area under the curve (AUC) of insulin degludec (IDeg) from 0 to 24 hours ($AUC_{IDeg,\ 0–24\ h}$), AUC of insulin aspart (IAsp) from 0 to the time of the last measurable value ($AUC_{IAsp,\ 0\text{-}t}$), and the peak concentration of IAsp ($C_{IAsp,\ max}$). PK equivalence would be established if the 90% confidence intervals (CIs) of least squares (LS) mean ratios of log-transformed values of primary PK endpoints for B01711 compared with Ryzodeg fell within the range of 80.0% to 125.0%. Safety was monitored throughout the study. The LS-mean ratios and corresponding 90% CIs were 106.1% (101.9%, 110.5%) for $AUC_{IDeg,\ 0–24\ h}$; 103.9% (100.2%, 107.6%) for $AUC_{IAsp,\ 0\text{-}t}$; and 110.1% (101.0%, 119.9%) for $C_{IAsp,\ max}$. Two treatment-emergent adverse events (TEAEs) were reported in two subjects (6.3%) in the B01711 group, and seven TEAEs were reported in seven subjects (21.9%) in the Ryzodeg group. The most common TEAE was a decrease in hemoglobin. The adverse events (AEs) of hypokalemia and hypoglycemia were identified as treatment-related AEs (TRAEs) and all TRAEs were mild.

Conclusion: This study demonstrated the PK equivalence of the two drugs and confirmed that both were well-tolerated.

Keywords: B01711, IDegAsp, pharmacokinetics, healthy subjects, Ryzodeg, phase I study

Introduction

The persistent global rise in diabetes prevalence underscores diabetes mellitus as a formidable global health challenge.[1] Poor glycemic management can lead to adverse neurological and cardiac complications, resulting in suboptimal outcomes.[2] Typically, patients with type 2 diabetes are initially prescribed basal insulin as the first class of insulin therapy. If monotherapy with basal insulin fails to achieve glycemic targets, prandial insulin will be added or therapy will be switched to premixed insulin in routine clinical practices.[3]

Received: 11 November 2024
Accepted: 4 April 2025
Published: 11 April 2025

Insulin degludec/insulin aspart (IDegAsp, 70/30) represents the third generation of insulin, characterized by a faster onset time and a more prolonged action period, closely mimicking physiological insulin secretion.[4] IDegAsp is a fixed-ratio formulation, combining 70% of IDeg and 30% of IAsp. Following subcutaneous injection of IDegAsp, the IAsp ingredient rapidly dissociates into its active monomeric form to induce a peak of insulin;[5] concurrently, the IDeg ingredient's stable dihexameric state and reversible albumin binding confer a long-lasting, peakless insulin effect.[6] The two processes occur independently without mutual interference. Owing to the longer half-life of degludec, IDegAsp may offer superior efficacy compared to the therapy of premixed insulin. Ryzodeg (Novo Nordisk A/S, Denmark) received approval from the European Medicines Agency (EMA) in 2013, the US Food and Drug Administration (FDA) in 2015, and China in 2019.

Affordable prescription medications are essential for managing diabetes effectively. Regrettably, even in developed countries like the United States, approximately 25%~30% of Americans with diabetes report rationing or skipping insulin due to its high cost.[7,8] Improving access to more affordable medications can be achieved through the introduction of generic drugs and biosimilars, extending the market exclusivity period for brand-name drugs, and eliminating anticompetitive pay-for-delay agreements.[9]

B01711, an insulin biosimilar to Ryzodeg, was developed by Hui Sheng Bio-pharmaceutical Co., Ltd., following guidelines from the EMA,[10] FDA,[11] and China,[12,13] sharing identical components with Ryzodeg. Preclinical studies in beagles demonstrated that B01711 had similar pharmacokinetic and pharmacodynamic profiles to Ryzodeg at a dose of 0.7 U/kg. At doses of 0.6 U/kg and 1.2 U/kg, no systemic toxic reactions of B01711, aside from expected insulin-related responses, were observed, aligning with findings for Ryzodeg. This was a first-in-human study designed to evaluate the pharmacokinetics (PK) and safety of B01711 compared to Ryzodeg in healthy Chinese volunteers.

Subjects and Methods

Subjects

Written consents from subjects were obtained before the commencement of any activities. Individuals aged 18 to 45 years, with a body mass index (BMI) ranging from 19.0 to 25.0 kg/m², and maintaining euglycemia [fasting glucose <6.1 mmol/L, glycated hemoglobin (HbA1c) <6.5%] were deemed eligible. During the screening, the results of physical examinations, laboratory tests (including complete blood count, liver and renal function tests, anti-insulin antibody assay, urinalysis, and coagulation tests), and a 12-lead electrocardiogram needed to be within normal limits or deemed clinically insignificant by the investigator. Effective contraceptive measures were required from the signing of the informed consent form until 30 days following the trial drug administration.

The primary exclusion criteria included: positive test results for hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus antibody, or Treponema pallidum antibody; a history of hypoglycemia; a clinically significant history of drug allergy or known hypersensitivity to the study drug or any of its components or related excipients; vaccination or any drug use within four weeks before screening; blood donation or significant blood loss exceeding 400 mL within the past three months; heavy smoking (more than five cigarettes per day) or alcohol abuse (more than 25 g of alcohol per day).

Study Design and Procedures

This was a phase I, single-center, open-label, randomized, single-dose, two-treatment, two-period, two-sequence, crossover study. It comprised a screening visit and two treatment visits with an interval of at least 14 days. The subjects were randomized into one of the two treatment arms (Figure 1). Each participant received both study drugs during the two dosing periods. They arrived at the clinical research unit the day before dosing. A fasting state of at least 10 hours before drug administration was ensured. The trial commenced on the morning of the dosing day. Venipuncture was performed using the median cubital vein for blood sampling, facilitated by heating the area with a warmed blanket. Following predosing blood sample collection, a 0.5-U/kg dose of either B01711 or Ryzodeg was subcutaneously injected into the abdominal wall. Subjects had breakfast post-injection and consumed lunch and dinner as usual. A 4-mL blood sample was collected at −15 (predose), 10, 20, 30, 40, 50, 60, 70, 80, 90, 120, 150, 180, 240, 300, 360, and 480 minutes for IAsp

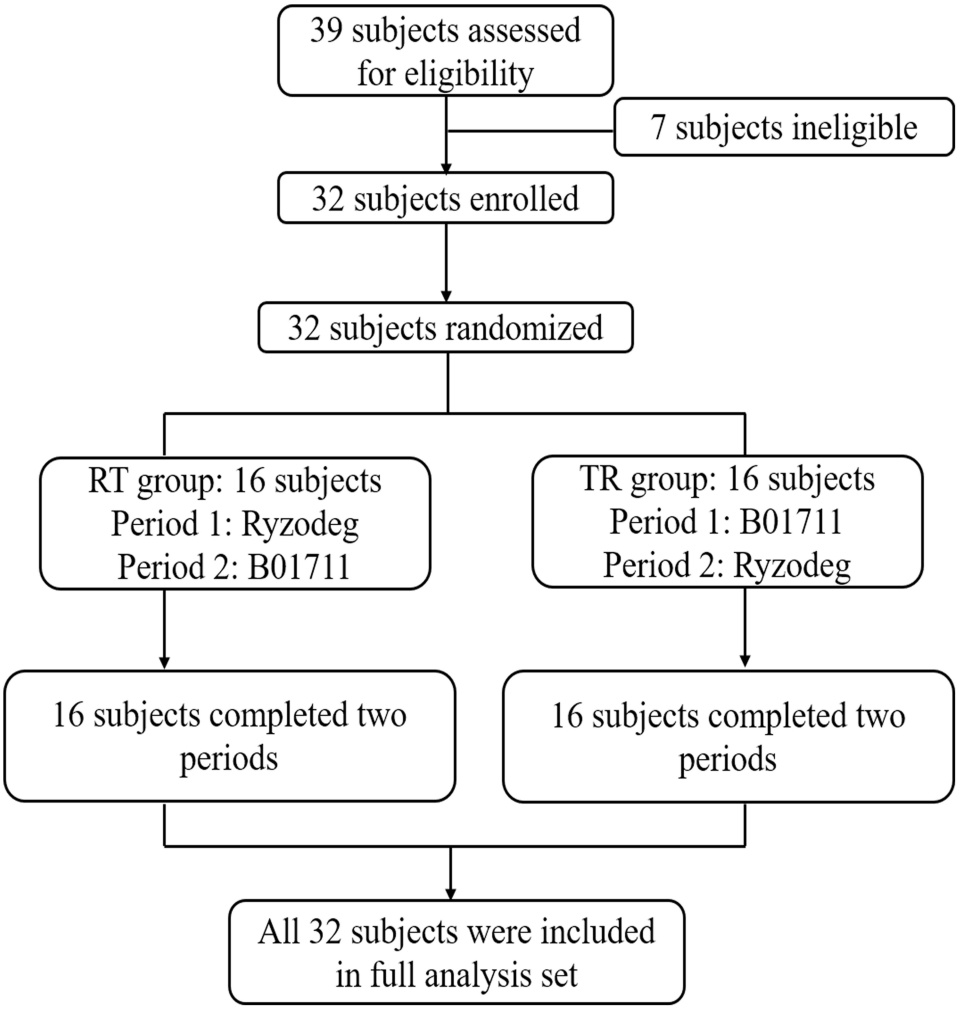

Figure 1 Sketch map of study design and subject flow chart.

concentration analysis. Another 4-mL blood sample was collected at −0.25 (predose), 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 36, 48, 72, 96, and 120 hours for IDeg level analysis. Additionally, a 0.1-mL blood sample was collected at the aforementioned time points to measure whole blood glucose levels immediately using the Biosen C-line glucose meter. Additional carbohydrates were administered when blood glucose levels fell below 3.6 mmol/L to prevent hypoglycemia. The study protocol was approved by the Ethics Committee of Sichuan University West China Hospital and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations. This study is registered at https://www.chictr.org.cn (ChiCTR2400083084).

PK samples were collected in tubes containing dipotassium ethylenediaminetetraacetic acid (K2EDTA) as a plasma stabilizer. The tubes were centrifuged at 1800 g for 15 minutes to obtain plasma which was then frozen at −60 °C until shipment for analysis. Plasma concentrations of IDeg and IAsp were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method by Labcorp Pharmaceutical Research and Development in Shanghai, China, with lower limits of quantification of 0.25 and 0.20 ng/mL, respectively. The liquid-liquid extraction method was employed to pretreat the PK samples.

Pharmacokinetic Endpoints

The value of PK sample measurements below the lower limit of quantification (BLQ) was regarded as zero. The primary PK endpoints included the maximum concentration of IAsp ($C_{IAsp,\ max}$), the area under the curve (AUC) of IAsp from 0 to the time

https://doi.org/10.2147/DDDT.S500347

of the last measurable value ($AUC_{IAsp,\ 0\text{-}t}$), and the AUC of IDeg from 0 to 24 hours ($AUC_{IDeg,\ 0–24\ h}$). The secondary PK endpoints included half-life ($t_{1/2}$), peak time (T_{max}), and AUC from 0 to infinity ($AUC_{0\text{-}\infty}$) for IAsp; C_{max}, $t_{1/2}$, T_{max}, $AUC_{0\text{-}\infty}$, AUC from 0 to 12 hours ($AUC_{0\text{-}12\ h}$), AUC from 12 to 24 hours ($AUC_{12\text{-}24\ h}$), AUC from 0 to 120 hours ($AUC_{0\text{-}120\ h}$) for IDeg.

Safety Assessments

Safety and tolerability were investigated through spontaneous reporting and inquiries regarding adverse events (AEs) and treatment-emergent adverse events (TEAEs) throughout the study. Additionally, physical examinations, vital sign measurements, 12-lead electrocardiogram, and laboratory tests, including serum chemistry, urinalysis, and hematology were monitored.

Sample Size and Statistical Methods

No data on the intra-subject coefficient of variation (CV) of IDegAsp was available. However, based on published pieces of literature, the intra-subject CV of primary PK-AUC estimates ranged from 17% to 21.2% for IDeg and 10% to 20% for IAsp, respectively. Assuming the intra-individual CVs were up to 21.2% and B01711 was no more than ±5% different from Ryzodeg, a minimum sample size of 28 subjects in a crossover design was determined to demonstrate bioequivalence with 90% power and a 5% type 1 error. To account for a potential 10% dropout, 32 subjects were planned.

Data analysis was performed by SAS® (version 9.4; SAS Institute Inc). and WinNonlin® (version 8.3; Certara L.P). Subjects with significant deviations affecting PK profiles, or a baseline value of ≥5% of $C_{IDeg,\ max}$ or $C_{IAsp,\ max}$, or those using other drugs interfering with PK assessment, or reaching peak level immediately following drug administration, were excluded from the PK analysis. The primary PK endpoints were calculated using raw, log-transformed data, and analyzed in a mixed-effects model with treatment (two levels), sequence (two levels), and period (two levels) as fixed effects, and subject-within-sequence as a random effect. The least squares (LS) mean of PK estimates of each investigational drug, and the ratio of B01711 to Ryzodeg, along with their 90% confidence intervals (CIs), were estimated. PK equivalence would be established if the 90% CIs of the estimated ratio of primary PK endpoints lay within the limits of 80.0%~125.0%. The normality of the data was examined with Q-Q plots. A nonparametric approach based on the Wilcoxon signed-rank test was applied to assess the differences in time-related parameters. All subjects who received at least one dose of the treatment were included in the safety analysis. A two-sided P value of <0.05 was considered statistically significant.

Results

Baseline Demographics and Characteristics

The study began in April 2022 and concluded in August 2022. As illustrated in Figure 1, a total of 39 participants were initially recruited, with 32 (22 males and 10 females) ultimately enrolling after screening. All enrolled participants received both drug administrations and completed the trial procedures. The participants had an average age of 27.6 years (range: 21~37 years), an average weight of 60.9 kg (range: 49.6~77.1 kg), an average height of 168.1 cm (range: 155.0~181.0 cm), an average BMI of 21.5 kg/m² (range: 19.1~25.0 kg/m²), an average fasting glucose level of 4.72 mmol/L (range: 3.71~5.76 mmol/L) and an average HbA1c level of 5.3% (range: 4.6%~5.9%) (Table 1).

Table 1 Demographics and Baseline Characteristics of the Participants

Variables	Value	Range
Full analysis set (n)	32	–
Female/male (n)	10/22	–
Nation: Chinese (%)	100	–
Age (year)	27.6±4.6[a]	21~37

(*Continued*)

Table 1 (Continued).

Variables	Value	Range
Height (cm)	168.1±7.4[a]	155.0~181.0
Weight (kg)	60.9±6.6[a]	49.6~77.1
BMI (kg/m^2)	21.5±1.7[a]	19.1~25.0
HbA1c (%)	5.3±0.3[a]	4.6~5.9
Fasting blood glucose (mmol/L)	4.72±0.40	3.71~5.76
Dose of IDegAsp	30.3±3.3[a]	25~38

Note: [a]Mean±standard deviation.
Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin.

Pharmacokinetics

Following drug administration, the IAsp ingredient was absorbed rapidly and reached a peak level at around 50 minutes. Approximately 97% of the total IAsp values at the eighth hour postinjection remained BLQ. The time profiles of the IAsp component for both drugs were similar (Figure 2A). The ratios of LS-means for $C_{IAsp,\ max}$, and $AUC_{IAsp,\ 0\text{-}t}$ between

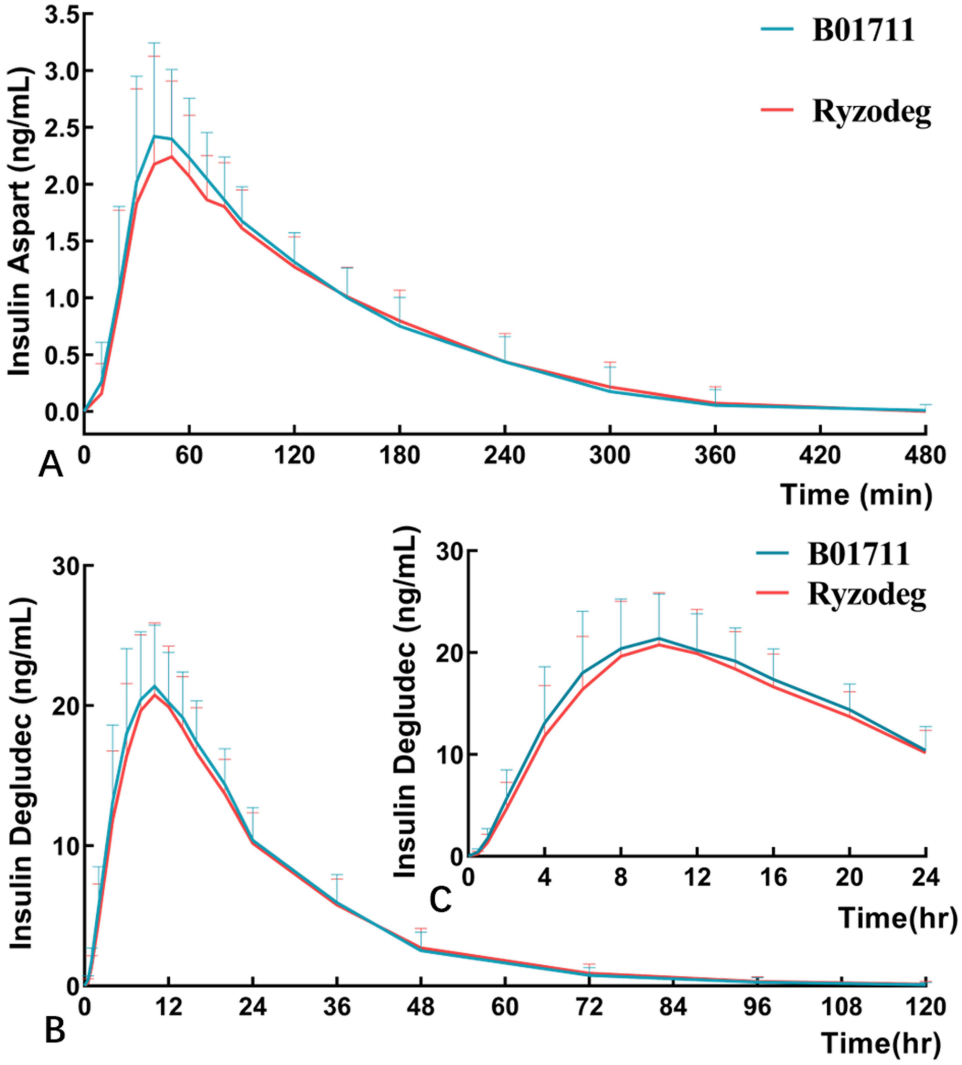

Figure 2 The time profile of mean IAsp levels from 0 to 8 hours (**A**) and time-concentration of mean IDeg from 0 to 120 hours (**B**) and 0 to 24 hours (**C**). The error bars represented the standard deviation.

https://doi.org/10.2147/DDDT.S500347

B01711 and Ryzodeg were both close to 1, with their respective 90% CIs falling within the range of 0.80 to 1.25. Moreover, the ratio of LS-mean of $AUC_{IAsp,\ 0\text{-}\infty}$ for B01711 compared to Ryzodeg was 102.3%, with a 90% CI of 99.6% to 105.0%. No significant differences were detected in $T_{IAsp,\ max}$, and $t_{1/2,\ IAsp}$ (P>0.05) (Table 2).

The IDeg component was gradually absorbed after injection, with its time profiles over the intervals of 0 to 120 hours and 0 to 24 hours depicted in Figure 2B and C, respectively. IDeg peak levels were reached at approximately 10~11 hours. Approximately 72%~75% of the total IDeg values were BLQ at the 120 hours post-injection. The LS-mean ratio of $AUC_{IDeg,\ 0–24\ h}$ for B01711 compared to Ryzodeg was 106.1%, with a 90% CI ranging from 101.9% to 110.5%. Furthermore, the values of $T_{IDeg,\ max}$, and $t_{1/2,\ IDeg}$ for both drugs were comparable (P>0.05). All 90% CIs of the LS-mean ratios for secondary PK estimates ($AUC_{IDeg,\ 0–12\ h}$, $AUC_{IDeg,\ 12–24\ h}$, $AUC_{IDeg,\ 0–120\ h}$, $AUC_{IDeg,\ 0\text{-}\infty}$, and $C_{IDeg,\ max}$) between the two formulations were within the range of 0.80 to 1.25 (Table 2).

Safety Evaluation

No serious AEs or discontinuations due to treatment-emergent AEs (TEAEs) were reported in either group. Table 3 shows that two TEAEs occurred in two subjects in the B01711 group, and seven TEAEs were reported in seven subjects in the Ryzodeg group. The monitoring of whole blood glucose levels is shown in Figure 3. A participant in the Ryzodeg group experienced a hypoglycemia event. The AEs (hemoglobin decreased, hemorrhage at the injection site, and vomiting) were considered unrelated to the study drug. However, hypokalemia and hypoglycemia were deemed treatment-related AEs (TRAEs) by the investigator. These TRAEs were mild and resolved. About two hours after subcutaneous administration of B01711 to the abdomen, one subject reported allergic dermatitis near the blood sampling site on the forearm, which had been warmed with a blanket. The blanket was removed immediately, and the condition was resolved within four hours. Consequently, the AE 'allergic dermatitis' was considered unrelated to the study drug. All AEs were mild in severity. To address the AE 'hemoglobin decreased', two subjects received a treatment regimen including a polysaccharide-iron complex

Table 2 Comparison of Pharmacokinetic Parameters Between B01711 and Ryzodeg

	Least-Square Mean [Standard Deviation]		Ratio (%)	90% CI	Within-Subject Variability (%)	Power (%)
	B01711 (N=32)	Ryzodeg (N=32)				
Primary PK parameters						
$AUC_{IAsp,\ 0\text{-}t}$ (ng/mL×h)	5.13 [0.89]	4.94 [0.87]	103.9	100.2~107.6	8.4	100
$C_{IAsp,\ max}$ (ng/mL)	2.50 [0.72]	2.28 [0.95]	110.1	101.0~119.9	20.4	79
$AUC_{IDeg,\ 0–24\ h}$ (ng/mL×h)	360.6 [55.4]	339.9 [66.9]	106.1	101.9~110.5	9.6	100
Secondary PK parameters						
$AUC_{IDeg,\ 0–12\ h}$ (ng/mL×h)	169.7 [46.1]	158.0 [47.2]	107.4	101.5~113.6	13.4	100
$AUC_{IDeg,\ 12–24\ h}$ (ng/mL×h)	186.7 [29.5]	179.1 [31.0]	104.3	99.8~108.9	10.3	100
$AUC_{IDeg,\ 0–120\ h}$ (ng/mL×h)	563.6 [78.0]	550.2 [77.9]	102.4	100.4~104.5	4.7	100
$AUC_{IDeg,\ 0\text{-}\infty}$ (ng/mL×h)	566.4 [79.8]	554.9 [79.0]	102.1	100.1~104.1	4.5	100
$C_{IDeg,\ max}$ (ng/mL)	22.2 [4.25]	20.9 [5.21]	106.3	100.8~112.1	12.6	100
$AUC_{IAsp,\ 0\text{-}\infty}$ (ng/mL×h)	5.67 [0.94]	5.54 [1.00]	102.3	99.6~105.0	6.3	100
Time-related parameters	**Median (IQR)**		***P*** value*			
$T_{IAsp,\ max}$ (h)	0.825 (0.250)	0.833 (0.250)	0.271			
$T_{IDeg,max}$ (h)	10.0 (2.0)	10.0 (2.0)	0.479			
$t_{1/2}$ of IAsp (h)	1.166 (0.469)	1.174 (0.466)	0.253			
$t_{1/2}$ of IDeg (h)	11.9 (5.99)	13.4 (8.131)	0.164			

Note: *Difference was detected by the Wilcoxon signed-rank test.
Abbreviations: PK, pharmacokinetics; AUC, area under the curve; IAsp, insulin aspart; IDeg, insulin degludec; $t_{1/2}$, half-life; IQR, inter-quartile range.

Table 3 Summary of Treatment-Emergent Adverse Events Reported in the Study

MedDRA 25.0 Preferred	B01711		Ryzodeg	
	N	Percentage	N	Percentage
Hemoglobin decreased	1	3.1%	3	9.4%
Hypokalemia	0	0	1	3.1%
Hypoglycemia	0	0	1	3.1%
Hemorrhage at the injection site	0	0	1	3.1%
Allergic dermatitis	1	3.1%	0	0
Vomiting	0	0	1	3.1
Total	2	6.3%	7	21.9%

capsule (150 mg once daily orally), a folic acid tablet (5 mg three times daily orally), and a compound vitamin B tablet (one tablet three times daily orally) for seven days, leading to normalized hemoglobin levels post-treatment. Both drugs were well tolerated in this study.

Discussion

The American Diabetes Association suggests maintaining a reasonable HbA1c target level below 7.0% (53 mmol/mol), and an astringent lower HbA1c level if possible without increasing the risk of hypoglycemia or other negative side effects.[14] However, most diabetic patients eventually fail to achieve the glycemic goal with lifestyle modifications and oral antidiabetic drugs alone.[15] Initiating and intensifying treatment with insulin is often the next step. Premixed insulin delivers both basal and mealtime coverage in a single injection. However, the protamine component can influence the soluble portion, resulting in a 'shoulder effect' and increasing the risk of hypoglycemia. Moreover, the protamination of short-acting insulin transforms it into intermediate-acting insulin with an extended glucose-lowering effect lasting approximately six hours, which is inadequate for consistent basal coverage compared to long-acting insulin.[16]

The IDegAsp co-formulation, consisting of 70% IDeg and 30% IAsp in a single pen, offers a continuous basal glucose-lowering effect and mealtime insulin coverage in one injection without the need for re-suspension. This study assessed the PK and safety of an IDegAsp biosimilar (B01711), with Ryzodeg as the reference. Hui Sheng Bio-pharmaceutical Co., Ltd. manufactures the IDeg component (B01411) and the IAsp component (B01511). Previous phase I euglycemic clamp studies (http://www.chinadrugtrials.org.cn/, No: CTR20190161 and CTR20192122) and phase III studies (http://www.chinadrugtrials.org.cn/, No: CTR20190121 and CTR20202005) demonstrated the pharmacokinetic and pharmacodynamic equivalence, efficacy, and safety of B01511 and B01411 in comparison to Novo Nordisk's reference products.[17] These results prompted the

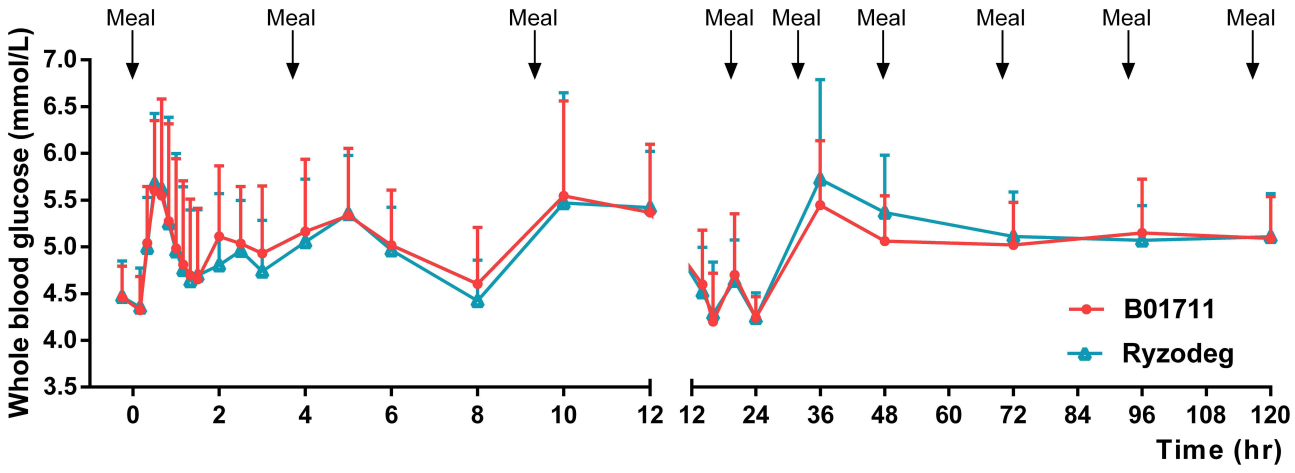

Figure 3 The monitored whole blood glucose levels in the study (mean with standard deviation).

https://doi.org/10.2147/DDDT.S500347

National Medical Products Administration of China to waive the pharmacodynamic comparison for the two drugs, thereby omitting the euglycemic clamp technique for pharmacodynamic evaluation.

The study was conducted in healthy subjects using the LC-MS/MS method to determine the concentrations of IAsp and IDeg, ensuring no interference from endogenous insulin.[18–20] Following subcutaneous injection, the IAsp component was rapidly absorbed into the circulation, reaching a peak level of around 2.28~2.50 ng/mL at approximately 50 minutes. The IDeg component gradually dissolved into the circulation and lasted for a long period. Compared with the reference product Ryzodeg, the 90% CIs of the LS-mean ratios for the primary PK endpoints ($AUC_{IAsp,\ 0\text{-}t}$, $C_{IAsp,\ max}$, and $AUC_{IDeg,\ 0–24\ h}$) were all in the acceptable range of 0.80~1.25. Moreover, the 90 CIs of the LS-mean ratios for the secondary PK parameters also stayed within the equivalent range. Time-related parameters were comparable between the two drugs. These results support the PK equivalence for B01711 compared to Ryzodeg.

The incidence of TEAEs was low, and all reported TEAEs were mild in this study. All AEs were resolved without any lasting effects. Both drugs were well-tolerated by healthy participants when administered as a single dose.

One limitation of this study is the absence of pharmacodynamic evaluation. Additionally, this study applied a single dose, and PK assessments were not conducted under multiple-dose or steady-state conditions in healthy subjects. Consequently, the obtained PK data cannot be directly extrapolated to clinical settings. A multicenter, randomized, open-label, parallel phase III study (http://www.chinadrugtrials.org.cn/, No: CTR20212490) was conducted in patients with type 2 diabetes to evaluate the efficacy and safety of B01711 compared to Ryzodeg.

Conclusion

This phase I study demonstrated the PK similarity of B01711 compared to Ryzodeg without significant safety concerns at a single dose.

Data Sharing Statement

Due to privacy policies and sponsorship from a pharmaceutical company, data sharing for this study is limited. Although the datasets generated and analyzed are not publicly available, they can be accessed upon reasonable request by contacting the corresponding author via email.

Ethics Statement

The study protocol was approved by the Ethics Committee of Sichuan University West China Hospital and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulations. The study was registered in the Chinese Clinical Trial Registry (https://www.chictr.org.cn, No: ChiCTR2400083084). All the participants provided written informed consent before this clinical trial initiation.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by Hui Sheng Bio-pharmaceutical Co., Ltd.

Disclosure

The authors (Haiyan Cao and Jingfang Sun) are employees of Hui Sheng Bio-pharmaceutical Co., Ltd and may hold stock, stock options, or both in Hui Sheng Bio-pharmaceutical Co., Ltd. The rest of the authors declared no competing interests.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 10th ed. Brussels, Belgium; 2022. Available from: https://www.diabetesatlas.org. Accessed March 15, 2022.
2. Wu ZH, Tang Y, Cheng Q. Diabetes increases the mortality of patients with COVID-19: a meta-analysis. *Acta Diabetol*. 2021;58(2):139–144. doi:10.1007/s00592-020-01546-0
3. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S125–43. doi:10.2337/dc22-S009
4. Chen BZ, Li WX, Feng YH, et al. Functional insulin aspart/insulin degludec-based microneedles for promoting postprandial glycemic control. *Acta Biomater*. 2023;171:350–362. doi:10.1016/j.actbio.2023.09.010
5. Rasmussen CH, Røge RM, Ma Z, et al. Insulin aspart pharmacokinetics: an assessment of its variability and underlying mechanisms. *Eur J Pharm Sci*. 2014;62:65–75. doi:10.1016/j.ejps.2014.05.010
6. Gough SC, Harris S, Woo V, Davies M. Insulin degludec: overview of a novel ultra long-acting basal insulin. *Diabetes Obes Metab*. 2013;15 (4):301–309. doi:10.1111/dom.12052
7. Herkert D, Vijayakumar P, Luo J, et al. Cost-related insulin underuse among patients with diabetes. *JAMA Intern Med*. 2019;179(1):112–114. doi:10.1001/jamainternmed.2018.5008
8. Pfiester E, Braune K, Thieffry A, Ballhausen H, Gajewska KA, O'Donnell S. Costs and underuse of insulin and diabetes supplies: findings from the 2020 T1International cross-sectional web-based survey [published online ahead of print, 2021. August 4]. *Diabetes Res Clin Pract*. 2021;179:108996. doi:10.1016/j.diabres.2021.108996
9. Herman WH, Kuo S. 100 years of insulin: why is insulin so expensive and what can be done to control its cost? *Endocrinol Metab Clin North Am*. 2021;50(3S):e21–e34. doi:10.1016/j.ecl.2021.09.001
10. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. European Medicines Agency; 2014. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf. Accessed December 10, 2021.
11. US Food and Drug Administration. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. US Food and Drug Administration; 2015. Available from: https://www.fda.gov/media/82647/download. Accessed December 18, 2021.
12. China Food and Drug Administration. Guidelines for the development and evaluation of similar biological products. China Food and Drug Administration; 2015. Available from: https://www.nmpa.gov.cn/yaopin/ypggtg/ypqtgg/20150228155701114.html. Accessed December 10, 2021.
13. China Food and Drug Administration. Technical guidelines for the study of human bioavailability and bioequivalence in chemical pharmaceutical preparations. China Food and Drug Administration; 2005. Available from: https://www.nmpa.gov.cn/wwwroot/gsz05106/08.pdf. Accessed December 10, 2021.
14. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2022;65(12):1925–1966. doi:10.1007/s00125-022-05787-2
15. Khunti K, Millar-Jones D. Clinical inertia to insulin initiation and intensification in the UK: a focused literature review. *Prim Care Diabetes*. 2017;11(1):3–12. doi:10.1016/j.pcd.2016.09.003
16. Fulcher GR, Jarlov H, Piltoft JS, et al. ARISE-a prospective, non-interventional, single-arm study assessing clinical parameters associated with the use of insulin degludec/insulin aspart in patients with type 2 diabetes in real-world settings: rationale and design. *Endocrine*. 2021;74(3):530–537. doi:10.1007/s12020-021-02887-8
17. Liu H, Li T, Yu H, et al. A phase-I randomized euglycemic clamp study to demonstrate the pharmacokinetic and pharmacodynamic equivalence of an insulin degludec biosimilar (B01411) with the reference product in healthy Chinese volunteers. *Expert Opin Investig Drugs*. 2023;32 (8):773–781. doi:10.1080/13543784.2023.2254690
18. Ziebarth J, Diedrich C, Schineider Machado C, Mara Mainardes R. Optimized LC-MS/MS method for quantifying insulin degludec and liraglutide in rat plasma and Tissues: application in pharmacokinetics and biodistribution. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2024;1234:124015. doi:10.1016/j.jchromb.2024.124015
19. Chambers EE, Legido-Quigley C, Smith N, Fountain KJ. Development of a fast method for direct analysis of intact synthetic insulins in human plasma: the large peptide challenge. *Bioanalysis*. 2013;5(1):65–81. doi:10.4155/bio.12.290
20. Chambers EE, Fountain KJ, Smith N, et al. Multidimensional LC-MS/MS enables simultaneous quantification of intact human insulin and five recombinant analogs in human plasma. *Anal Chem*. 2014;86(1):694–702. doi:10.1021/ac403055d