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ORIGINAL RESEARCH ARTICLE

Unveiling the Influence of a High-Fat Meal on the Pharmacokinetics of Oral Globalagliatin, A Glucokinase Activator, in Healthy Chinese Volunteers

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Abstract

Introduction Glucokinase (GK) plays a pivotal role in maintaining glucose homeostasis; globalagliatin, a newly developed drug, is a GK activator (GKA). This study constitutes a randomized, open-label, two-cycle, two-crossover, single-dose, phase I clinical trial conducted at a single center with healthy Chinese volunteers, aiming to examine the influence of a high-fat meal on the pharmacokinetics (PK) of orally administered globalagliatin.

Methods Twenty-four healthy volunteers were randomly divided into two groups, with a washout period of 16 days between the two cycles. The first cycle involved Group 1 volunteers who were orally administered globalagliatin 80 mg with 240 mL of water while fasting on Day 1. In contrast, Group 2 volunteers began oral administration of globalagliatin 80 mg with 240 mL of water, 30 min after consuming a high-fat meal (where high-fat content contributed to 54% of the total calories; the high-calorie meal amounted to 988.4 kcal). After the washout period, both groups of volunteers entered the second cycle of drug administration, with meals and medication being swapped on Day 17. Each volunteer collected blood samples at the following time points: 0 h (within 1 h before administration), and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, and 168 h after administration on both trial Day 1 and Day 17. The primary and secondary PK parameters were collected. The validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was used to determine the concentration of globalagliatin in collected plasma samples, and the results were analyzed using Phoenix WinNonlin software. Safety evaluation was conducted by detecting or observing various adverse events (AEs) and serious AEs (SAEs).

Results All 24 healthy Chinese volunteers enrolled completed the study and underwent PK analysis. The maximum concentration (C_{max}; ng/mL), area under the plasma concentration-time curve (AUC) from time zero to time of the last quantifiable concentration (AUC_t; h·ng/mL), and AUC from time zero extrapolated to infinity (AUC_∞; h·ng/mL) of fasting administration were 22.35 ± 7.02, 725.74 ± 303.04, and 774.07 ± 343.89, respectively, while the C_{max}, AUC_t, and AUC_∞ administered after a high-fat meal were 28.95 ± 12.60, 964.84 ± 333.99, and 1031.28 ± 392.80, respectively. The geometric mean ratios of C_{max}, AUC_t, and AUC_∞ for high-fat meal/fasting administration of globalagliatin were 124.81%, 135.24%, and 135.42%, respectively, with 90% confidence intervals of 109.97–141.65, 124.24–147.20, and 124.42–147.39, respectively. Compared with the fasting state, healthy volunteers who consumed a high-fat meal showed a 24.8% increase in C_{max}, a 35.2% increase in AUC_t, and a 35.4% increase in AUC_∞. The geometric mean of T_{max} was 4.69 h under fasting conditions and 5.93 h in a high-fat state, with a median of 4.98 h. Among the 24 enrolled volunteers, 9 cases (37.5%) had 11 AEs, and 6 cases (25.0%) had 7 adverse drug reactions (ADRs) after medication, all of which were cured or improved without taking any treatment measures. There were no SAEs in this study, no volunteers withdrew from the study due to AEs or ADRs, and no hypoglycemic events occurred during the trial.

Conclusion A high-fat meal increased the C_{max}, AUC_t, and AUC_∞ of globalagliatin compared with fasting conditions in healthy Chinese adult volunteers. Meanwhile, globalagliatin showed favorable safety and tolerability under fasting or high-fat meal conditions.

Extended author information available on the last page of the article

Key Summary Points

A high-fat meal increased the maximum concentration (C_{max}), area under the plasma concentration-time curve (AUC) from time zero to time of the last quantifiable concentration (AUC_t), and AUC from time zero extrapolated to infinity (AUC_∞) of globalagliatin compared with fasting conditions in healthy Chinese adult volunteers.

A single oral administration of globalagliatin 80 mg under fasting or high-fat meal conditions showed favorable safety and tolerability.

1 Introduction

Type 2 diabetes mellitus (T2DM) is a serious chronic metabolic disease that is manifested by insulin resistance, enhanced hepatic glucose production, dysregulation of glucagon and incretin, and progressive destruction of pancreatic β-cells. With acceleration of the aging process and changes in lifestyle in China, the prevalence of diabetes mellitus is rapidly rising, making it a significant non-communicable disease that poses a substantial threat to public health, following closely behind cardio cerebrovascular diseases and cancer [1]. According to the estimation of the International Diabetes Federation, there are approximately 537 million adults with diabetes worldwide, including about 140 million diabetes patients in China, the majority being T2DM patients [2, 3].

Currently, the medications used to manage diabetes encompass insulin sensitizers, insulin secretagogues α-glycosidase inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, etc. [4]. However, blood glucose regulation is insufficient to meet treatment demands and relies on a singular mechanism. The clinical need for new diabetes medications with novel hypoglycemic mechanisms, better oral tolerance, and fewer adverse reactions is pressing [5, 6].

Glucokinase (GK) is a typical hexokinase isoenzyme in hepatocytes, which catalyzes glucose metabolism. Elevated blood sugar levels trigger increased GK activity, leading to enhanced liver glycogen synthesis. Activating GK is advantageous for heightening pancreatic islet sensitivity to insulin secretion and effectively lowering the blood glucose threshold for insulin release [7, 8] Globalagliatin (SY004), a selective GK agonist co-developed by Eli Lilly Pharmaceuticals and Yabao Pharmaceuticals, shows promise in treating T2DM by bolstering insulin secretion and influencing hepatic glucose metabolism. A new class 1.1 chemical drug, it successfully obtained clinical trial approval by the China National Medical Products Administration, with the approval number 2017L00469. To date, four phase I clinical trials (GKBA study, GKBB study, GKBE study, and GKBG study) evaluating the safety, tolerability, pharmacokinetic (PK) characteristics, and pharmacodynamic (PD) features of globalagliatin in healthy subjects and T2DM patients have been completed by Eli Lilly Pharmaceuticals. The results from these four studies indicate that globalagliatin is continuously and slowly absorbed in both healthy subjects and T2DM patients, reaching peak blood concentration within 5–6 h. The changes in AUC and C_{max} are directly proportional to the dose. The average elimination half-life ($t_{½}$) ranges from 31.7 to 73.37 h. The average CL/F ranges from 33.1 to 98.5 L/h, and clearance decreases as the dose increases, possibly due to saturation of the elimination pathway for globalagliatin, although the specific mechanism is unclear. The average apparent volume of distribution at steady state (Vss/*F*) ranges from 1310 to 4930 L. In China, based on these results, Yabao Pharmaceuticals conducted phase Ia and Ib clinical trials [9, 10]. The completed domestic and international clinical studies indicate that globalagliatin is well tolerated and safe in healthy subjects and T2DM patients in doses ranging from 2 to 400 mg. Additionally, globalagliatin demonstrates a clear hypoglycemic effect, and the PK and PD characteristics in both domestic and international settings are similar.

Food effect (FE) research is an important component of clinical pharmacology studies on new drugs. Concurrent ingestion of food and medication may affect the absorption and systemic exposure of drugs, including delaying gastric emptying, increasing visceral blood flow, and stimulating bile flow, among other effects [11, 12], leading to changes in the safety and efficacy of drugs. Consequently, in the early clinical development of innovative drugs, when strict fasting conditions cannot be guaranteed, it is imperative to conduct FE research in advance, This study intends to use a randomized, open, two-cycle, two-crossover, single-dose, single-center, phase I clinical trial, with volunteers on an empty stomach as the controls, to evaluate the PK effects of a high-fat meal on healthy Chinese volunteers after oral administration of globalagliatin.

2 Materials and Methods

2.1 Ethics Approval

This clinical study was initiated by Suzhou Yabao Pharmaceutical R&D Co. Ltd, the sponsor, and the study protocol was approved and authorized by the Drug and Medical Device Branch of Wannan Medical College Yijishan Hospital Institutional Review Board (IRB). All clinical

procedures were carried out in the phase I Clinical Trial Unit of the Wannan Medical College Yijishan Hospital. Furthermore, this study was conducted according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice (GCP). The clinical registration number is CTR20210958 (http://www.chinadrugtrials.org.cn/clinicaltrials.searchlist.dhtml). All recruited volunteers agreed to and provided written informed consent before the study was initiated.

2.2 Drug

The experimental drug used in this study was globalagliatin hydrochloride capsules with the following specifications: 80 mg/capsule. These capsules were stored in a sealed and dry environment within a temperature range of 10–30 ℃. Quality inspection confirmed that the capsules met the required drug standards, and they were produced and supplied by Yabao Company. Throughout this study, only capsules from the same batch, with batch number 821050021, were used.

2.3 Inclusion and Exclusion Criteria

2.3.1 Inclusion Criteria

(1) The subjects were able to communicate well with the researchers, understand and comply with the requirements of this study, and willingly provided written informed consent. (2) Age on the day of signing the informed consent form: healthy subjects aged 18 years and above, both male and female. (3) Male participants weighed no less than 50.0 kg, while female participants weighed no less than 45.0 kg. Body mass index (BMI) ranged from 19.0 to 26.0 kg/m^2. (4) Fasting blood glucose levels were between $\geq$ 3.9 and $<$ 6.1 mmol/L. (5) The subjects and their partners had not engaged in family planning and had voluntarily implemented effective contraceptive measures from 1 month before signing the informed consent form until 3 months following the final medication dose. Additionally, they had no intentions to donate sperm or eggs.

2.3.2 Exclusion Criteria

(1) Within the 3 months preceding the screening, participation in or completion of any clinical trial, withdrawal from a clinical trial, or ongoing involvement in medical trial activities that the researcher deemed incompatible with this study. (2) A history of serious systemic diseases or a family history of such conditions (including those affecting the cardiovascular, digestive, or urinary systems, etc.), where the researcher determined that these conditions could significantly alter the absorption, distribution, metabolism, or excretion of the investigational drug or increase the risk of the subject. (3) Known allergic disposition, a history of food allergies, or documented allergies to the study drug or similar substances. (4) Individuals with a history of hypoglycemia in the past. (5) A history of postural hypotension. (6) Individuals with a history of drug abuse, drug use, or positive urine drug screening results within the past 5 years. (7) Individuals who donate blood or experience significant blood loss exceeding 400 mL within the initial 4 weeks of screening, have received blood or blood component transfusions within the initial 4 weeks of screening, or have intentions to donate blood components within 3 months after the study concludes. (8) A history of needle or blood-related fainting, intolerance to venipuncture, or difficulties with blood collection. (9) Severe infections, injuries, or major surgical procedures within the initial 4 weeks of screening, or plans for surgery during the study period, including dental surgery. (10) The use of any prescription drugs, over-the-counter medications, herbal supplements, or health products within 2 weeks prior to screening. (11) The use of medications that inhibit or induce hepatic drug metabolism enzymes within 30 days prior to screening. (12) Consumption of alcohol exceeding an average of 14 units per week (1 unit = 360 mL of beer, 45 mL of 40% alcohol, or 150 mL of wine) within the initial 3 months of screening, inability to abstain from alcohol during the trial, or positive alcohol breathalyzer results. (13) Smoking five or more cigarettes per day within the initial 3 months of screening or an unwillingness/inability to quit smoking during the study. (14) Special dietary requirements that prevent adherence to a standardized dietary regimen. (15) Inability to abstain from consuming chocolate, caffeine-containing foods or beverages, or items known to influence test results (e.g., pitaya, pomelo, grapefruit, orange juice, mango, etc.) for 48 h before drug administration and during the study. (16) Pregnancy, lactation, or positive pregnancy test results. (17) Positive screening results for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, treponema pallidum (TP) antibody, or HIV antibody. (18) Elevated alanine transaminase (ALT; $>1.5 \times$ the upper limit of normal [ULN] value during screening), aspartate transaminase (AST; $>1.5 \times$ ULN), or total bilirubin (TBIL; $>1.5 \times$ ULN). (19) During screening, 12-lead ECG results showed a QT interval (QTcB) exceeding 450 ms for males or 470 ms for females. (20) During the screening period, physical examination, vital signs, abdominal ultrasound (liver, gallbladder, pancreas, spleen, kidney), chest computed tomography (CT), electrocardiogram examination, laboratory examination items, and auxiliary examination results related to the experiment were determined by the researcher to be unsuitable for participants in the experiment. (21) Subjects who

have been determined by the researcher to have other unsuitable factors for participating in this experiment.

2.4 Study Design and Administration

This study adopted a randomized, open-label, two-cycle, two-crossover, single-dose, single-center, phase I clinical trial design conducted with healthy Chinese volunteers. The 24 healthy volunteers were randomly divided into two groups and the trial was structured into two cycles, as detailed in Table 1.

This study draws on relevant domestic and foreign guidelines, and employs a randomized, single-dose medication approach with two treatment methods, namely diet and fasting [13–15]. The study follows a two-cycle, two-sequence crossover design, incorporating sufficient washout periods between the two cycles. Healthy subjects were selected, with an anticipated enrollment of 24 participants. Twenty-four healthy volunteers were randomly divided into two groups, with a washout period of 16 days between the two cycles. The first cycle involved Group 1 volunteers who were orally administered globalagliatin 80 mg with 240 mL of water while fasting on Day 1. In contrast, Group 2 volunteers began oral administration of globalagliatin 80 mg with 240 mL of water, 30 min after consuming a high-fat meal (where high-fat content contributed to 54% of the total calories; the high-calorie meal amounted to 988.4 kcal). After the washout period, both groups of volunteers entered the second cycle of drug administration, with meals and medication being swapped on Day 17. The study's objective was to investigate the impact of 80 mg of standard medication when administered with high-fat, high-calorie meals (as detailed in Table 2). This meal composition, comprising approximately 50% of total calories and totaling around 800–1000 calories, was designed to maximize its influence on gastrointestinal physiological functions, ultimately affecting drug bioavailability.

The GKBA study and China phase Ia study show that globalagliatin is well tolerated and safe in healthy subjects following single-dose administration in a dose range of 2–120 mg. Within the range of 20–120 mg, where complete PK profiles can be obtained, the drug exhibits favorable PK characteristics. Preliminary PD analysis suggests that 40 mg may be the minimum effective dose and 80 mg demonstrates a clear hypoglycemic effect. Therefore, 80 mg was chosen as the dosing level for this study as it should be safe and well tolerated in healthy subjects, and drug concentrations within the detectable range can be used to assess the impact of diet on PK characteristics.

A domestic clinical phase Ia study showed that after a single oral administration dose of globalagliatin in healthy subjects, the time to peak blood concentration (T_{max}) in each dose group (20, 40, 80, and 120 mg) was approximately 2–5 h, and the $t_{½}$ ranged from 37.6 to 49.9 h, indicating a slow elimination from the body. To cover the terminal elimination phase, samples for PK were collected following the reference of both the GKBA study and the China phase Ia clinical study up to 168 h post-dosing (Day 8). To prevent any potential influence of the first dosing cycle on the second dosing cycle, a washout period of at least seven half-lives was established between the two dosing cycles, resulting in a 16-day interval between Day 1 and Day 17 for dosing.

2.5 Tolerability Measurements

Safety assessments encompassed the detection and observation of various adverse events (AEs), serious AEs (SAEs), laboratory tests, vital signs, physical examination, 12-lead ECG, and hypoglycemic events. Based on the safety analysis

Table 1 Schematic diagram of the research design process

Group	First cycle (D1–D8)	Washout period (D9–D16)	Second cycle (D17–D24)
Group 1 ($n = 12$)	Fasting	Our group	High-fat meal
Group 2 ($n = 12$)	High-fat meal		Fasting

D day

Table 2 Composition of a high-fat meal

Ingredient	Size	Calories (Kcal)	Protein (Kcal)	Protein (g)	Fat (Kcal)	Fat (g)	Carbohydrate (Kcal)	Carbohydrate (g)
McDonald's Angus Beef Bacon Burger	1	600	–	34.2	–	38.5	–	43.6
McDonald's crisp hash browns	1	163	–	1.4	–	10.7	–	14.6
Yili pure milk (mL)	250	165.4	–	8	–	9.5	–	12
Total heat/weight (Kcal/g)	–	988.4	174.4	43.6	528.3	58.7	280.8	70.2

set, the relevant information of all AEs was meticulously documented. This comprehensive documentation includes details such as whether the event qualified as an SAE, the severity of the event, whether concomitant treatment was administered, and the outcome of the AE. Furthermore, each treatment-emergent AE (TEAE) and adverse drug reaction (ADR) was systematically coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, specifying Preferred Terms (PT) and System Organ Classes (SOCs). Severity categorization adhered to the National Cancer Institute Common Terminology Criteria (NCI-CTC) 5.0 classification standard.

Hypoglycemic events stemming from the investigational drug were subject to descriptive analysis. This entailed capturing the number of subjects experiencing at least one hypoglycemic event, the corresponding percentage of subjects affected, and an account of the total number of events. The analysis also delved into summarizing the severity of hypoglycemia occurrences and the precise timing of their manifestation.

2.6 Pharmacokinetic Assessment

For the PK assessment, 3 mL of blood samples were collected into a K2EDTA anticoagulant PK blood collection vessel at different time points: 0 h (within 1 h prior to administration), and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, and 168 h after administration. These blood samples were promptly centrifuged at temperatures ranging from 2 to 8°C, at 1700 g for 10 min. Subsequently, plasma was meticulously isolated, stored separately, and preserved within a − 80°C freezer before analysis. Utilizing non-compartmental methodologies, the PK parameters of globalagliatin were computed based on plasma concentrations through the application of Phoenix WinNonlin (version 8.1). The primary PK parameters included AUC_t, AUC_∞ and C_{max}, while secondary PK parameters encompassed T_{max}, t_{lag}, $t_{½z}$, CL_z/F, V_z/F, λ_z, and $AUC_{\_\%extrap}$ (Table 3). All samples were meticulously analyzed by Shanghai Xihua Testing Technology Service Co., Ltd (Shanghai, China), utilizing a validated liquid chromatography-tandem mass spectrometry method.

2.7 Statistical Analysis

Statistical analysis involved a logarithmic transformation of AUC_t, AUC_∞, and C_{max}, followed by the application of a linear mixed-effects model using Phoenix WinNonlin (version 8.1). This model incorporated period, sequence, and administration conditions as fixed effects, with subjects (sequences) considered as random effects. The geometric mean ratios of AUC_t, AUC_∞, and C_{max} under different dietary conditions (high-fat meal/fasting) and corresponding 90% confidence intervals were calculated to evaluate the impact of a high-fat meal on the in vivo exposure of oral globalagliatin. Additionally, a non-parametric test (Wilcoxon pairing) was employed to evaluate whether there were statistical differences in T_{max} among subjects exposed to different dietary conditions (fasting and high-fat meal).

3 Results

3.1 Demographics of the Fasting and Fed Groups

From an initial pool of 54 candidates, a cohort of 24 volunteers was carefully selected for comprehensive safety analysis throughout the study's duration. Among the 30 individuals who were not included, two did not meet the specified inclusion criteria, while 23 were excluded due to non-compliance with the exclusion criteria. Additionally, one candidate failed to meet both the inclusion and exclusion criteria and four others voluntarily withdrew from participation in the trial. The demographic profiles of the 24 (18 males and 6 females) enrolled volunteers are thoughtfully summarized in Table 4.

Table 3 Description of primary and secondary pharmacokinetic parameters

Parameters	Description
C_{max}	Maximum concentration
AUC_t	Area under the plasma concentration-time curve from time zero to the last time of quantifiable concentration
AUC_∞	Area under the plasma concentration-time curve from time zero extrapolated to infinity
T_{max}	Time to reach maximum concentration
t_{lag}	Lag time. The observation time before the first measurable blood concentration was observed
$t_{½z}$	Terminal elimination half-life.
V_z/F	Apparent volume of distribution
CL_z/F	Apparent clearance
λ_z	Elimination rate constant
$AUC_{\_\%Extrap}$	Residual area percentage

3.2 Food Effect on the Pharmacokinetics of Globalagliatin

The concentration-time profile of globalagliatin is visually represented in Fig. 1. Notably, the results reveal distinct PK parameters under fasting and high-fat meal conditions. Specifically, for fasting administration, the C_{max} (ng/mL), AUC_t (h·ng/mL), and AUC_∞ (h·ng/mL) were measured at 22.35 ± 7.02, 725.74 ± 303.04, and 774.07 ± 343.89, respectively. In contrast, administration following a high-fat meal resulted in C_{max} (ng/mL), AUC_t (h·ng/mL), and AUC_∞ (h·ng/mL) values of 28.95 ± 12.60, 964.84 ± 333.99, and 1031.28 ± 392.80, respectively, indicating an increase in exposure when taken in conjunction with a high-fat meal. Further analysis revealed that the geometric mean ratios of C_{max}, AUC_t, and AUC_∞ for all selected subjects receiving a high-fat meal/fasting administration of globalagliatin were 124.81% (90% CI 109.97–141.65%), 135.24% (90% CI 124.24–147.20%), and 135.42% (90% CI 124.42–147.39%), respectively. The geometric mean of T_{max} was 4.69 h in a fasting state and 5.93 h under high-fat meal conditions, while the median value was 4.98 h in both cases. There was a statistically significant difference between T_{max} and t_{lag}. Moreover, the exposure levels (C_{max}, AUC) of orally administered globalagliatin at a single 80 mg dose increased by 1.24–1.35 times when taken with a high-fat meal compared with fasting conditions. For more comprehensive details, please refer to Tables 5, 6 and 7.

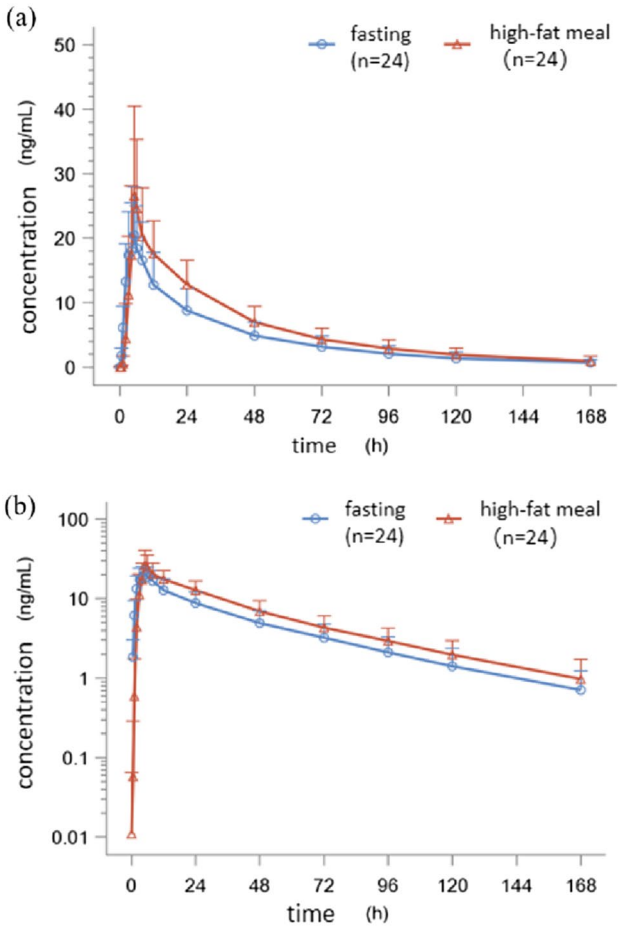

Fig. 1 Mean plasma concentration time (**a**) and semi-log plot of mean plasma concentration time (**b**) after oral administration of globalagliatin 80 mg in healthy subjects (mean + standard deviation)

3.3 Safety

Among the 24 participants included in the study, 9 (37.5%) encountered a total of 11 TEAEs, while 6 subjects (25.0%) experienced 7 ADRs after medication. The following is a breakdown of these occurrences during different phases. Fasting phase: six patients (25.0%) had a total of seven TEAEs, including elevated alanine aminotransferase (two cases, 8.3%), elevated amylase (one case, 4.2%), positive urinary leukocyte (one case, 4.2%), decreased leukocyte count (one case, 4.2%), detected urinary sediment (one case, 4.2%), and sinus bradycardia (one case, 4.2%). According to the investigator's assessment, all two cases of elevated alanine aminotransferase, one case of elevated amylase, and one case of decreased white blood cell count were considered ADRs. High-fat diet phase: four subjects (16.7%) encountered four TEAEs, including elevated amylase (one case, 4.2%), positive urinary leukocyte (one case, 4.2%), elevated serum uric acid (one case, 4.2%), and myoclonus (one case, 4.2%). Per the investigator's judgment, one case of elevated amylase, one case of elevated serum uric acid, and one case of myoclonus were designated as ADRs.

Notably, one TEAE was rated as severity level II, while 10 TEAEs were classified as severity level I. Two cases were considered to be in remission and nine cases were categorized as having fully recovered. Throughout the study, no AEs were categorized as level III or higher, and neither SAEs nor TEAEs prompted withdrawal from the study.

Table 4 Demographic characteristics ($N = 24$)

Parameter	Age	Height (cm)	Weight (kg)	BMI (kg/m^2)
Mean ± SD	25.1 ± 6.82	169.9 ± 6.89	63.0 ± 7.51	21.80 ± 1.876
Median	22.0	169.0	61.5	22.35
Minimum–maximum	19–42	158–182	52–76	19.1–24.9

BMI body mass index, *SD* standard deviation

Table 5 Analysis of variance results of pharmacokinetic parameters after logarithmic transformation in healthy subjects after oral administration of globalagliatin 80 mg

Parameter	Variation	*f*-value	*p*-value
C_{max} ($N = 24$)	Sequence	0.016	0.900
	Cycle	2.668	0.117
	Administration conditions	9.037	0.007
AUC_t ($N = 24$)	Sequence	0.016	0.899
	Cycle	4.071	0.056
	Administration conditions	37.390	< 0.001
AUC_∞ ($N = 24$)	Sequence	0.007	0.936
	Cycle	4.155	0.054
	Administration conditions	37.778	<0.001

C_{max} maximum concentration, AUC_t area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration, AUC_∞ area under the plasma concentration-time curve from time zero extrapolated to infinity

Additionally, no hypoglycemia event occurred and no prolongation of the ECG QT interval occurred. Comparative with baseline, no anomalies were observed in laboratory examinations, vital signs, or physical examinations. In summary, healthy Chinese adult subjects exhibited favorable safety and tolerability profiles when administered a single oral dose of globalagliatin 80 mg under fasting and high-fat meal conditions (see Tables 8, 9).

4 Discussion

This clinical trial, conducted among healthy Chinese subjects, adhered to a randomized, open, two-cycle, double-crossover, single-dose, single-center, phase I design. The trial was meticulously executed within a drug clinical trial institution registered with the National Medical Products Administration. Stringent adherence to GCP principles and pertinent laws and regulations was maintained throughout the trial. Following ethical review and approval by the trial institution, 24 subjects were randomly selected for participation in this study. Throughout the trial, subjects exhibited commendable compliance, strictly adhering to the phase I clinical trial ward and protocol requirements during blood sample collection. Importantly, there were no significant protocol violations throughout the entirety of the experimental process. Based on the PK parameter results, compared with the fasting state, healthy subjects who consumed a high-fat diet (988.4 Kcal, 54% fat) experienced a 24.8% increase in C_{max}, a 35.2% increase in AUC_t, and a 35.4% increase in AUC_∞ of globalagliatin. This indicates that a high-fat meal increased the absorption rate and degree of globalagliatin in healthy Chinese volunteers. The non-parametric test for T_{max} and t_{lag} revealed a p-value of < 0.05, signifying a statistically significant difference. This suggests that in comparison with the fasting group, the consumption of a high-fat meal led to a delayed absorption of globalagliatin into the bloodstream, potentially due to its influence on gastric emptying. Based on the safety analysis results, it is shown that although the absorption rate and extent of globalagliatin increased after a high-fat meal, this exposure increase did not result in an increased safety and tolerance risk based on safety data analysis.

Table 7 Non-parametric tests for T_{max} and t_{lag} in healthy subjects after oral administration of globalagliatin 80 mg ($N = 24$)

Parameter	Statistic	*p*-Value	Statistical method
T_{max}	40.000	0.021	Paired Wilcoxon method
t_{lag}	126.500	< 0.001	Paired Wilcoxon method

T_{max} time to reach maximum concentration, t_{lag} lag time (the observation time before the first measurable blood concentration was observed)

GK activators (GKAs) represent a novel class of drugs for diabetes treatment, improving the body's sensitivity to glucose through joint action on the pancreas and liver. The GK junction domain, located in the connected domain of the kinase structure, serves as the binding site for GKA and glucose. By controlling the conformation of GK, GKA maintains GK activity, thereby accelerating the conversion of hexose to hexose 6-phosphate [16]. Thus far, various GKA drugs, including AZD1656, MK-0941, dorzagliatin, PF-04937319, and others have entered clinical trials [17–20]. A high-fat meal, as the most common dietary factor, may affect the absorption or metabolism of some drugs [21, 22]. Globalagliatin is a GKA developed by Eli Lilly (Indianapolis, IN, USA) and Yabao Pharmaceuticals

Table 6 90% CI test of pharmacokinetic parameters after logarithmic conversion in healthy subjects after oral administration of globalagliatin 80 mg

Parameter	Geometric mean (high-fat meal, $N = 24$)	Geometric mean (fasting, $N = 24$)	Ratio % (high-fat meal/fasting)	90% CI
C_{max} (ng/mL)	26.60	21.31	124.81	109.97–141.65
AUC_t (h*ng/mL)	917.50	678.44	135.24	124.24–147.20
AUC_∞ (h*ng/mL)	973.57	718.93	135.42	124.42–147.39

CI confidence interval, C_{max} maximum concentration, AUC_t area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration, AUC_∞ area under the plasma concentration-time curve from time zero extrapolated to infinity

Table 8 Analysis of treatment-emergent adverse event subsystems

SOC	Fasting		High-fat meal		Total	
PT	*n* (%)	Frequency	*n* (%)	Frequency	*n* (%)	Frequency
N	24		24		24	
Total	6 (25.0)	7	4 (16.7)	4	9 (37.5)	11
Various inspections	5 (20.8)	6	3 (12.5)	3	7 (29.2)	9
Elevated alanine aminotransferase	2 (8.3)	2	0 (0)	0	2 (8.3)	2
Elevated amylase	1 (4.2)	1	1 (4.2)	1	2 (8.3)	2
Positive urinary leukocyte	1 (4.2)	1	1 (4.2)	1	2 (8.3)	2
Decreased leukocyte count	1 (4.2)	1	0 (0)	0	1 (4.2)	1
Detected urinary sediment	1 (4.2)	1	0 (0)	0	1 (4.2)	1
Elevated serum uric acid	0 (0)	0	1 (4.2)	1	1 (4.2)	1
Various nervous system diseases	0 (0)	0	1 (4.2)	1	1 (4.2)	1
Myoclonus	0 (0)	0	1 (4.2)	1	1 (4.2)	1
Heart organ diseases	1 (4.2)	1	0 (0)	0	1 (4.2)	1
Sinus bradycardia	1 (4.2)	1	0 (0)	0	1 (4.2)	1

SOC System Organ Class, *PT* Preferred Term

Table 9 Analysis of adverse drug reaction subsystems

SOC	Fasting		High-fat meal		Total	
PT	*n* (%)	Frequency	*n* (%)	Frequency	*n* (%)	Frequency
N	24		24		24	
Total	4 (16.7)	4	3 (12.5)	3	6 (25.0)	7
Various inspections	4 (16.7)	4	2 (8.3)	2	5 (20.8)	6
Elevated alanine aminotransferase	2 (8.3)	2	0 (0)	0	2 (8.3)	2
Elevated amylase	1 (4.2)	1	1 (4.2)	1	2 (8.3)	2
Decreased leukocyte count	1 (4.2)	1	0 (0)	0	1 (4.2)	1
Elevated serum uric acid	0 (0)	0	1 (4.2)	1	1 (4.2)	1
Various nervous system diseases	0 (0)	0	1 (4.2)	1	1 (4.2)	1
Myoclonus	0 (0)	0	1 (4.2)	1	1 (4.2)	1

SOC System Organ Class, *PT* Preferred Term

(Suzhou, China). There are no research reports on the impact of a high-fat meal on the PK of globalagliatin in Chinese volunteers. Based on our results, a high-fat meal slightly increased the exposure of globalagliatin in the human body. While there is one report indicating that the oral administration of the liver GKA, TMG-123, can be rapidly absorbed on an empty stomach without being affected by eating [16], the above studies indicate that the PK performance of a high-fat meal varies among different GKA groups.

The safety of GKA has been a key factor limiting its clinical use. The first generation of GKA exhibited significant cardiovascular toxicity, leading to the development of a second-generation GKA such as piragliatin. However, these drugs showed potential liver cell damage or inflammation in human metabolism. Hoffmann-La Roche AG developed the fourth-generation GKA HMS5552, also known as dorzagliatin, to address the issues associated with second-generation GKA [23]. One research study reported the safety, PK, and PD of globalagliatin in Chinese patients with T2DM [10]. Despite several adverse reactions observed in this study, the author believes that the drug has good safety and tolerability for the Chinese population. However, an increase in TG levels was associated with the administration of globalagliatin [24], and it remains unclear whether a high-fat meal exacerbates this adverse reaction. Fortunately, we did not observe this phenomenon of TG stacking in our research results. In our trial, although we observed various types of TEAEs and ADRs, the increased exposure to globalagliatin did not lead to an elevated safety or tolerance risk in Chinese volunteers. Moreover, the incidence of AEs observed in this study closely aligns with that in the domestic phase Ia and Ib clinical trials of globalagliatin [9, 10]. Therefore, we conclude that the frequency and severity of TEAEs and ADRs in this study fall within the acceptable range. Our trial provides theoretical support for the rational use of globalagliatin in clinical practice.

There are some limitations to our study. First, the relatively small sample size and inclusion of only Chinese participants may affect the generalizability of our findings. However, we conducted dual-cycle experiments to obtain as accurate and reliable data as possible. Second, we did not assess insulin resistance levels in this trial. While some research reports suggest that high drug exposure can reduce insulin resistance [10], it is unclear how a high-fat meal may impact insulin resistance in the presence of increased globalagliatin exposure. This aspect requires further investigation.

5 Conclusions

A high-fat meal increased the C_{max}, AUC_t, and AUC_∞ of globalagliatin compared with fasting conditions in healthy Chinese adult volunteers. Meanwhile, globalagliatin showed favorable safety and tolerability under fasting or high-fat meal conditions.

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Declarations

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Conflicts of Interest/Competing interests Maodi Xu, Yaqin Wang, Xiaohu Wang, Zhichen Pu, Ya Liu, Cuilian Jiang, Xiaokun Shen, Hua Sun, and Haitang Xie declare no conflicts of interest in relation to this work.

Availability of Data and Material The data are unavailable for confidentiality reasons.

Ethics Approval The protocol of this study was approved and authorized by the Drug and Medical Device Branch of Wannan Medical College Yijishan Hospital IRB, Wuhu, China.

Consent to Participate All recruited volunteers agreed to participate and provided written informed consent before the study was initiated.

Consent for Publication All authors approved the publication of this manuscript.

Code Availability Not applicable.

Authors' Contributions This study was designed by CJ, XS, HS and HX, while MX, YW, XW, ZP, and YL performed the research. All authors read and approved the manuscript.

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