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The safety, tolerability, pharmacokinetics and pharmacodynamics of GZR18 in healthy American and Chinese adult subjects

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Abstract

Aims: GZR18, a novel long-acting GLP-1 receptor agonist, has demonstrated substantial metabolic improvements in diabetic and obese animal models. The present studies aimed to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of the ascending dose of GZR18 in healthy American and Chinese subjects.

Materials and Methods: In these phases 1, randomized, double-blind, placebo-controlled, sequential, dose-escalation US and Chinese studies, healthy American and Chinese adults with similar age were enrolled to once-weekly subcutaneous injection of GZR18 or placebo. The studies included three cohorts of male American subjects (cohorts US-1–3) and six cohorts of Chinese subjects (cohorts CN-1–6, male and female), each with a specified target dose of GZR18 ranging from 1 to 50 μg/kg (1–10 μg/kg for US study and 5–50 μg/kg for Chinese study). The primary endpoints were the safety and tolerability of GZR18. Blood samples were collected for PK and PD analysis of GZR18 before and after dosing. A population PK analysis of GZR18 was conducted to ascertain whether there are ethnic PK differences between American and Chinese adults.

Results: The exposure of GZR18 was comparable between healthy American and Chinese subjects, with the geometric mean ratio between the two populations for $AUC_{0\text{-}t}$ and C_{max} close to 1. A dose-dependent increase in $AUC_{0\text{-}t}$ and C_{max} occurred in both populations. The median time to maximum plasma concentrations (T_{max}) in American subjects ranged from 72 to 96 h, and the mean T_{max} ranged from 60 to 72 h in Chinese subjects. The half-life of GZR18 was approximately 7 days in both American and Chinese subjects. Evident body weight reduction was observed in GZR18 treatment groups in Chinese subjects (cohorts CN-3–6 on Day 15, −1.25 to

Yue Liu and Wei Chen contributed equally to this study.

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−1.86 kg; −1.88% to −3.11%). No deaths, serious adverse events or hypoglycaemia were reported. Decreased appetite and nausea were the most frequently reported treatment-emergent adverse events, observed in Chinese study and mild in severity. The safety profile of GZR18 was generally consistent with the same class of drugs.

Conclusions: GZR18 demonstrates good tolerability in healthy American and Chinese subjects. No ethnic differences were observed between healthy American and Chinese subjects. The safety, PK and PD profiles of GZR18 support its further clinical evaluation for glycaemic and body weight control.

KEYWORDS

glucagon-like peptide-1 receptor agonist, GZR18, diabetes, obesity, pharmacokinetics

1 | INTRODUCTION

The global prevalence of overweight and obesity (body mass index [BMI] ≥25 kg/m^2) is projected to surpass four billion people by 2035, compared to over 2.6 billion in 2020.[1] The prevalence of overweight and obesity has rapidly increased globally, becoming a serious public health issue.[2,3] Obesity and overweight are linked to various health problems,[4] including high blood pressure,[5] high cholesterol, asthma, sleep disorders, liver disease, type 2 diabetes mellitus (T2DM), coronary heart disease, stroke[6] and cancer.[7] As obesity is a significant risk factor for developing T2DM, the rising rates of obesity worldwide exacerbate the urgency to address both conditions with more effective and safer therapeutic options. With the increasing prevalence of type 2 diabetes, there is an urgent need to develop therapeutic drugs to manage both obesity and T2DM with improved efficacy, safety and convenience.[8]

Glucagon-like peptide-1 (GLP-1), secreted by L cells in the small intestine, stimulates insulin secretion and decreases glucagon secretion in a glucose-dependent manner,[9] delay gastric emptying[10] and decrease appetite.[11,12] Due to GLP-1's glucose-lowering and weight-loss effects, GLP-1 receptor agonists (RA) have emerged as recognized treatment options for T2DM[13] and overweight or obesity.[14] GLP-1 RA drugs have been developed from daily formulations to weekly formulations, as well as longer dosing intervals, to improve patient compliance and treatment convenience.[15]

In recent years, based on GLP-1, there has been an increasing prevalence of dual-target or triple-target incretin analog RAs or antagonists undergoing clinical studies, to obtain more efficacious weight loss outcomes.[16] Further investigation though is required to elucidate the precise molecular mechanistic role of incretin targets other than GLP-1 in weight loss.[17] It remains unclear whether there is superior efficacy for multi-target incretin analogs versus single-target incretins in obesity treatment. The single-target GLP-1 RA has a relatively straightforward structure and an unambiguous mechanism of action, which has been shown to provide several benefits, including cardiovascular protection, blood pressure reduction and improvement in blood lipid profiles.[18–20]

GZR18 is a subcutaneously administered GLP-1 analog currently under development for the treatment of T2DM and weight management. GZR18 exhibits 94% amino acid sequence homology (same with semaglutide) to native human GLP-1 without unnatural amino acids. This has resulted in a reduction in immunogenicity, an enhancement in safety, a streamlined production process and an overall improvement in the pharmacological profile compared with GLP-1 agonists that contain artificial amino acids.[21] The GZR18 peptide has been modified from the native GLP-1 with a 22C fatty acid side chain, which renders it less susceptible to degradation by dipeptidyl peptidase 4 and enhances its specific high-affinity binding to albumin. Preclinical pharmacological studies have demonstrated GZR18's low affinity for the GLP-1 receptor and its extended half-life, suggesting a longer duration of action, longer dosing intervals and higher adherence in clinical treatment.[21] Additionally, preclinical studies have confirmed the safety, glycaemic improvement and weight loss effects of GZR18 in rat and mouse models.[21] In these randomized, double-blind, placebo-controlled, dose-escalation phase 1 US and China studies, the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of GZR18 were investigated in healthy American and Chinese subjects, and the PK characteristics on the two populations were comparatively analysed.

2 | METHODS

2.1 | Trial design

The Trial A was conducted in the United States and enrolled healthy male American subjects at a site in the United States of America (Celerion, Lincoln, Nebraska). Trial B was conducted in China and enrolled healthy Chinese subjects at a site in Beijing city (the Clinical Trial Center, Beijing Hospital, Beijing). Both trials were approved by the Ethics Committee. These clinical trials of GZR18 were randomized, double-blind, placebo-controlled, dose-escalation trial. Trial A included three cohorts (cohorts US-1–3), and Trial B included six cohorts (cohorts CN-1–6), with target doses of GZR18 ranging from 1 to 50 μg/kg (1–10 μg/kg for Trial A and 5–50 μg/kg for Trial B). In Trial A, all subjects received a single injection of GZR18 at the target dose or placebo. In Trial B, subjects in cohorts CN-1–2 (5–10 μg/kg) received a single dose of GZR18 or placebo, while those in cohorts

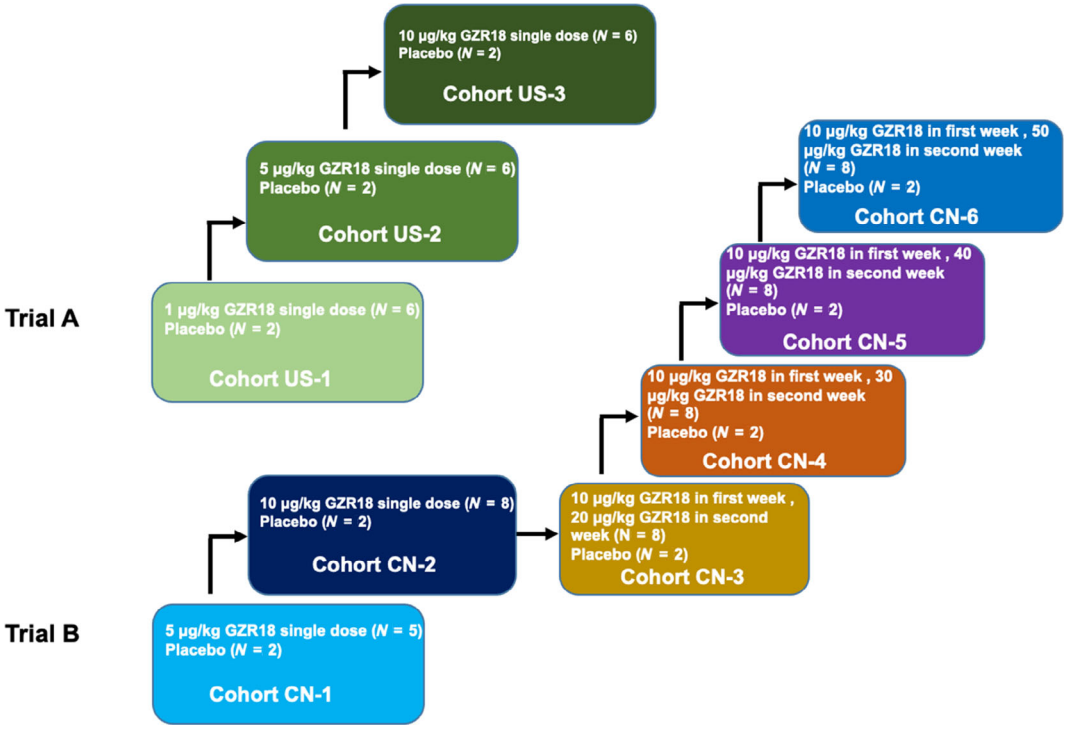

FIGURE 1 Design of the trials. A single dose and a gradual once a week dose to the target dose of GZR18 in healthy subjects.

CN-3–6 (20–50 μg/kg) received 10 μg/kg of GZR18 or placebo in the first week, followed by the second dose of GZR18 at the target dose or placebo in the second week (Table S1). The detailed trial design of the studies is shown in Figure 1 and Table S1. The studies were conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Guidance for Good Clinical Practice, and all applicable local laws and requirements. All subjects provided written informed consent before the study.

2.2 | Primary objective and secondary objective

The primary objective was to evaluate the safety and tolerability of GZR18 in healthy American and Chinese subjects. The secondary objective was to evaluate the PK and PD characteristics of GZR18 in healthy American and Chinese subjects.

2.3 | Trial endpoints

The primary endpoint of the trial was the safety indicators: the incidence of treatment-emergent adverse events (TEAEs) during treatment, including but not limited to hypoglycaemia, injection site reactions, clinical laboratory tests (blood routine, blood biochemistry, urine routine, etc.), 12-lead electrocardiogram, clinically significant abnormalities in vital signs and physical examination.

Secondary PK endpoints for GZR18 included the maximum drug concentration (C_{max}) after reaching the target dose, the area under the drug concentration–time curve ($AUC_{0\text{-last}}$) from 0 to the last accurate concentration time and the drug concentration–time from 0 to infinity area under the curve ($AUC_{0\text{-inf}}$), the time to maximum drug concentration (T_{max}) and terminal elimination half-life ($t_{1/2}$).

Secondary PD endpoints after the first dose of GZR18 were PD indicators: area under the concentration–time curve of blood glucose, C-peptide and insulin, fasting blood glucose, C-peptide and insulin, body weight and BMI.

2.4 | Inclusion and exclusion criteria

A total of 24 American subjects (male with BMI 20.0–35.0 kg/m^2) (A) and 57 Chinese subjects (male or female with BMI 19.0–26.0 kg/m^2) (B) were enrolled, respectively, in the two phase 1 trials (Trial A and Trial B). Subjects were evaluated for eligibility after they signed a written informed consent form. Subjects must maintain a good daily routine, communicate well with investigators and comply with the various requirements of clinical trials. No evidence of other disease was present.

Subjects meeting any of the following criteria were excluded: active coinfection with hepatitis A, B or C viruses, the presence of human immunodeficiency virus infection, hepatocellular carcinoma, fulminant liver failure, known or suspected allergy to test-related products, history of drug food allergy or history of allergy-related diseases. The detailed inclusion and exclusion criteria information is shown in the Supporting Information.

2.5 | Safety assessments

Safety assessments included adverse events (AEs), episodes of hypoglycaemia, laboratory safety parameters, a physical examination, vital signs and an electrocardiogram. The incidence of hypoglycaemia was monitored at the trial site during the in-house visits by means of glucose measurement. Hypoglycaemia was classified as severe if a plasma glucose value of less than 2.8 mmol/L was confirmed by a blood glucose measurement and if the subject exhibited symptoms indicative of hypoglycaemia that the subject was unable to self-medicate and that placed the subject at risk of self-injury or harm to others.

The safety follow-up time in Trial A and Trial B were 23 and 20 days, respectively.

2.6 | PK and PD assessments

In Trial A, the blood samples of American subjects for PK determination of GZR18 were collected at the following time points: 0, 1, 2, 3, 6, 8, 12, 24, 72, 96, 120, 168, 264, 432 and 720 h after dose. In Trial B, the blood samples of Chinese subjects for PK assessment of GZR18 were collected at the following time points post-dose for cohorts CN-1–2: 0, 1, 2, 3, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 264, 432 and 648 h. For cohorts CN-3–6, samples were taken at the following time points after the first dose: 0, 1, 2, 3, 6, 8, 12, 24, 48, 60, 72, 96, 120, 144 and 168 h. After the second dose, samples for cohorts CN-3–6 were collected at: 0, 1, 2, 3, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 264, 432 and 648 h. Bioanalysis of blood samples was performed using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) assay.

In Trial A, the blood samples for PD assessment of GZR18 were collected at the following time points: 0, 1, 2, 3, 6, 8, 10, 12, 13, 14, 24, 48, 72, 96, 120, 168, 264, 432 and 720 h post-dose. In Trial B, the blood samples for determination of glucose, insulin and C-peptide were collected at the following time points post-dose for cohorts CN-1–2: 1, 2, 3, 5, 6, 8, 11, 12, 13 and 14 h. For cohorts CN-3–6, samples were taken at the same time points after the first and second doses: 1, 2, 3, 5, 6, 8, 11, 12, 13 and 14 h.

2.7 | Analysis

A formal statistical evaluation of the sample size was not conducted due to the absence of prior human data for GZR18. Instead, the sample size was determined based on available data from initial human trials of semaglutide, a comparable drug on the market. The sample size was also based on information considered sufficient by the investigator and sponsor to achieve the trial objectives (Supporting Information).

The PK and PD parameters were estimated using Phoenix WinNonlin 8.3 software, while statistical analysis was conducted with SAS software (version 9.4). Phoenix WinNonlin was employed to estimate and analyse the PD parameters of blood glucose, C-peptide and insulin concentrations using a non-compartmental model, and the PD parameters were subsequently calculated. AEs were coded using the International Dictionary of Medical Terms (MedDRA, version 27.1) and categorized by dose group. AEs that occurred prior to the first dosing were excluded from the analysis and were only presented in the list. Missing data were not inputted. No sensitivity analysis was conducted for the two experiments. The safety of the study subjects was evaluated based on the safety analysis set, which was randomly assigned to receive either GZR18 or a placebo and had at least one safety recording after administration.

2.8 | Population pharmacokinetic model of GZR18 in healthy adult subjects

A population PK model was developed based on the PK data collected in Trial A and Trial B, both within healthy adult subjects. The structural population PK model was developed with data collected from subjects who were administered a single subcutaneous injection of GZR18 at a dose level of 5 and 10 μg/kg. Plasma concentration-time data of GZR18 was analysed using a nonlinear mixed effects modelling approach. Multiple compartmental models (1-, 2-compartment models) were investigated to optimally characterize the PK of GZR18. More detail of the PK model was presented in the Supporting Information.

3 | RESULTS

3.1 | Demographic and baseline characteristics

Between 8 March 2022 and 9 March 2023, a total of 24 male American subjects were enrolled in the Trial A. There were 24 subjects included in the safety and PD analyses. All 18 subjects who received the active treatment were included in the PK analysis. Two (8.3%) subjects were of Hispanic or Latino ethnicity, and 22 (91.7%) subjects belonged to other ethnic groups. Fifteen subjects (62.5%) were white race, eight subjects (33.3%) were black or African American, and one subject (4.2%) was American Indian. The mean age was 35.9 ± 13.2 years and the mean BMI was 25.64 ± 3.82 kg/m^2 in the GZR18 group. The mean age was 31.7 ± 6.02 years, and the mean BMI was 30.36 ± 3.23 kg/m^2 in the placebo group (Table 1).

Between 2 December 2021 and 20 October 2022, a total of 305 Chinese subjects were screened for eligibility in Trial B, and 57 subjects were randomly enrolled in this study, comprising 35 males (61.4%) and 22 females (38.6%). Fifty-six (98.2%) subjects were of Han nationality, and one (1.8%) subject belonged to other ethnic groups. The mean age was 33.1 ± 7.34 years, ranging from 22 to 52 years, and the mean BMI was 22.70 ± 1.65 kg/m^2 (Table 1).

The demographics and baseline characteristics of the subjects are summarized in Table 1. The flow diagram for the overall study is detailed in Figure 2. These characteristics were consistent across all groups, both in American and Chinese subjects.

TABLE 1 Summary of demographics and baseline characteristics.

	Chinese subjects							American subjects			
	Cohort CN-1 (5 μg/kg)	Cohort CN-2 (10 μg/kg)	Cohort CN-3 (20 μg/kg)	Cohort CN-4 (30 μg/kg)	Cohort CN-5 (40 μg/kg)	Cohort CN-6 (50 μg/kg)	Total placebo	Cohort US-1 (1 μg/kg)	Cohort US-2 (5 μg/kg)	Cohort US-3 (10 μg/kg)	Total placebo
	N = 5	*N* = 8	*N* = 8	*N* = 8	*N* = 8	*N* = 8	*N* = 12	*N* = 6	*N* = 6	*N* = 6	*N* = 6
Age (years)	31.0 (9.17)	29.6 (6.23)	36.0 (6.39)	33.9 (6.38)	29.9 (5.74)	30.4 (6.72)	37.8 (7.96)	45.5 (13.31)	30.3 (7.99)	32.0 (13.61)	31.7 (6.02)
Gender, *n* (%) M	5 (100)	5 (62.5)	4 (50.0)	4 (50.0)	6 (75.0)	6 (75.0)	5 (41.7)	6 (100%)	6 (100%)	6 (100%)	6 (100%)
Gender, *n* (%) F	0	3 (37.5)	4 (50.0)	4 (50.0)	2 (25.0)	2 (25.0)	7 (58.3)	0	0	0	0
Race—American Indian	–	–	–	–	–	–	–	0 (0%)	0 (0%)	1 (17%)	0 (0%)
Race—Black or African American	–	–	–	–	–	–	–	2 (33%)	2 (33%)	2 (33%)	2 (33%)
Race—White	–	–	–	–	–	–	–	4 (67%)	4 (67%)	3 (50%)	4 (67%)
Ethnicity*, *n* (%)	5 (100)	8 (100)	7 (87.5)	8 (100)	8 (100)	8 (100)	12 (100)	–	–	–	–
Ethnicity, *n* (%) Others	0	0	1 (12.5)	0	0	0	0	–	–	–	–
Hispanic or Latino	–	–	–	–	–	–	–	1 (17%)	0 (0%)	0 (0%)	1 (17%)
Not Hispanic or Latino	–	–	–	–	–	–	–	5 (83%)	6 (100%)	6 (100%)	5 (83%)
Weight (kg)	64.06 (6.10)	62.40 (7.38)	61.31 (10.17)	63.01 (7.57)	62.38 (9.21)	65.81 (7.32)	60.56 (6.34)	78.93 (5.52)	72.05 (9.05)	84.23 (21.51)	91.58 (13.18)
Body height (cm)	167.96 (2.68)	165.18 (7.05)	165.56 (10.49)	164.16 (7.91)	168.15 (9.71)	170.18 (8.89)	162.28 (6.28)	170.00 (6.2)	177.70 (2.73)	177.20 (10.68)	173.30 (4.93)
BMI (kg/m^2)	22.66 (1.54)	22.81 (1.21)	22.26 (1.93)	23.34 (1.97)	22.04 (2.25)	22.73 (1.55)	22.94 (1.26)	27.39 (2.08)	22.89 (3.12)	26.62 (4.63)	30.36 (3.2)
HSA (g/L)	48.0 (1.58)	47.3 (3.77)	47.6 (2.88)	46.1 (2.03)	46.6 (1.3)	46.1 (2.03)	44.7 (1.97)	45.5 (2.74)	48.7 (6.77)	47 (3.16)	47.7 (3.77)

Note: Data are *n* (%) or mean (SD). Ethnicity* = Han in Chinese subjects, others = Not Han in Chinese subjects.

Abbreviations: BMI, body mass index; F, female; HSA, human serum albumin; M, male; *N*, number of subjects in each group.

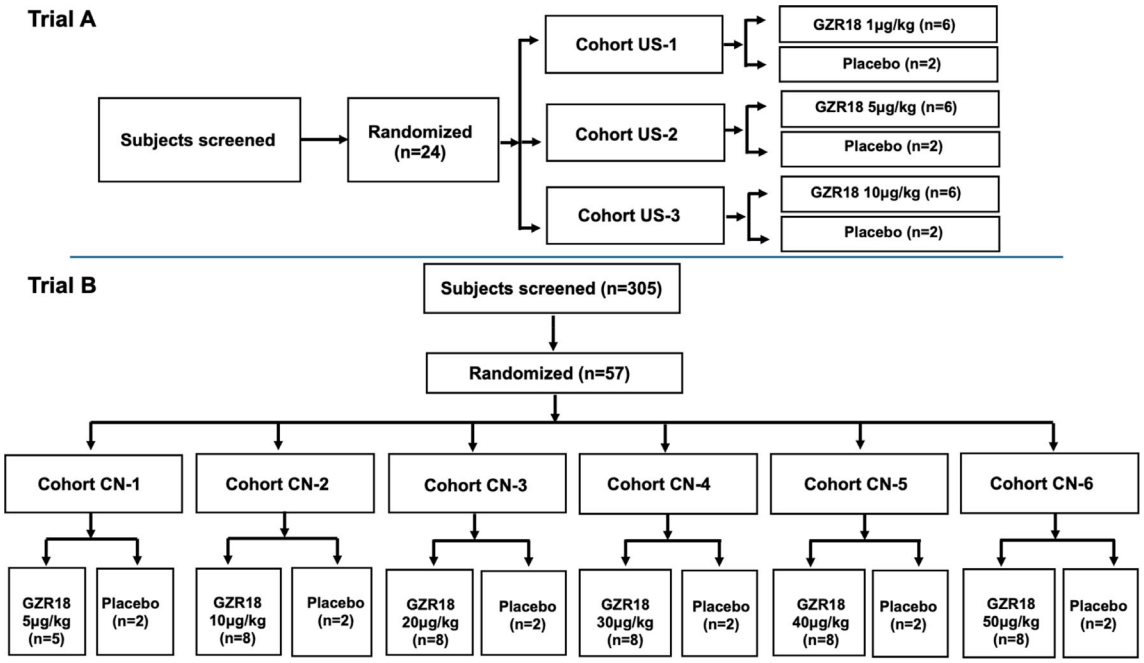

FIGURE 2 Flow diagram of the trials.

3.2 | Safety

In Trial A, 23 American subjects completed the study. One subject was lost to follow-up due to their decision to withdraw from the study on Day 12, citing an unwillingness to complete return visits. Eleven TEAEs were reported by three (17%) subjects following the administration of GZR18, including one (17%) subject received 1.0 μg/kg and two (33%) subjects received 5.0 μg/kg. Six TEAEs were reported by two (33%) subjects following the administration of placebo (Table 2). Headache was the most frequently reported AE, which occurred in three cases affecting two subjects, including one subject received 1.0 μg/kg and one subject received placebo. Except for a Grade 2 (moderate) tachycardia[22] in placebo group, all AEs were Grade 1 (mild) in severity. One event was considered to be likely related to the study drug (increased blood creatinine [cohort US-2]), four events were deemed possibly related and twelve events were determined to be unrelated.

In Trial B, a total of 56 Chinese subjects completed the study, with one subject discontinuing due to an AE of urticaria in the placebo group. The incidence of AEs in the GZR18 group was similar to that in the placebo group. There were 43 TEAEs reported among 45 subjects receiving GZR18 and nine TEAEs among 12 subjects receiving placebo. In the GZR18 group, the most common TEAEs were decreased appetite (14.0%), increased blood uric acid (7.0%) and epistaxis (7.0%), compared to 0% for each in the placebo group (Table 2). There were 19 AEs associated with the investigational product in the GZR18 group, distributed as follows: two events in the cohort CN-2 (10 μg/kg), eight events in the cohort CN-4 (30 μg/kg), four events in the cohort CN-5 (40 μg/kg) and five events in the cohort CN-6 (50 μg/kg).

No deaths or anti-GZR18 antibodies were reported in either Trial A or Trial B. Additionally, no injection site reactions or serious AEs occurred even at the highest dose of 50 μg/kg (approximately 3.5 mg for a 70 kg subject). Most AEs were grade 1 in severity, of mild intensity and resolved without the need for intervention. Additionally, no hypoglycaemic events or unexpected adverse reactions were observed during the study.

3.3 | Pharmacokinetics

In Trial A, following single subcutaneous administration of 1, 5 and 10 μg/kg GZR18, mean $AUC_{0\text{-inf}}$ increased with increasing dose, with mean (± standard deviation) values of 1402 ± 234.1, 7962 ± 1297.8 and 19 427 ± 2914 h*ng/mL for $AUC_{0\text{-inf}}$, respectively. The raw mean plasma GZR18 peak concentrations (C_{max}) for the 1, 5 and 10 μg/kg dose levels were 4.59 ± 0.79, 27.1 ± 4.09 and 67.5 ± 14.1 ng/mL, respectively, and occurred at 96, 72 and 72 h (median T_{max}), respectively. Mean GZR18 $t_{½}$ values were 169 ± 48.5, 152 ± 18.1 and 149 ± 18.3 h for the 1, 5 and 10 μg/kg dose levels, respectively (Table 3).

In Trial B, a single subcutaneous injection of GZR18 resulted in a peak serum concentration of the drug at approximately 60 h post-administration (i.e., 10 μg/kg). Following this peak, the concentration declined, with parallel elimination phases observed across all dose groups. A dose-proportional PK response was observed. Specifically, the raw mean maximum plasma concentrations (C_{max}) in cohorts CN-1 and CN-2 were 33.64 ± 5.52 and 68.55 ± 7.34 ng/mL, and the mean C_{max} ranged from 143.80 ± 22.04 to 344.10 ± 50.16 ng/mL in cohorts CN-3–6 (Table 4). The median time to reach maximum concentration

TABLE 2 Summary of AEs (safety analysis set).

	Chinese subjects							American subjects			
	Cohort CN-1 (5 μg/kg)	Cohort CN-2 (10 μg/kg)	Cohort CN-3 (20 μg/kg)	Cohort CN-4 (30 μg/kg)	Cohort CN-5 (40 μg/kg)	Cohort CN-6 (50 μg/kg)	Total placebo	Cohort US-1 (1 μg/kg)	Cohort US-2 (5 μg/kg)	Cohort US-3 (10 μg/kg)	Total placebo
	N = 5	*N* = 8	*N* = 8	*N* = 8	*N* = 8	*N* = 8	*N* = 12	*N* = 6	*N* = 6	*N* = 6	*N* = 6
Treatment-emergent adverse event *n* (%) *E*	3 (60) 7	3 (37.5) 3	4 (50) 5	5 (62.5) 15	4 (50) 6	6 (75) 7	6 (50) 9	1 (17) 9	2 (33) 2	0 (0) 0	2 (33) 6
SAEs	0	0	0	0	0	0	0	0	0	0	0
SARs	0	0	0	0	0	0	0	0	0	0	0
AEs leading to early termination *n* (%) *E*	0	0	0	0	0	0	1 (8.3) 1	0	0	0	0
ARs leading to early termination *n* (%) *E*	0	0	0	0	0	0	1 (8.3) 1	0	0	0	0
AEs with severity of ≥Grade 3	0	0	0	0	0	0	0	0	0	0	0
ARs with severity of ≥Grade 3	0	0	0	0	0	0	0	0	0	0	0
Hypoglycaemia event (AESI)	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal adverse reaction (AESI) *n* (%) *E*	0	0	1 (12.5) 1	2 (25) 4	3 (37.5) 3	3 (37.5) 4	0	0	0	0	0
Suspected unexpected serious adverse reaction	0	0	0	0	0	0	0	0	0	0	0

Note: TEAE means treatment-emergent adverse event, defined as an AE occurring after injection of GZR18 or placebo at treatment period (D1 for cohorts CN-1–2; D1 and D8 for cohorts CN-3–6). AEs that occur pre-dose and worsen during the study are also considered TEAEs. Gastrointestinal adverse reaction (AESI): decreased appetite, nausea, vomiting, diarrhoea and constipation.
Abbreviations: %, percentage of subjects in each category; AEs, adverse events; ARs, adverse reactions; AESI, adverse events of special interest; *E*, number of adverse events; *n*, number of subjects in each categories; *N*, number of subjects in each group; SAEs, severe adverse events; SARs, severe adverse reactions.

TABLE 3 Pharmacokinetic parameters of GZR18 after single administration.

Pharmacokinetic parameters	Chinese subjects		American subjects			Fold change (Chinese/American)	
	Cohort CN-1 (5 μg/kg) ($N = 5$)	Cohort CN-2 (10 μg/kg) ($N = 8$)	Cohort US-1 (1 μg/kg) ($N = 6$)	Cohort US-2 (5 μg/kg) ($N = 6$)	Cohort US-3 (10 μg/kg) ($N = 6$)		
	Mean (CV%)	Mean (CV%)	Mean (CV%)	Mean (CV%)	Mean (CV%)	5 μg/kg	10 μg/kg
C_{max} ([ng/mL]/[μg/kg])[a]	424.54 (16.4)	432.55 (10.7)	342.87 (17.2)	423.30 (15.1)	527.18 (20.9)	1.00	0.82
$AUC_{0\text{-}t}$ ([h*ng/mL]/[μg/kg])[a]	125 733.06 (8.8)	128 440.05 (5.9)	68 798 (31.4)	117 243.72 (18.1)	145 031.70 (14.4)	1.07	0.89
$AUC_{0\text{-}inf}$ ([h*ng/mL]/[μg/kg])[a]	13 3961.30 (9.5)	136 996.41 (5.3)	104 729 (16.7)	124 366.44 (16.3)	151 724.87 (15.0)	1.08	0.90
T_{max}[b] (h)	72 (60, 96)	60 (48, 96)	96 (72–97)	72 (24–96)	72 (72–96)	–	–
$t_{1/2}$ (h)	158.10 (8.0)	154.76 (7.2)	169 (28.7)	152 (11.9)	149 (12.3)	–	–

Abbreviations: AUC, area under the curve; C_{max}, maximum drug concentration; CV, coefficient of variation; N, number of subjects in each group; T_{max}, time to maximum plasma concentrations.
[a]Data were calibrated based on dose and the mean weights of both populations (63.1 kg for Chinese subjects and 78.1 kg for American subjects): C_{max}/(dose/body weight); $AUC_{0\text{-}t}$/(dose/body weight); $AUC_{0\text{-}t}$/(dose/body weight).
[b]Median (minimum, maximum).

(T_{max}) for target doses ranging from 5 to 50 μg/kg spanned from 60 (36, 96) to 72 (48, 120) h, and the area under the curve from time zero to the last measurable concentration ($AUC_{0\text{-}t}$) ranged from 9963.29 ± 873.69 to 109 037.06 ± 12 594.89 h*ng/mL. The mean half-life ($t_{1/2}$) values ranged from 154.76 ± 11.22 to 163.88 ± 18.89 h across all treatments.

The mean GZR18 concentration–time profile was comparable between American and Chinese subjects same dose group (5 and 10 μg/kg, Figure 3). The exposure of GZR18 ($AUC_{0\text{-}t}$) was found to increase in a dose-dependent manner and to be comparable between American and Chinese subjects in both 5.0 and 10.0 μg/kg dose groups.

In Trial A, dose proportionality assessment of PK parameters ($AUC_{0\text{-}168}$, $AUC_{0\text{-}inf}$ and C_{max}) was performed using a power model over the 1.0–10.0 μg/kg dose range. The point estimates and 95% confidence intervals (CIs) for slope terms (β1 or slope) of the linear power model for $AUC_{0\text{-}168}$, $AUC_{0\text{-}inf}$ and C_{max} were 1.17 (95% CI 1.07–1.27), 1.13 (95% CI 1.05–1.22) and 1.15 (95% CI 1.06–1.25), respectively (Table S2). Slope estimates were all within the 0.80–1.20 interval, but close to the upper bound of 1.20. However, for all the PK parameters, the 95% CI around the slope ß1 did not include 1. Overall, results suggested that following a single dose of GZR18, the increase in exposure over the dose range of 1.0–10.0 μg/kg generally appeared to be slightly more than dose proportional.

In Trial B, the power model was employed to assess the PK parameters, specifically the proportional dose–response relationship. Within the dose range of 5–50 μg/kg (cohorts CN-1–2, and the second dose for cohorts CN-3–6), the 90% CIs of the slopes of the primary PK parameters, C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of GZR18 are 0.97–1.08, 1.01–1.11 and 1.02–1.12, respectively (Table S3). The 90% CI of the C_{max} slope contains 1. This finding suggests that C_{max} exposure demonstrates a proportional dose–response relationship with the administered dose. Conversely, the 90% CIs of the $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ slopes does not include 1, indicating that $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ exposure does not demonstrate a proportional dose–response relationship with the administered dose.

In the range of doses between 20 and 50 μg/kg (the second dose of D8 days for cohorts CN-3–6), the 90% CIs of the slopes of the primary PK parameters C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of GZR18 are 0.77–1.07, 0.77–1.02 and 0.75–1.03, respectively, all containing 1 (Table S4). This indicated that for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, there was dose proportionality for the doses 20–50 μg/kg.

3.4 | Pharmacodynamics

In Trial A, American subjects must fast from all food and drink, with the exception of water, for 8 h prior to blood draws for clinical laboratory tests. Following the administration of single doses of 1, 5 and 10 μg/kg of GZR18 or placebo to American subjects, no discernible dose- or treatment-related trend was evident in the baseline-adjusted serum glucose and insulin between the active treatments and the placebo (Table 5). The mean change in body weight and BMI was

TABLE 4 Pharmacokinetic parameters of GZR18 after the second administration in cohort CN-3–6 in the Chinese health subjects (mean ± SD).

Pharmacokinetic parameters	Unit	Cohort CN-3 (20 μg/kg) ($N = 8$) Mean ± SD	Cohort CN-4 (30 μg/kg) ($N = 8$) Mean ± SD	Cohort CN-5 (40 μg/kg) ($N = 8$) Mean ± SD	Cohort CN-6 (50 μg/kg) ($N = 8$) Mean ± SD
C_{max}	ng/mL	143.80 ± 22.04	246.50 ± 47.46	279.00 ± 44.47	344.10 ± 50.16
AUC_{0-t}	h*ng/mL	47 146.48 ± 6953.26	76 743.67 ± 11 694.78	89 726.89 ± 13 410.27	109 037.06 ± 12 594.89
AUC_{0-inf}	h*ng/mL	50 990.01 ± 8489.66	82 929.08 ± 13 123.78	96 981.68 ± 15 892.92	117 096.80 ± 14 822.73
T_{max}[a]	h	72 (48,120)	66 (48, 120)	60 (36, 96)	60 (24, 72)
$t_{1/2}$	h	161.49 ± 18.57	159.60 ± 12.91	163.88 ± 18.89	157.96 ± 19.52
λ_z	h^{-1}	0.0043 ± 0.0004	0.0044 ± 0.0004	0.0043 ± 0.0005	0.0044 ± 0.0006
$AUC_{\_\%Extrap}$	%	7.30 ± 2.15	7.37 ± 1.79	7.27 ± 1.79	6.76 ± 2.01

Abbreviations: AUC, area under the curve; C_{max}, maximum drug concentration; T_{max}, time to maximum plasma concentrations.
[a]Median (minimum, maximum).

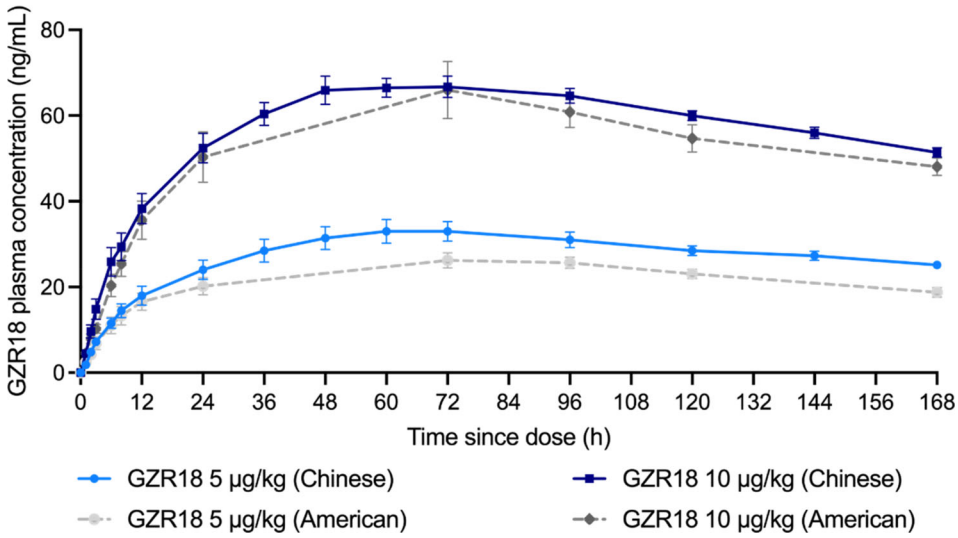

FIGURE 3 Mean blood concentration–time curve of GZR18 after single subcutaneous injection of different doses of GZR18 in healthy American ($N = 6$, each group) and Chinese subjects ($N = 8$, each group). Data are mean ± SE. SE, standard error.

minimal, and no clear trend was observed between the active and placebo treatments. No clinically significant changes in the various parameters of glucose metabolism were observed from baseline to the end of treatment.

In Trial B, the timing of breakfast is approximately 30 min before dosing, while lunch is scheduled approximately 4 h after dosing and dinner is approximately 10 h after dosing. The primary PD parameters of GZR18 ($AUC_{glucose0-14h}$, $AUC_{c\text{-}peptide0-14h}$ and $AUC_{insulin0-14h}$) within the dose ranges of 5–50 μg/kg were shown in Tables 5 and 6. Although subjects who received different doses of GZR18 exhibited varying degrees of reduction in fasting plasma glucose from baseline, the reduction was not significant due to the subjects' health status (data not shown). The mean change in body weight from baseline to Day 15 was −2.63 ± 1.90% in the GZR18 50 μg/kg dose group, compared to −0.23 ± 1.94% in the placebo group (Figure S1). The least-squares mean difference in body weight change from baseline to the end of treatment (Day 15) between the GZR18 50 μg/kg dose group and the placebo group was −2.40%. The mean change in BMI from baseline to day 15 was −0.63 ± 0.44 kg/m^2 in the GZR18 50 μg/kg group and −0.06 ± 0.44 kg/m^2 in the placebo group, with mean percentage changes from baseline of −2.68 ± 1.85% and −0.26 ± 2.01%, respectively. These results indicate that GZR18 provides comprehensive benefits, including a tendency to reduce fasting blood glucose and body weight at relatively higher dose levels (≥ 30 μg/kg).

3.5 | Quantitative pharmacological analysis between healthy American and Chinese subjects

The impact of ethnicity on PK profiles of GZR18 was evaluated based on AUC_{0-t} and C_{max} derived from individual time profiles of GZR18 simulated based on posterior Bayes parameters at 5 and 10 μg/kg (12 American and 13 Chinese subjects receiving 5 and 10 μg/kg). The mean of AUC_{0-t} and C_{max} were estimated for American and Chinese subjects in doses of 5 and 10 μg/kg (Table S5). The geometric mean ratio between Chinese and American subjects for AUC_{0-t} after a single subcutaneous injection of 5 or 10 μg/kg GZR18 was 1.02465 (95% CI, 1.02434, 1.02497) with $p > 0.05$. The geometric mean ratio between Chinese and American subjects for C_{max} after a single subcutaneous injection of 5 or 10 μg/kg GZR18 was 0.98 with $p > 0.05$.

TABLE 5 Summary of pharmacodynamics parameters in American and Chinese subjects.

	Chinese subjects			American subjects				
	Cohort CN-1 (5 μg/kg)	Cohort CN-2 (10 μg/kg)	Total placebo[a]		Cohort US-1 (1 μg/kg)	Cohort US-2 (5 μg/kg)	Cohort US-3 (10 μg/kg)	Total placebo
	N = 5	N = 8	N = 4		N = 6	N = 6	N = 6	N = 6
$AUC_{glucose0-14h}$ (h*mmol/L)	88.24 (7.36)	85.13 (6.96)	95.90 (19.01)	$AUEC_{glucose0-14h}$ (h*mmol/L)	0.39 (3.26)	8.11 (9.36)	2.49 (6.37)	4.08 (8.72)
$AUC_{insulin0-14h}$ (h*mIU/L)	810.96 (370.44)	457.07 (149.35)[b]	612.40 (271.82)	$AUEC_{insulin0-14h}$ (h*mIU/L)	380.7 (171.53)	435.4 (192.20)	369.9 (241.88)	413.9 (214.77)
$AUC_{C-peptide0-14h}$ (h*ng/mL)	98.68 (17.65)	77.06 (10.64)	77.97 (22.00)	$AUEC_{C-peptide0-14h}$ (h*ng/mL)	NA	NA	NA	NA

Note: The $AUEC_{glucose0-14h}$ was calculated for the areas above and below the baseline (absolute value). Calculated using the linear trapezoidal with linear interpolation method using a drug effect model. Data are shown as mean (SD).

Abbreviations: AUC, the area under the curve; $AUC_{glucose0-14h}$, the area under the curve of blood glucose measured from time 0 (predose) to 14 h post dose; AUEC, the area under the effect curve; $AUEC_{glucose0-14h}$, the area under the glucose changes from baseline versus time curve from time 0 (predose) to 14 h post dose; *N*, number of subjects in each group; NA, data were not available.

[a]"Placebo" is the pooled results of placebo subjects in dose cohorts CN-1–2.

[b]$N = 7$.

Inter-individual variability analysis data were presented in the Table S6. The results of these simulations indicate that Chinese subjects are likely to experience comparable exposures to those observed in American subjects who received the same dose.

4 | DISCUSSION

The GZR18 pharmacokinetic profiles and parameters exhibited consistency across American and Chinese populations. Overall, treatment with GZR18 up to 50 μg/kg was generally well tolerated and safe in subjects. This phase 1 trial also demonstrates the preliminary efficacy in blood glucose reduction and weight loss with a higher dose of GZR18.

The initial dosage of GZR18 was determined to be 1.0 μg/kg in American subjects, based on the first-in-human (FIH) starting dose of semaglutide due to the main chain structure similarity between GZR18 and semaglutide. This conservative starting dose was also deemed safe, well within the projected maximum recommended starting dose and devoid of any pharmacological activity. The dose titration of GLP-1 RA has previously been well demonstrated to be able to effectively prevent gastrointestinal side effects and enhance tolerability.[15] Before administering the higher target dose of 20–50 μg/kg, the Chinese subjects were initially given an initial dose of 10 μg/kg to mitigate the possible gastrointestinal side effects, mimic the dosing strategy in future clinical trials and facilitate a more favourable tolerability profile. In the present FIH study of GZR18, the dose was escalated to 50 μg/kg, with a dose range of approximately 2.5–4.0 mg per individual. In contrast, the maximum tolerated dose for a single dose in the FIH study of semaglutide was 15 μg/kg body weight (∼mean 1.25 mg per individual, range 1.10–1.40 mg).[23]

Gastrointestinal AEs, such as decreased appetite, diarrhoea and vomiting, common among GLP-1 RA drugs, were designated as AEs of special interest. The safety and tolerability profile of GZR18 appears consistent with that of other GLP-1 RAs,[24,25] with the most common TEAEs being decreased appetite, diarrhoea, vomiting and constipation.[26] However, the most frequently reported AEs among American subjects is headache, which may be associated with the relatively limited sample size. In contrast, the Chinese cohorts, with a larger sample size, showed AEs similar to those observed with other GLP-1 RA drugs. Importantly, no hypoglycaemic events, grade 3 or higher AEs or AEs leading to death were observed in either the American or Chinese subjects. No serious AEs or new safety signals were identified, and all AEs were mild and consistent with those listed on the semaglutide label. GZR18 demonstrated good tolerability and safety in these trials (up to 50 μg/kg) and in the Phase 2b clinical trial for obesity management (up to 48 mg).[27] The AEs associated with GZR18 were consistent with those observed for other GLP-1 RAs. The safety findings suggest that GZR18 may be more tolerable than semaglutide in healthy subjects, consistent with preclinical studies.[21] The 22-carbon fatty acid side chain of GZR18 has been shown to enhance albumin affinity, slow drug clearance and lower affinity to the GLP-1 receptor,[21] resulting in a moderate and gentle bioactivity. These

TABLE 6 Summary of $AUC_{glucose\ 0-14h}$, $AUC_{c\text{-}peptide\ 0-14h}$ and $AUC_{insulin\ 0-14h}$ in cohort CN-3–6 of the Chinese health subjects.

	Cohort CN-3 (20 μg/kg)	Cohort CN-4 (30 μg/kg)	Cohort CN-5 (40 μg/kg)	Cohort CN-6 (50 μg/kg)	Total placebo[a]
First dose	*N* = 8	*N* = 8	*N* = 8	*N* = 8	*N* = 8
$AUC_{glucose0-14h}$ (h*mmol/L)	83.25 (7.15)	86.74 (7.16)	87.44 (4.60)	90.97 (6.82)	92.92 (6.33)
$AUC_{c\text{-}peptide0-14h}$ (h*ng/mL)	85.27 (16.64)	92.08 (25.30)	102.77 (16.43)	94.38 (18.71)	99.85 (22.79)
$AUC_{insulin0-14h}$ (h*mIU/L)	613.09 (245.45 S)	676.87 (351.93)	786.26 (290.99)	762.66 (307.99)	870.89 (437.54)
Second dose	*N* = 8	*N* = 8	*N* = 8	*N* = 8	*N* = 7
$AUC_{glucose0-14h}$ (h*mmol/L)	84.75 (5.69)	84.21 (5.34)	83.50 (8.48)	80.06 (8.56)	100.30 (11.27)
$AUC_{c\text{-}peptide0-14h}$ (h*ng/mL)	85.12 (15.85)	81.82 (21.35)	86.13 (26.38)	74.11 (23.24)	106.70 (24.73)
$AUC_{insulin0-14h}$ (h*mIU/L)	577.41 (216.67)	584.75 (318.77)	598.04 (194.75)	542.90 (295.92)	980.15 (511.13)

Note: Data are mean (SD).
Abbreviations: AUC, the area under the curve; *N*, number of subjects in each group.
[a]"Placebo" is the pooled results of placebo subjects in cohorts CN-3–6.

properties might greatly contribute to the drug's overall tolerability, particularly during the initial phase of dose escalation.

In Chinese subjects, within the dose range of 5–10 and 20–50 μg/kg (second dose in cohorts CN-3–6), the primary PK parameters of GZR18 exposure (C_{max}, AUC_{0-t} and AUC_{0-inf}) and dose exhibit a proportional dose–response relationship. In comparison, the AUC_{0-t} and AUC_{0-inf} did not demonstrate dose proportionality in the dose of 5–50 μg/kg (5, 10 μg/kg of cohorts CN-1–2, 20–50 μg/kg of cohort CN-3–6 in second dose). This is greatly associated with the residual GZR18 of the first 10 μg/kg dose, and this compounded the exposure of the second dose (cohorts CN-3–6). In American subjects, the increase in exposure following a single dose of GZR18 generally appeared to be slightly more than dose-proportional over the dose range of 1.0–10.0 μg/kg.

The population pharmacokinetic analysis revealed that GZR18 exposure was generally similar between American and Chinese subjects. In a previous study, this analysis also supported similar pharmacokinetic exposures for liraglutide in adolescents and adults.[28] In the current analysis, the estimated race ratios for AUC_{0-t} between Chinese and American subjects were 1.02 for both the 5 μg/kg dose and the 10 μg/kg dose. For C_{max}, the estimated race ratios were both 0.98. These data indicate that the geometric mean ratios for AUC_{0-t} and C_{max} between the two populations approached 1. Furthermore, no statistically significant differences in AUC_{0-t} or C_{max} were observed between American and Chinese subjects. Overall, the results demonstrate that no significant ethnic differences were observed between healthy American and Chinese subjects.

Following the administration of GZR18, $t_{1/2}$ and T_{max} were observed to be comparable between Chinese and American populations, despite a slightly higher T_{max} in American subjects (72–96 h in American subjects and 60–72 h in Chinese subjects). A comparison of the PK data from a phase 1 trial of GZR18 in healthy subjects with historical data for semaglutide[29] revealed that the T_{max} for GZR18 may be approximately twice that of semaglutide (32 vs. 60 h). Furthermore, the PK profile comparison indicated that GZR18 reaches its maximum drug concentration with a more gradual increase than that observed for semaglutide. In both American and Chinese subjects, the mean half-life of GZR18 was approximately 1 week, which supports ultralong interval dosing.

In corresponding with the preclinical study that GZR18 significantly improves glycaemic control and reduces body weight in diabetic rats and mice,[21] the current trial demonstrated that Chinese subjects who received GZR18 exhibited a notable reduction in body weight (up to −3.11% in 30 μg/kg, at 2 weeks) compared to those who received placebo, even after a single dose administration. Nevertheless, minimal changes in body weight were observed among American subjects with a higher mean body weight at the baseline, which may be attributed to the relatively lower dose compared to that of the Chinese subjects (50 vs. 10 μg/kg).

In Chinese subjects, a review of the dose proportionality in PD parameter revealed that within the dose ranges of 5–50 μg/kg, the primary PD parameters of GZR18 ($AUC_{glucose0-14h}$, $AUC_{c\text{-}peptide0-14h}$ and $AUC_{insulin0-14h}$) did not demonstrate dose proportionality. Similar results were found in the American subjects. This may be influenced by various factors, including the pharmacological mechanism, the characteristics of the healthy subjects and the sample size, particularly the pharmacological mechanism, as the subjects did not have diabetes. Therefore, further verification is necessary in future clinical trials with larger sample sizes in patients with T2DM, obesity/overweight.[30]

The limitations of the current trials were relatively brief in duration and included a limited number of subjects. Furthermore, all subjects were healthy individuals thus with no apparent impact on pharmacodynamic parameters were observed. In addition, the study population did not entirely represent the targeted obese or T2DM population. However, the positive safety profile and initial

effectiveness of GZR18 observed in this study suggests that GZR18 could be a viable therapeutic option for people with T2DM and overweight or obesity. GZR18 has undergone a series of clinical trials.[30] A number of them have examined the effectiveness and safety of GZR18 as a biweekly formulation for the treatment of T2DM and obesity (NCT06256562, NCT06256523).[27] Further phase 2 and phase 3 trials are underway to confirm these findings in more extensive, multicentre, longer duration studies (NCT06737042, NCT06728124 and NCT06778967).

In conclusion, the safety and tolerability profile of GZR18 appears to be favourable among healthy subjects from both American and Chinese populations. No significant ethnic differences were identified between these groups. Additionally, the pharmacokinetic and pharmacodynamic profiles support further clinical development of GZR18 as an effective treatment for T2DM and overweight or obesity.

AUTHOR CONTRIBUTIONS

YL, WC, XH, LZ, JZ, AHu and AS contributed to the study conduct and data analysis. WC, AHe, TX, YL and ZG contributed to the writing and editing of the manuscript. WC and AS contributed to the project management of the study. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

WC, AHe, LZ, TX, YL, JZ and ZG are employees of Gan & Lee Pharmaceuticals. The authors affirm that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Further inquiries of data can be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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