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ORIGINAL ARTICLE

Pharmacokinetics, pharmacodynamics and safety of vutiglabridin after multiple oral administrations in healthy female and obese subjects

Sooyoun Lee[1] | Hyun Chul Kim[1] | Young Ran Yoon[2,3] | In-Jin Jang[1] | Sang-Ku Yoo[4] | Kyung-Sang Yu[1]

[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea

[2]School of Medicine, Kyungpook National University, Daegu, Republic of Korea

[3]Department of Clinical Pharmacology, Kyungpook National University Hospital, Daegu, Republic of Korea

[4]Glaceum Inc., Suwon, Republic of Korea

Correspondence
Kyung-Sang Yu, Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
Email: ksyu@snu.ac.kr

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Aims: Vutiglabridin (HSG4112) is a novel drug under clinical development for antiobesity treatment. This study aimed to evaluate the pharmacokinetics (PKs) and safety of vutiglabridin after multiple oral administrations in healthy Korean female and obese subjects and explore short-term pharmacodynamic (PD) responses.

Methods: Two separate randomized, double-blind, placebo-controlled studies were conducted in healthy female and obese subjects. The subjects in each dose group (480 or 720 mg) received vutiglabridin or placebo once daily for 14 days under fed conditions at an 8:2 ratio. Serial blood samples were collected on days 1 and 14 for PK analysis. PD biomarkers related to obesity and inflammation were assessed, and safety and tolerability were evaluated throughout the study.

Results: At steady state, obese subjects exhibited a 9%–13% higher maximum concentration ($C_{max,ss}$) and a 17%–19% lower area under the plasma concentration–time curve for a dosing interval at steady state ($AUC_{\tau,ss}$). This profile reflects altered absorption and distribution due to obesity-related physiological changes. After 14 days of treatment, compared with healthy females, obese subjects had greater decreases in baseline-corrected body weights in the 480 mg, 720 mg and placebo groups. Vutiglabridin was safe and well tolerated in both groups.

Conclusions: Vutiglabridin presented higher peak plasma concentrations but lower systemic exposure in obese subjects than in healthy females. Additionally, a modest downward trend in body weight was observed in obese subjects relative to healthy female subjects. These findings support further long-term phase II clinical trials.

KEYWORDS
obesity, pharmacodynamics, pharmacokinetics, phase 1, safety, vutiglabridin

1 | INTRODUCTION

Obesity is a chronic disease characterized by relapsing health risks defined by excess body fat and a high body mass index (BMI).[1,2] It is a major public health issue associated with increased mortality and comorbidities, including diabetes mellitus, hypertension, dyslipidaemia and certain cancers.[2,3] Lifestyle interventions—such as dietary modification, physical activity and behavioural therapy—are fundamental to

obesity management. However, pharmacotherapy is often required as an adjunct treatment to achieve and maintain clinically meaningful weight loss.[4]

Among pharmacological options, the US Food and Drug Administration (FDA) has approved seven drugs for chronic weight management.[5] Orlistat (Xenical, Alli) is a lipase inhibitor that reduces dietary fat absorption by inhibiting gastrointestinal lipases.[6] Phentermine-topiramate (Qsymia) and naltrexone-bupropion (Contrave) act centrally to suppress appetite. Phentermine-topiramate works via catecholaminergic pathways, whereas naltrexone-bupropion modulates hypothalamic appetite regulation and the mesolimbic reward system.[7,8] Glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide (Saxenda) and semaglutide (Wegovy) increase satiety and delay gastric emptying.[8] Tirzepatide (Zepbound), a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, also suppresses appetite and improves metabolic parameters.[9] Setmelanotide (Imcivree), a melanocortin-4 receptor (MC4R) agonist, is approved for the treatment of rare genetic obesity disorders.[10] While most of these agents achieve weight loss by reducing food intake, they may also result in the loss of lean body and muscle mass, thereby increasing the risk of sarcopenia and disturbing metabolic homeostasis.[11–13]

Glabridin, an extract from *Glycyrrhiza glabra* L. (licorice) roots, has demonstrated antiobesity effects through the activation of AMP-activated protein kinase (AMPK), mitochondrial activity and fatty acid oxidation.[14] However, its clinical utility is limited by low physicochemical stability and poor bioavailability.[15] Vutiglabridin (2-(8,8-dimethyl-2,3,4,8,9,10-hexahydropyrano[2,3-f]chromen-3-yl)-5-ethoxyphenol) is a chemically modified derivative of glabridin that was developed to address these limitations and improve antiobesity efficacy by promoting weight loss and increasing energy expenditure.[16,17] It consists of a racemic mixture of (R)- and (S)-isomers, with the (S)-isomer demonstrating a greater ability to reduce body weight.[17]

In preclinical studies using diet-induced obese mice, vutiglabridin improved lipid profiles by lowering serum triglyceride levels and normalizing high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol levels. It also promoted lipolysis by modulating inflammation in adipose tissue, suggesting its potential for both weight loss and broader metabolic benefits.[17–20] Transcriptomic analyses further demonstrated the upregulation of genes involved in fatty acid oxidation, lipid metabolism and glucose metabolism, indicating increased energy expenditure.[17] Reproductive toxicity—including adrenal cortex hypertrophy, testicular seminiferous tubule degeneration and uterine atrophy—was observed in both male and female rats, leading to the exclusion of female subjects in the first-in-human (FIH) study.[21]

The FIH and food-effect studies, conducted exclusively in healthy male subjects, evaluated the pharmacokinetics (PKs), safety and influence of food on absorption.[21,22] Single doses up to 720 mg were well tolerated, with no dose-limiting toxicity observed. Exploratory pharmacodynamic markers—including adiponectin, C-peptide and CCL2—showed favourable trends at higher exposures, suggesting pathway engagement.[21] On the basis of these findings, doses of 480 and 720 mg were selected for further evaluation, which is consistent with regulatory recommendations for exploring a wide range of doses in early-phase development.[23] Reproductive toxicity was not observed, as evidence by normal findings in sperm analysis, which provided the rationale for expanding trial to healthy female subjects to further assess sex-related safety.

Therefore, this study aimed primarily to evaluate the PKs and safety of vutiglabridin at doses of 480 and 720 mg after multiple oral administrations in healthy Korean females and obese subjects and to explore the short-term pharmacodynamic (PD) responses.

What is already known about this subject

- Vutiglabridin, a synthetic derivative of glabridin, has been developed to increase metabolic stability and oral bioavailability for antiobesity treatment.
- Clinical data on vutiglabridin remain limited for healthy females and obese individuals, highlighting the need for further pharmacokinetic and safety evaluations in these groups.

What this study adds

- The plasma concentration of vutiglabridin reached higher peak levels but was associated with lower systemic exposure in obese subjects than in healthy females, although the overall pharmacokinetic profiles were comparable.
- Short-term exploratory pharmacodynamic assessments suggested potential metabolic benefits, supporting the need for further evaluation in long-term clinical trials.

2 | METHODS

2.1 | Ethics

This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital and Seoul National University Hospital. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. The trial was registered with the Clinical Research Information Service of the Ministry of Health and Welfare of the Republic of Korea (KCT 0005693) and in an open registry (NCT04703764). Written informed consent was obtained from all the subjects before they participated in this study.

2.2 | Subjects

Healthy female and obese subjects aged between 19 and 50 years were recruited. The enrolled subjects had no clinically significant

abnormalities in terms of medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) or clinical laboratory tests. For both healthy female and obese subjects, individuals with known hypersensitivity to licorice, aspirin or antibiotics were excluded. Additionally, the use of any medication, herbal remedies or vitamin supplements within 7 days prior to initial dosing was prohibited.

Healthy female subjects with BMIs ranging from 18 to 25 kg/m^2 who were not pregnant or lactating and who had a regular menstrual cycle (ranging from 28 ± 7 days) were enrolled. Obese subjects with BMIs of 30 kg/m^2 or higher and waist circumferences of 90 cm or greater for males or 85 cm or greater for females were enrolled.[5,23]

To exclude subjects with underlying metabolic dysfunction or hepatic abnormalities, upper thresholds were applied to alanine aminotransferase (ALT), aspartate aminotransferase (AST) and fasting glucose levels. For healthy female subjects, the exclusion criteria included ALT levels greater than 60 IU/L and glucose levels greater than 110 mg/dL or less than 70 mg/dL. For obese subjects, the exclusion criteria included ALT and AST levels greater than 100 IU/L, cholesterol and triglyceride levels greater than 300 mg/dL and glucose levels of 126 mg/dL or higher.

2.3 | Study design

Two separate randomized, double-blind, placebo-controlled, multiple-dosing studies were conducted on healthy female and obese subjects.

Healthy female subjects were treated at two centres: Kyungpook National University Hospital (130, Dongdeok-ro, Jung-gu, Daegu, Republic of Korea) and Seoul National University Hospital (101, Daehak-ro, Jongno-gu, Seoul, Republic of Korea). The subjects were admitted from day −1 to day 2 and readmitted from days 11 to 17.

A protocol amendment was made to ensure that the study design for obese subjects was consistent with that for healthy female subjects.

Obese subjects were treated at a single centre: Seoul National University Hospital (101, Daehak-ro, Jongno-gu, Seoul, Republic of Korea). As the dietary habits of obese subjects were considered less balanced and potentially poorer than those of healthy female subjects, obese subjects were admitted from day −1 to day 17.

For both healthy female and obese subjects, the subjects were randomly assigned to either the vutiglabridin group or the placebo group at an 8:2 ratio (480 or 720 mg dose group). Vutiglabridin was administered once daily from days 1 to 14. The placebo formulation contained polyethylene glycol, microcrystalline cellulose, ethanol and sterile water, and was identical in appearance to the active drug.[21] As a Biopharmaceutics Classification System (BCS) class II drug with high lipophilicity and limited solubility, vutiglabridin was administered under fed conditions to enhance absorption.[22] Therefore, in this study, all the subjects were required to consume an entire high-fat meal (total calories over 800–1000 kcal, with fat content over 500–600 kcal) within 20 min, and vutiglabridin was administered 30 min after completion of the meal.

On dosing days, healthy female subjects visited the clinical trial centre in the morning and consumed the same standardized high-fat meal under supervision, ensuring dietary consistency with the regimen used for obese subjects who were staying at the centre. All investigational products were administered at scheduled visits by the investigator, and compliance was confirmed through post-dose oral cavity checks to ensure complete ingestion.

On the basis of the elimination half-life ($t_{1/2}$) of 79.3 h for 480 mg and 85.4 h for 720 mg, vutiglabridin was expected to reach a steady-state by days 13 and 14.[21] Therefore, blood samples for PK assessment were collected at multiple times: on day 1 (0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h), days 12 and 13 (0 h) and day 14 (0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 144 and 192 h).

Body weight and waist circumference were measured in healthy female subjects on days −1, 8, 15 and 22, and body weight was measured daily in obese subjects from days 1 to 18 and on days 20 and 22. Waist circumference, BMI and per cent body fat in obese subjects were assessed on days 1, 8, 15 and 22. PD assessments for both healthy female and obese subjects were conducted in the fasted state prior to breakfast.

Obesity-related biomarkers, including leptin, adiponectin, insulin, C-peptide, IL-6, TNFα and CCL2 levels, were evaluated. Blood samples for PD assessments were collected before dosing on days 1 and 14 (Figure 1). The blood samples were centrifuged at 3000 rpm for 10 min at 4°C, and the plasma samples were obtained and stored at −70°C until analysis.

2.4 | PK and statistical analyses

The total plasma concentration of vutiglabridin was calculated by adding the concentration values of (R)- and (S)-vutiglabridin. The PK parameters were calculated with a non-compartmental analysis using Phoenix WinNonlin software (version 8.3; Certara, NJ, USA).

The PK parameters measured on day 1 were the maximum plasma concentration (C_{max}), the time to reach C_{max} (T_{max}) and the area under the concentration–time curve (AUC) to the last measurable time point (AUC_{last}). On day 14, the time for the maximum plasma concentration at steady state ($T_{max,ss}$), the maximum plasma concentration at steady state ($C_{max,ss}$), the area under the plasma concentration–time curve for a dosing interval at steady state ($AUC_{\tau,ss}$), the elimination half-life at steady state ($t_{1/2,ss}$), the apparent clearance at steady state (CL_{ss}/F), the apparent volume of distribution at steady state ($V_{d,ss}/F$) and the accumulation ratio were measured. The C_{max} and T_{max} were obtained directly from the observed values. The AUC was calculated using the linear-up/log-down trapezoidal method. The accumulation ratio was calculated as the ratio of the AUC_{τ} after the last administration of vutiglabridin to that after the first dose.

Exploratory comparisons were conducted to assess potential differences in PK profiles between healthy female and obese subjects using SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA). The geometric mean ratios (GMRs) and 90% confidence intervals (CIs)

Assessment	-1d	1d	2d	3d~10d	11d	12d~16d	17d	18d	20d	22d	23d~27d
Admission	■				•						
Administration[1]		■	■	■	■	■					
Discharge			•				■				
Post-study visit (PSV)											■
Pharmacokinetic sampling [2]		■	■			■	■	■	■	■	
Pharmacodynamic sampling [3]		■				■					
Pharmacodynamic measurement											
Body weight [4]	•	△	△	■	△	■	△	△	△	■	
Waist circumference [5]	•	△		■		■				■	
Percent body fat [6]		△		△		△				△	
Body Mass Index (BMI) [6]		△		△		△				△	

■, both healthy and obese subjects; •, healthy subjects; △, obese subjects

[1] Vutiglabridin was administered from 1d to 14d.
[2] Pharmacokinetic samples were collected on 1d pre-dose (0h), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24h post-dose, 12d 0h, 13d 0h, 14d pre-dose (0h), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 h, 36h (15d 12h), 48h (16d 0h), 72h (17d 0h), 96h (18d 0h), 144h (20d 0h), 192h (22d 0h) post-dose.
[3] Pharmacodynamic samples were collected on 1d and 14d pre-dose.
[4] Body weight was collected on -1d, 8d, 15d, 22d for healthy subjects and 1d–18d, 20d, 22d for obese subjects. For both healthy female and obese subjects, weight was measured before breakfast.
[5] Waist circumference measurements were collected on -1d, 8d, 15d, 22d for healthy subjects, and 1d, 8d, 15d, 22d for obese subjects.
[6] Percent body fat and BMI measurements were collected on 1d, 8d, 15d, and 22d for obese subjects.

FIGURE 1 Study design.

of C_{max}, $C_{max,ss}$, AUC_{last} and $AUC_{\tau,ss}$ at each dose were estimated, and the ratios of obese subjects to healthy subjects were compared using a linear mixed-effects model. The model included the treatment groups (healthy female and obese subjects) as fixed effects.

2.5 | PD analysis

PD measurements and obesity-related biomarkers were baseline corrected using values obtained prior to the first dose, and comparisons among the 480 mg, 720 mg and placebo groups were conducted for healthy female and obese subjects.

2.6 | Safety and tolerability assessment

Safety and tolerability were assessed in all subjects who received at least one dose of the study drug. The evaluation included monitoring adverse events (AEs), 12-lead ECG, physical examination, vital signs and clinical laboratory tests.

In healthy female subjects, drug administration was initiated 5–7 days after the onset of the last menstrual period to minimize interindividual variability. Menstrual cycle characteristics—including cycle length, regularity, duration and the start and end dates of menstruation—were collected at screening and at the post-study visit (PSV) to assess the potential effects of the drug on menstrual function as part of the safety evaluation.

In both healthy female and obese subjects, testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and inhibin B levels were measured prior to dosing on day 1 and at the PSV.[21] The following reference ranges were used: LH (0.57–12.07 IU/L in males and 0.56–89.08 IU/L in females), FSH (0.95–11.95 IU/L in males and 1.38–16.69 IU/L in females) and testosterone (2.49–8.36 nmol/L in males).

3 | RESULTS

3.1 | Demographics

In both healthy female and obese subjects, demographic characteristics were comparable across the 480 mg, 720 mg and placebo groups (Table 1).

3.2 | PK

Total vutiglabridin was rapidly absorbed over time in both healthy female and obese subjects (Figure 2 and Figure S1). In obese subjects, the median T_{max} and $T_{max,ss}$ of vutiglabridin were 2.75 and 3.00 h, respectively, for the 480 mg dose and 2.75 and 2.50 h, respectively, for the 720 mg dose. In healthy female subjects, these values were slightly longer, with T_{max} and $T_{max,ss}$ values of 3.00 and 3.25 h, respectively, for the 480 mg dose and 4.67 and 4.00 h, respectively, for the 720 mg dose. The C_{max} and $C_{max,ss}$ in obese subjects were 20%–29% and 9%–13% higher, respectively, than those in healthy females. In contrast, AUC_{last} and $AUC_{\tau,ss}$ were 8%–19% and 18%–19% lower, respectively, in obese subjects. The mean $t_{1/2,ss}$ values were greater in obese subjects (156.4–159.1 h) than in healthy female subjects (105.0–107.0 h). The mean CL_{ss}/F and $V_{d,ss}/F$ values were greater in obese subjects (CL_{ss}/F, 23.2–24.5 L/h; $V_{d,ss}/F$, 5270–5615 L) than in healthy female subjects (CL_{ss}/F, 19.1–20.2 L/h; $V_{d,ss}/F$, 2988–

TABLE 1 Demographic characteristics.

	Healthy subjects			Obese subjects		
	480 mg ($N = 8$)	720 mg ($N = 6$)	Placebo ($N = 4$)	480 mg ($N = 8$)	720 mg ($N = 8$)	Placebo ($N = 4$)
Age (y)	26.5 ± 5.7	32.9 ± 9.0	30.3 ± 7.7	34.4 ± 6.5	32.3 ± 7.7	31.5 ± 7.0
Gender						
Male *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	6 (75.0)	6 (75.0)	3 (75.0)
Female *n* (%)	8 (100.0)	8 (100.0)	8 (100.0)	2 (25.0)	2 (25.0)	1 (25.0)
Height (cm)	165.0 ± 6.3	163.3 ± 8.4	164.4 ± 7.5	170.5 ± 7.9	172.7 ± 7.7	172.2 ± 1.7
Weight (kg)	60.1 ± 7.2	60.2 ± 10.7	58.6 ± 5.7	94.2 ± 9.7	96.5 ± 9.2	97.6 ± 8.3
Body mass index (kg/m^2)	22.1 ± 2.2	22.4 ± 2.0	21.7 ± 2.4	32.4 ± 2.5	32.4 ± 2.7	32.9 ± 2.2
Waist circumference (cm)	83.6 ± 6.0	87.7 ± 8.9	85.3 ± 5.4	102.8 ± 6.4	107.2 ± 10.7	107.4 ± 8.5

Note: Data are shown as the mean ± standard deviation.

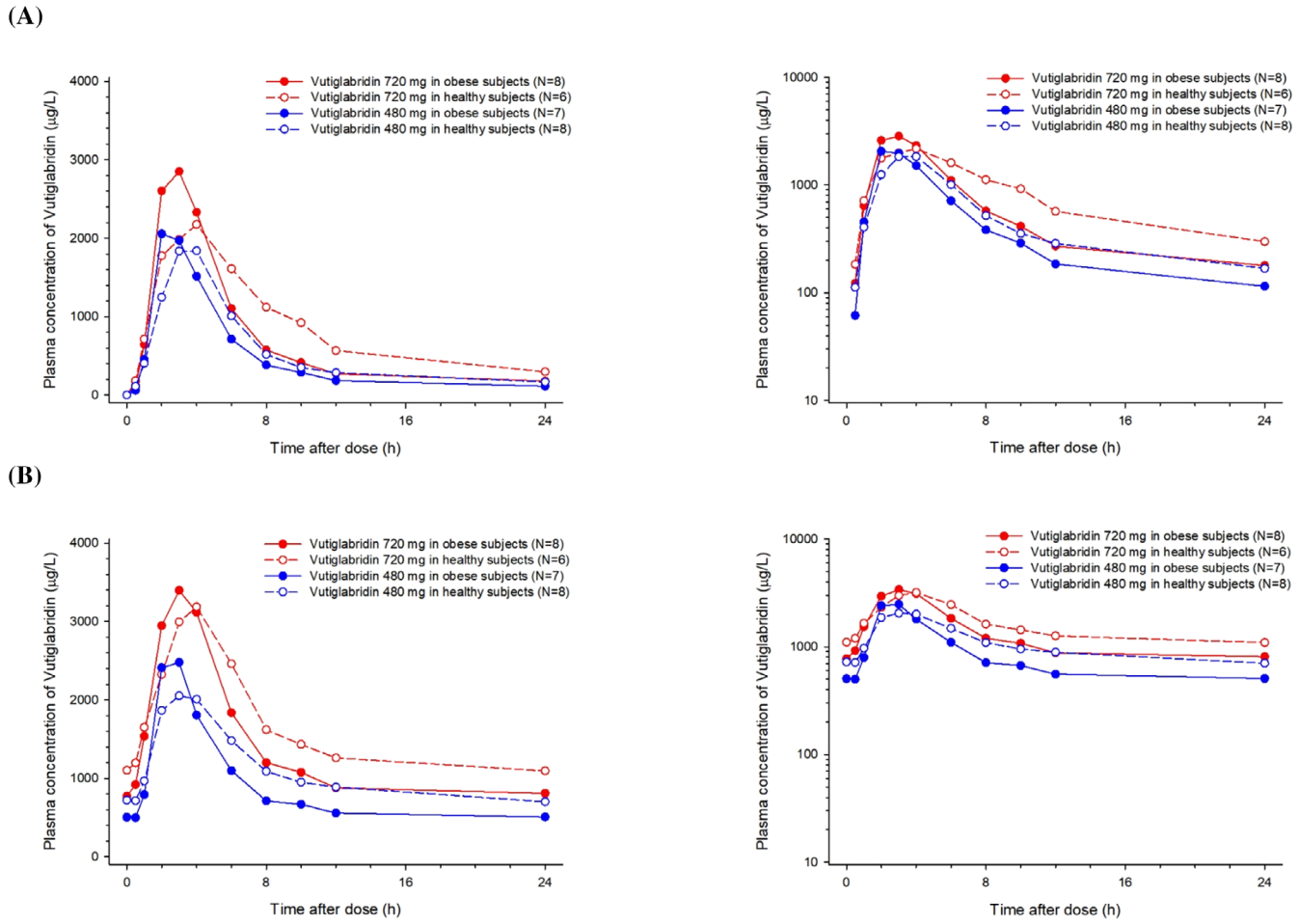

FIGURE 2 Mean plasma concentration–time profiles of total vutiglabridin following (A) a single oral administration on day 1 and (B) multiple oral administrations on day 14. The right panels represent the profiles on a semi-logarithmic scale.

3061 L). The mean accumulation ratios were comparable between the two subject groups (1.85–2.13) (Table 2). In an exploratory analysis, the PK parameters were comparable between healthy female and obese subjects (Table S5).

The PK profiles of (S)-vutiglabridin were similar to those of total vutiglabridin, whereas (R)-vutiglabridin exhibited lower systemic exposure than (S)-vutiglabridin (Figures S2 and S3; Tables S2 and S3).

TABLE 2 Pharmacokinetic parameters of total vutiglabridin after single and multiple oral administrations of 480 mg or 720 mg in healthy and obese subjects.

Parameter	480 mg			720 mg		
	Healthy subjects ($N = 8$)	Obese subjects ($N = 7$)	Geometric mean ratios [90% CI][a]	Healthy subjects ($N = 6$)	Obese subjects ($N = 8$)	Geometric mean ratios [90% CI][a]
Day 1						
T_{max} (h)	3.00 [2.00–4.00]	2.57 [2.00–4.00]		4.67 [2.00–8.00]	2.75 [2.00–4.00]	
C_{max} (μg/L)	2039 ± 897	2492 ± 679	1.29 (0.94–1.76)	2847 ± 1129	3271 ± 656	1.20 (0.91–1.58)
AUC_{last} (h·μg/L)	12 745 ± 5767	11 055 ± 2875	0.92 (0.66–1.28)	20 283 ± 5998	16 176 ± 3121	0.81 (0.65–1.02)
Day 14						
$T_{max,ss}$ (h)	3.25 [2.00–6.00]	3.00 [2.00–6.00]		4.00 [2.00–6.00]	2.50 [2.00–4.00]	
$C_{max,ss}$ (μg/L)	2437 ± 522	2817 ± 872	1.13 (0.88–1.44)	3444 ± 420	3801 ± 722	1.09 (0.93–1.28)
$AUC_{\tau,ss}$ (h·μg/L)	25 526 ± 7719	20 332 ± 4681	0.81 (0.64–1.02)	38 462 ± 6198	31 859 ± 5013	0.82 (0.70–0.97)
$t_{1/2,ss}$ (h)	105.0 ± 20.0	159.1 ± 36.3		107.0 ± 19.2	156.4 ± 49.6	
CL_{ss}/F (L/h)	20.2 ± 5.7	24.5 ± 4.5		19.1 ± 2.9	23.2 ± 4.3	
$V_{d,ss}/F$ (L)	3061 ± 1067	5615 ± 1684		2988 ± 933	5270 ± 1920	
Accumulation ratio	2.13 ± 0.47	1.85 ± 0.23		1.97 ± 0.45	1.99 ± 0.38	

Note: Data are shown as the mean ± standard deviation except for T_{max}, which is shown as the median [minimum–maximum].
Abbreviations: AUC_{last}, area under the plasma concentration–time curve from zero to the last measurable time point; $AUC_{\tau,ss}$, area under the plasma concentration–time curve for a dosing interval at steady state; CI, confidence interval; CL_{ss}/F, apparent clearance at steady state; C_{max}, maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady state; $t_{1/2,ss}$, elimination half-life at steady state; T_{max}, time for the maximum plasma concentration; $T_{max,ss}$, time for the maximum plasma concentration at steady state; $V_{d,ss}/F$, apparent volume of distribution at steady state.
[a]Geometric mean ratios and their 90% CIs are the ratio of the obese subjects to healthy subjects.

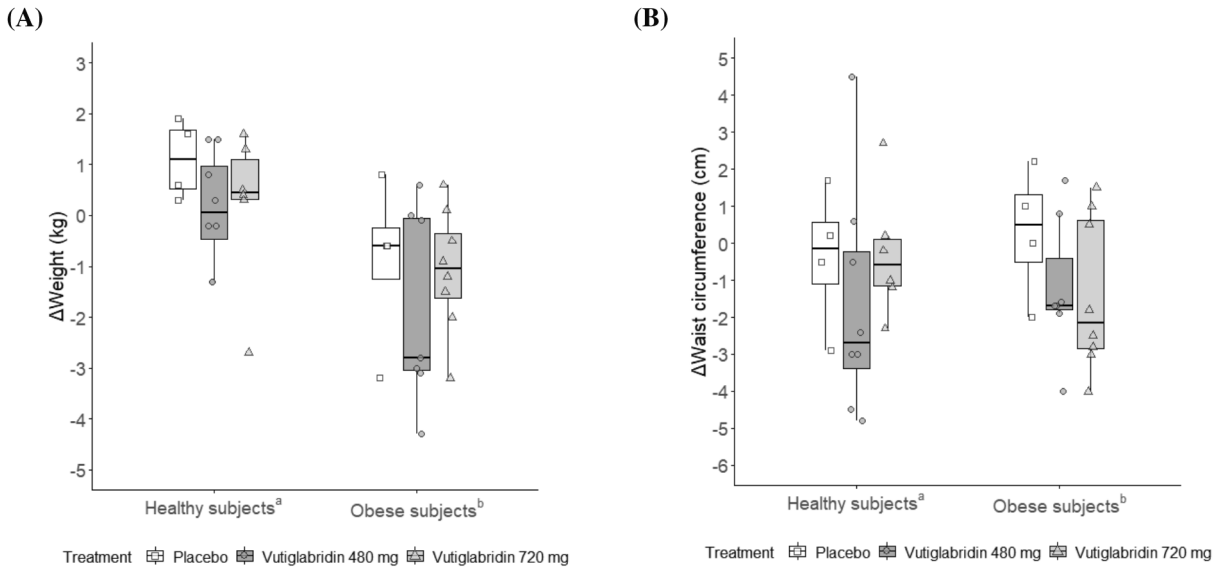

FIGURE 3 Comparison of changes from baseline in (A) body weight and (B) waist circumference on day 15 in healthy female and obese subjects. *Note*: Boxplots represent the interquartile range (IQR) with whiskers extending from 1.5 IQR. [a]$N = 4, 8, 6$ (placebo, 480 mg, 720 mg). [b]$N = 4, 7, 8$ (placebo, 480 mg, 720 mg).

3.3 | PD

After 14 days of repeated oral administration, vutiglabridin induced modest reductions in body weight and waist circumference in healthy female subjects. In obese subjects, compared with the placebo, the 480 and 720 mg doses resulted in greater mean reductions in baseline-corrected body weight and waist circumference (Figure 3 and Figures S4–S7).

In healthy female subjects, the mean changes in body weight (mean ± standard deviation) were 0.14 ± 1.10 kg for the

480 mg dose, 0.23 ± 1.53 kg for the 720 mg dose and 1.10 ± 0.77 kg for the placebo. The waist circumference changes were −1.64 ± 3.08 cm for the 480 mg dose, −0.30 ± 1.71 cm for the 720 mg dose and −0.38 ± 1.92 cm for the placebo. Additionally, adiponectin levels were greater in the 720 mg dose group (2968 ± 2305 ng/mL) than in the placebo group (2056 ± 5497 ng/mL) and the IL-6, TNFα and CCL2 levels tended to decrease (Table S4).

In obese subjects, the mean changes in body weight (mean ± standard deviation) were −1.81 ± 1.93 kg for the 480 mg dose, −1.08 ± 1.20 kg for the 720 mg dose and −0.90 ± 1.67 kg for the placebo. The corresponding changes in waist circumference were −1.20 ± 1.89 cm for the 480 mg dose, −1.39 ± 2.08 cm for the 720 mg dose and 0.30 ± 1.78 cm for the placebo. Adiponectin levels were greater in the 720 mg dose group (−3385 ± 3911 ng/mL) than in the 480 mg dose group (−618 ± 1286 ng/mL) and the placebo group (−1020 ± 756 ng/mL). The levels of other biomarkers, including leptin, insulin, C-peptide, TNFα and CCL2, remained stable across all groups, with no differences observed between the dose groups and the placebo group (Table S4).

3.4 | Safety and tolerability

Among the healthy female subjects, 28 treatment-emergent adverse events (TEAEs) were reported by 11 subjects (Table S1). Among the TEAEs, 26 were mild, and two were moderate (ligament sprain, headache). Diarrhoea was the most frequently reported TEAE and was observed in three subjects (three cases) in the 720 mg dose group.

Among the obese subjects, 40 TEAEs were reported in 15 subjects (Table S1). All the TEAEs were mild, and all the subjects recovered without sequelae. A total of 12 cases of diarrhoea were reported: five subjects in the 480 mg dose group (seven cases), five subjects in the 720 mg dose group (six cases) and two subjects in the placebo group (two cases) (Figure S8).

No clinically significant changes were observed in clinical laboratory tests, physical examinations, vital signs or 12-lead ECGs. Similarly, no clinically meaningful changes in the menstrual cycle were observed among healthy female subjects. All hormone levels remained stable following vutiglabridin administration.

4 | DISCUSSION

This study was conducted to compare the PKs and safety of vutiglabridin between healthy females and obese subjects and to explore short-term PD responses following oral administration of vutiglabridin. A PK comparison between these groups at the same dosage levels revealed that obese subjects presented a 9%–13% higher $C_{max,ss}$ than healthy female subjects, and the $AUC_{\tau,ss}$ was 8%–9% lower in obese subjects. All reported TEAEs were mild or moderate in severity, and all resolved without sequelae.

Given the lipophilic nature of vutiglabridin (logP = 4.6), obesity-related changes in body composition may have influenced its distribution. The increased adipose tissue in obese subjects could have contributed to a greater volume of distribution.[24,25] Although an increased volume of distribution typically results in a lower C_{max}, vutiglabridin exhibited a higher C_{max} in obese subjects. This finding may be attributed to the biphasic PK profile of vutiglabridin, which is characterized by rapid initial absorption followed by delayed distribution into peripheral compartments such as adipose tissue. The prolonged distribution phase may have also contributed to the extended terminal elimination half-life observed in obese individuals.

In preclinical studies, vutiglabridin dose-dependently reduced body weight by enhancing fatty acid oxidation and mitochondrial activity without reducing food intake and by upregulating genes involved in lipid and glucose metabolism.[17] In this study, although vutiglabridin did not result in statistically significant reductions in body weight or waist circumference in healthy female subjects after 14 days, obese subjects receiving repeated administration of vutiglabridin showed greater reductions than those receiving the placebo. Changes in levels of inflammatory markers were modest. The rationale for assessing adiponectin, leptin, insulin-related markers and pro-inflammatory cytokines/chemokines (IL-6, TNFα and CCL2) lies in their central roles in obesity-related pathophysiology and the compound's proposed mechanism of action. Adiponectin and leptin reflect adipose tissue function and insulin sensitivity; insulin and C-peptide indicate β-cell activity and glucose-insulin homeostasis; and IL-6, TNFα and CCL2 are key mediators of the chronic low-grade inflammation characteristic of obesity.[26] In healthy female subjects, the level of adiponectin—an adipokine that enhances insulin sensitivity and reduces inflammation—tended to increase, whereas in obese subjects receiving 720 mg, it decreased relative to levels observed in the placebo group, although the difference was not statistically significant ($p = .1288$) (Table S4).[27] The levels of inflammatory cytokines IL-6 and TNFα also decreased modestly but not significantly, further suggesting that more pronounced or prolonged effects may require extended treatment or greater weight loss.[27,28] Previous studies suggest that weight loss ≥ 10% may be required to elicit significant changes, and the relatively short treatment duration may have further limited the detection of such delayed effects.[29]

Existing antiobesity treatments have resulted in varying degrees of weight loss with longer treatment durations. Orlistat resulted in a mean weight loss of 7.37 ± 0.6 kg after 12 months of treatment, whereas liraglutide induced a mean weight loss of 8.4 ± 7.3 kg over 56 weeks.[6,30] In comparison, once-daily administration of vutiglabridin for 14 days resulted in a mean body weight reduction of 1.81 ± 1.93 kg in obese subjects. Vutiglabridin appears to promote lipolysis by decreasing the levels of inflammation-related markers in immune cells within adipose tissue, suggesting a potentially safer and physiologically favourable mechanism of action. As direct comparisons are limited by the short treatment duration in this study, further studies involving longer treatment periods in diverse populations are needed to evaluate the clinical potential of vutiglabridin.

Reproductive safety monitoring in healthy females revealed no clinically meaningful changes in the menstrual cycle or hormone levels (testosterone, LH, FSH or inhibin B) following 14 days of administration. Given that reproductive toxicity in rodents likely reflects species-specific reduction in epididymal fat, these findings suggest a minimal risk of clinically relevant reproductive effects in humans.[25]

Gastrointestinal AEs, particularly diarrhoea, increased in a dose-dependent manner in both healthy female and obese subjects. While diarrhoea is frequently reported with antiobesity agents such as semaglutide and liraglutide, mainly because they suppress appetite and reduce food intake, vutiglabridin promotes weight loss through increasing energy expenditure and improving hepatic steatosis associated with inflammation.[31,32] Thus, the observed events are more likely related to the formulation, potentially due to excipients such as medium-chain triglycerides, which are known to induce gastrointestinal symptoms including borborygmi, cramps and diarrhoea.[33] In the 720 mg dose group of healthy female subjects, three cases of diarrhoea were reported. In obese subjects, increased absorption may have led to greater systemic exposure, which could have contributed to a higher incidence of diarrhoea (Figure S8).

The primary limitation of this study was the difference in discharge and admission schedules between healthy female and obese subjects. Both groups were initially admitted on day −1; however, healthy female subjects were discharged on day 2 and readmitted on day 11. Differences in scheduling might have led to complexity in the management of subjects and potentially affected the PD outcomes. Accordingly, direct comparisons of PD outcomes between healthy female and obese subjects may be inappropriate. However, within each dose group, the effects of vutiglabridin relative to the placebo remained assessable.

5 | CONCLUSION

The plasma concentration of vutiglabridin reached higher peak levels but was associated with lower systemic exposure in obese subjects than in healthy female subjects. However, the overall PK profiles were comparable between the two groups. Vutiglabridin was well tolerated in both healthy female and obese subjects following multiple oral doses of up to 720 mg. These results support the advancement of vutiglabridin into phase II clinical trials.

AUTHOR CONTRIBUTIONS

Sooyoun Lee, Hyun Chul Kim and Kyung-Sang Yu drafted the manuscript. Sooyoun Lee and Hyun Chul Kim analysed the data. All the authors reviewed, revised and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Sang-Ku Yoo is a current employee of Glaceum, Inc., and holds stocks/shares. Glaceum, Inc., provided funding for this research and holds Patent US9783551B2, which grants intellectual properties (IPs) for the synthesis and use of the compounds in the article. All the other authors declare that they have no competing interests for this work. The authors confirm that the principal investigators for this paper are Young Ran Yoon and Kyung-Sang Yu. They had direct clinical responsibility for the subjects.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Sooyoun Lee https://orcid.org/0009-0000-3211-4166
Hyun Chul Kim https://orcid.org/0000-0002-8819-4780
Young Ran Yoon https://orcid.org/0000-0003-2166-7579
In-Jin Jang https://orcid.org/0000-0002-8384-3139
Kyung-Sang Yu https://orcid.org/0000-0003-0921-7225

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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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