A Phase 1, randomized, double-blind, single-ascending dose study of KAI-9531, a novel GLP-1/GIP receptor dual agonist in development for people living with overweight/obesity

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Objective

- This Phase 1 bridging study conducted in participants of non-Asian and Asian descent evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a single subcutaneous dose of ribupatide without titration.

Introduction

- Obesity is a serious, chronic, and progressive disease that can cause medical complications and reduce life expectancy.[1,2]
- Current obesity management medications have demonstrated clinically meaningful weight loss in randomized controlled trials;[3,4] however, an unmet need persists for high-efficacy treatments, especially in individuals with higher levels of obesity.[5]
- Ribupatide (formerly KAI-9531, HRS-9531) is a novel GLP-1/GIP receptor dual agonist in development for overweight/obesity as a once-weekly injectable formulation and as a once-daily oral tablet formulation.
- In trials of ribupatide conducted by Jiangsu Hengrui Pharmaceuticals Co., Ltd. in China, subcutaneous injection of ribupatide generated clinically meaningful improvements across multiple studies to date.
  - In a 36-week Phase 2 study, participants taking the 8 mg dose achieved a 23.6% mean weight loss (21.7% placebo-subtracted) at Week 36 (efficacy estimand).[6-8]
  - In a 48-week Phase 3 study, participants taking the 6 mg dose achieved a 19.2% mean weight loss (17.7% placebo-subtracted) at Week 48 (efficacy estimand).[8,9]

Methods

Study design and participants

- This was a randomized, double-blind, placebo-controlled, single-ascending dose Phase 1 study conducted at a single center in Australia.
- Participants were assigned to 5 cohorts, randomized to receive a single subcutaneous dose of ribupatide without titration (1 mg, 2 mg, or 3 mg) or placebo, and were followed for 29 days to the end of study (EOS) (**Figure 1**).
- All participants were admitted to the Clinical Research Unit for 4 days following dosing, then returned on Days 5, 6, 8, 14, and 22 for safety, PK, and PD assessments, and on Day 29 for EOS assessments.
- Participants of non-Asian descent were enrolled in Cohorts 1 to 4, and participants of Asian descent were enrolled in Cohort 5.
  - The effect of Asian descent on ribupatide PK was evaluated by comparing PK parameters from this study and by assessing them in a population PK model.
- Key inclusion criteria were: body mass index (BMI) ≥22.0 and ≤35.0 kg/m^2, with a body weight (BW) ≥60 kg and ≤130 kg at screening.

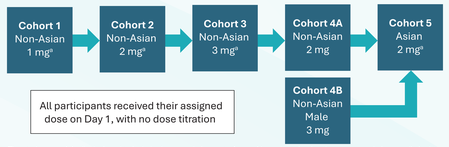
Endpoints

- Primary safety endpoints included treatment-emergent adverse events (TEAEs).
- Secondary endpoints included PK analysis in non-Asian and Asian participants (including $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, and $t_{1/2}$).
- Exploratory endpoints included PD analyses of BW, glycated hemoglobin (HbA1c), continuous glucose monitoring, fasting plasma glucose, and fasting serum insulin.

Statistical analysis

- No formal sample size calculations were performed; however, because this was an early-phase study, the sample size of up to 50 participants across 5 cohorts was considered sufficient for the study objectives.

Figure 1. Study design



Note: The study was originally designed to include dose escalation up to 6 mg with no dose titration; however, escalation was limited to 3 mg after 5 participants met the protocol-defined stopping criterion for moderate or higher nausea. As a result, Cohort 4 was revised to Cohorts 4A and 4B. In addition, a cohort of Asian participants was included. Each cohort began with 2 sentinel participants, 1 randomized to receive ribupatide and the other randomized to receive placebo.
[a]Sentinel + placebo control required.

- Endpoints were analyzed by treatment group (placebo and treatment dose) with non-Asian and Asian summarized separately and/or combined for each treatment as appropriate.
- Dose proportionality was evaluated using a log-transformed power model and was concluded if the 95% confidence intervals (CIs) for the slope (β_1) included 1 and were contained within 0.80 to 1.25.
- Descriptive statistics were used to summarize PK parameters and PD data.

Results

Participants

- Overall, 49 participants were randomized and dosed (ribupatide, n=39; placebo, n=10); 10 participants were of Asian descent (Cohort 5: 2 mg, n=8; placebo, n=2).
- At baseline, median (range) age was 28.0 (18 to 55) years, BMI was 27.0 (22.6 to 34.0) kg/m^2, and BW was 78 (60.3 to 118.4) kg (**Table 1**); 55% were female.
  - Non-Asian participants had a higher BW at baseline compared with Asian participants.

Table 1. Baseline characteristics

Variable	Placebo (n=10)	Ribupatide					All participants (n=49)
		1 mg	2 mg		3 mg	All treated participants (n=39)	
		Non-Asian (n=8)	Non-Asian (n=12)	Asian (n=8)	Non-Asian (n=11)		
Age, years							
Median (range)	26.5 (18, 52)	26.0 (24, 55)	32.0 (20, 52)	28.0 (23, 48)	29.0 (20, 55)	29.0 (20, 55)	28.0 (18, 55)
Sex, n (%)							
Female	5 (50.0)	3 (37.5)	6 (50.0)	6 (75.0)	7 (63.6)	22 (56.4)	27 (55.1)
Race, n (%)[a]							
White	6 (60.0)	8 (100)	11 (91.7)	0	7 (63.6)	26 (66.7)	32 (65.3)
Asian	2 (20.0)	0	0	8 (100)	0	8 (20.5)	10 (20.4)
Black or African American	1 (10.0)	0	0	0	0	0	1 (2.0)
Weight, kg							
Median (range)	75 (62.0, 96.2)	84 (62.4, 99.2)	88 (62.5, 118.4)	70 (60.3, 82.5)	81 (66.8, 94.9)	81 (60.3, 118.4)	78 (60.3, 118.4)
BMI, kg/m^2							
Median (range)	25.0 (23.4, 32.9)	27.2 (22.6, 33.0)	29.2 (23.1, 34.0)	26.1 (23.0, 32.5)	27.1 (23.6, 33.5)	27.1 (22.6, 34.0)	27.0 (22.6, 34.0)

BMI, body mass index.
Note: Percentages are subject to rounding.
[a]In total, 6 participants were of other or unknown race.

Table 2. Summary of TEAEs

Participants, n (%)	Placebo (n=10)	Ribupatide					All participants (n=49)
		1 mg	2 mg		3 mg	All treated participants (n=39)	
		Non-Asian (n=8)	Non-Asian (n=12)	Asian (n=8)	Non-Asian (n=11)		
Any TEAE	7 (70.0)	6 (75.0)	12 (100)	7 (87.5)	11 (100)	36 (92.3)	43 (87.8)
TEAE severity							
Mild	5 (50.0)	3 (37.5)	6 (50.0)	6 (75.0)	5 (45.5)	20 (51.3)	25 (51.0)
Moderate	2 (20.0)	3 (37.5)	6 (50.0)	1 (12.5)	6 (54.5)	16 (41.0)	18 (36.7)
Severe	0	0	0	0	0	0	0
Treatment-related TEAE[a]	4 (40.0)	5 (62.5)	11 (91.7)	6 (75.0)	10 (90.9)	32 (82.1)	36 (73.5)
Mild	4 (40.0)	3 (37.5)	5 (41.7)	5 (62.5)	4 (36.4)	17 (43.6)	21 (42.9)
Moderate	0	2 (25.0)	6 (50.0)	1 (12.5)	6 (54.5)	15 (38.5)	15 (30.6)
Severe	0	0	0	0	0	0	0
Serious TEAE	0	0	0	0	0	0	0
TEAEs leading to study discontinuation	0	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0
Most common TEAEs (reported in >10% of participants treated with ribupatide at any dose)							
Decreased appetite	1 (10.0)	5 (62.5)	8 (66.7)	5 (62.5)	9 (81.8)	27 (69.2)	28 (57.1)
Nausea	0	2 (25.0)	9 (75.0)	6 (75.0)	7 (63.6)	24 (61.5)	24 (49.0)
Vomiting	0	0	6 (50.0)	3 (37.5)	5 (45.5)	14 (35.9)	14 (28.6)
Headache	2 (20.0)	1 (12.5)	3 (25.0)	4 (50.0)	5 (45.5)	13 (33.3)	15 (30.6)
Dizziness	0	0	4 (33.3)	1 (12.5)	3 (27.3)	8 (20.5)	8 (16.3)
Abdominal pain	1 (10.0)	0	2 (16.7)	0	3 (27.3)	5 (12.8)	6 (12.2)
Gastroesophageal reflux disease	0	0	1 (8.3)	0	3 (27.3)	4 (10.3)	4 (8.2)
Myalgia	0	0	2 (16.7)	0	2 (18.2)	4 (10.3)	4 (8.2)

TEAE, treatment-emergent adverse event.
Note: Common TEAEs ranked by reporting frequency in all treated participants. All participants received their randomized dose without titration.
[a]TEAEs were counted once at their maximum severity.

Primary endpoints

Safety

- Most TEAEs were mild in severity, and no serious TEAEs, TEAEs leading to study discontinuation or death, or severe TEAEs were reported (**Table 2**).
- The most common TEAEs with ribupatide were decreased appetite (69.2%), nausea (61.5%), and vomiting (35.9%) (**Table 2**).
  - The observed TEAE rates were generally as expected based on non-titrated dosing in this study.

Secondary endpoints

Pharmacokinetics

- Geometric mean values of CL/F, V_{ss}/F, and V_z/F in Asian participants were lower than in non-Asian participants; however, mean $t_{1/2}$ values were similar (**Table 3**).
- Systemic exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$) and peak exposure (C_{max}) were higher in Asian participants compared with non-Asian participants.
  - Exposures in Asian and non-Asian participants were similar when adjusted for baseline BW (**Figure 2**).
- Asian descent was not a significant covariate for ribupatide PK when evaluated in the population PK model.
- Exposure (ie, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}) increased with increasing dose in a dose-proportional manner (**Table 3**).

Exploratory endpoints

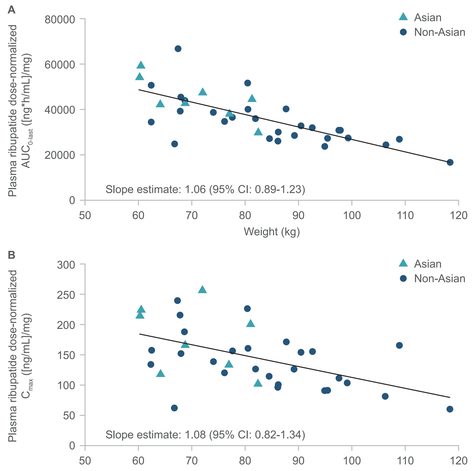
Body weight

- Overall, ribupatide demonstrated a dose-dependent reduction in BW from baseline to EOS with a mean (standard deviation [SD]) decrease in BW of 3.1% (2.5%) in all ribupatide-treated participants vs 0.4% (2.1%) in placebo-treated participants. Weight loss was similar in Asian and non-Asian participants (**Figure 3**).

Glucose parameters

- Single-dose ribupatide was associated with greater improvements compared with placebo in fasting glucose (mean change from baseline to Day 29 [EOS] -0.9 [SD 6.5] mg/dL vs 2.4 [3.3] mg/dL, respectively), fasting insulin (0.4 [3.4] mU/L vs 2.7 [3.3] mU/L), and HbA1c (-0.2% [0.1%] vs -0.0% [0.2%]), irrespective of race.

Figure 2. Dose-normalized PK vs BW after a single subcutaneous dose of ribupatide: (A) $AUC_{0\text{-last}}$ and (B) C_{max}



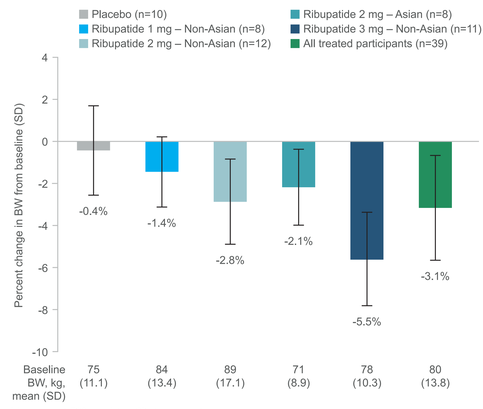
AUC, area under the concentration-time curve; $AUC_{0\text{-inf}}$, AUC from time zero to infinity; $AUC_{0\text{-last}}$, AUC from time zero to the time of the last quantifiable concentration; BW, body weight; CI, confidence interval; C_{max}, maximum plasma concentration; PK, pharmacokinetics.
Note: Similar findings were observed for plasma ribupatide dose-normalized $AUC_{0\text{-inf}}$ (data not shown).

Table 3. Plasma PK parameters after a single subcutaneous dose of ribupatide

	Ribupatide			
	1 mg	2 mg		3 mg
	Non-Asian (n=8)	Non-Asian (n=11)[a]	Asian (n=8)	Non-Asian (n=11)
Geometric mean (geometric CV%)[b]				
$AUC_{0\text{-last}}$, ng*h/mL	33800 (23.0)	57800 (24.9)	88700 (21.0)	122000 (31.0)
$AUC_{0\text{-inf}}$, ng*h/mL	37300 (25.9)	62900 (25.4)	97600 (21.2)	128000 (31.6)
C_{max}, ng/mL	124 (19.6)	230 (33.2)	340 (33.8)	472 (48.7)
T_{max}, h, median (range)	36.0 (12.0, 97.1)	24.0 (8.0, 94.4)	30.0 (4.0, 60.0)	12.0 (8.0, 124)
$t_{1/2}$, h	188 (17.8)	181 (7.7)	184 (14.1)	176 (10.5)
CL/F, L/h	0.0268 (25.9)	0.0318 (25.4)	0.0205 (21.2)	0.0234 (31.6)
V_{ss}/F, L	7.52 (16.7)	8.54 (25.8)	5.70 (24.9)	6.36 (40.6)
V_z/F, L	7.29 (17.9)	8.30 (24.1)	5.45 (20.5)	5.93 (39.0)

AUC, area under the concentration-time curve; $AUC_{0\text{-last}}$, AUC from time zero to infinity; $AUC_{0\text{-last}}$, AUC from time zero to the time of the last quantifiable concentration; CL/F, apparent oral clearance after extravascular administration; C_{max}, maximum plasma concentration; CV%, percent coefficient of variation; PK, pharmacokinetics; T_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal half-life; V_{ss}/F, apparent volume of distribution at steady state after extravascular administration; V_z/F, apparent volume of distribution during the terminal phase after extravascular administration.
[a]One participant did not have sufficient PK data for analysis. [b]Unless stated otherwise, PK parameters are presented as geometric mean (CV%), except T_{max}, which is presented as median (range).

Figure 3. Percent change in BW from baseline to Day 29 (EOS)



BW, body weight; EOS, end of study; SD, standard deviation.

Conclusions

- In this randomized, double-blind, single-ascending dose, Phase 1 study conducted without titration, ribupatide was generally well tolerated after a single subcutaneous dose, both in non-Asian and Asian participants.
- Similar exposure to ribupatide was observed between non-Asian and Asian participants once adjusted for baseline BW.
- Ribupatide reduced BW dose-dependently, with no differences observed in percentage BW reduction between non-Asian and Asian participants.
- Overall, the results from this Phase 1 study support further investigation of ribupatide; a Phase 3 program is underway to evaluate titrated ribupatide in a diverse population beyond exclusively Asian participants.

Abbreviations

AE, adverse events; AUC, area under the concentration-time curve; $AUC_{0\text{-inf}}$, AUC from time zero to infinity; $AUC_{0\text{-last}}$, AUC from time zero to the time of the last quantifiable concentration; BMI, body mass index; BW, body weight; CI, confidence interval; CL/F, apparent oral clearance after extravascular administration; C_{max}, maximum plasma concentration; CV%, percent coefficient of variation; EOS, end of study; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation; TEAE, treatment-emergent adverse event; T_{max}, time to maximum plasma concentration; $t_{1/2}$, terminal half-life; V_{ss}/F, apparent volume of distribution at steady state after extravascular administration; V_z/F, apparent volume of distribution during the terminal phase after extravascular administration.

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Disclosures

LK: SAB member for Kailera, CEO of Koslapp Therapeutics, and Board Chair of RefuelBio. **ACM**: SAB member for Kailera and owns stock options in Kailera. **AC**, **SD**, **AF**, **HZ**, **SW**: employees of Kailera and may own stock/options in the company.

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