Rationale and design of the KaiNETIC-1 and -2 trials of ribupatide in people living with obesity

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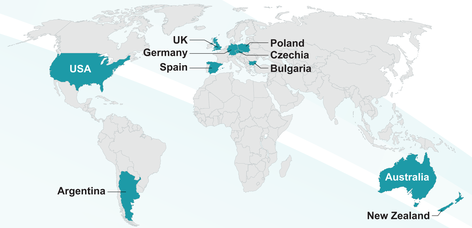
Objective

- To describe the rationale and design of two international Phase 3 trials evaluating the efficacy and safety of ribupatide (up to 10 mg weekly) in adults living with overweight or obesity, and with and without type 2 diabetes mellitus (T2DM).

Introduction

- Overweight and obesity are associated with increased risk of metabolic and long-term comorbidities.[1]
- There is an expanding role for glucagon-like peptide-1 (GLP-1) receptor agonists and multiagonists in obesity management medication.[2,3]
- Ribupatide (KAI-9531; HRS9531) is an investigational once-weekly (half-life of ~7 days) injectable GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonist in development to treat overweight/obesity.[4]
- In clinical trials by Jiangsu Hengrui Pharmaceuticals Co., Ltd, mean weight loss of up to 23.6% was observed at 36 weeks in Chinese adults living with overweight or obesity (efficacy estimand, Phase 2 study, ribupatide 8 mg weekly).[5–7]
- Ribupatide has now advanced to Phase 3 investigation in the international KaiNETIC clinical trial program; the designs of KaiNETIC-1 and KaiNETIC-2 are described here.
  - Clinical trial site locations are shown in **Figure 1**.

Figure 1. KaiNETIC-1 and KaiNETIC-2 clinical trial site locations



Trial site locations updated August 2026.

Methods

Study design and participants

- KaiNETIC-1 (NCT07284875) and KaiNETIC-2 (NCT07284901) are Phase 3, multicenter, international, randomized, double-blind, placebo-controlled trials in adults ≥18 years old living with overweight or obesity.
  - KaiNETIC-1 has enrolled adults without T2DM.[8]
  - KaiNETIC-2 has enrolled adults with T2DM.[9]
  - The study inclusion and exclusion criteria are presented in **Table 1**.
- KaiNETIC-1 has enrolled ~2530 participants at 110 locations, and KaiNETIC-2 has enrolled ~1270 participants at 174 locations.
- After ≤4 weeks of screening, participants are randomized to once-weekly self-administered subcutaneous ribupatide 4 mg, 6 mg, 8 mg, or 10 mg, or placebo (**Figure 2**).

Table 1. Key inclusion and exclusion criteria for KaiNETIC-1 and KaiNETIC-2

Key eligibility criteria		KaiNETIC-1	KaiNETIC-2
Inclusion criteria	History of being non-responsive to at least 1 self-reported effort to lose weight with diet and/or physical activity in the past 6 months	✓	✓
	BMI ≥30 kg/m² or BMI ≥27 kg/m² and a diagnosis of ≥1 of the following: hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease	✓	–
	BMI ≥27 kg/m²	–	✓
	Diagnosis of T2DM with HbA_{1c} ≥6.5% to ≤9.5% at screening	–	✓
	Receiving stable T2DM therapy for ≥3 months before screening[a]	–	✓
Exclusion criteria	Received semaglutide, tirzepatide, or a GLP-1, GLP-1/GIP, or glucagon receptor agonist within 3 months before screening	✓	✓
	Current diagnosis or history of diabetes mellitus, including T1DM or T2DM, history of diabetic ketoacidosis, or hyperosmolar state/coma	✓	–
	Current diagnosis or history of T1DM or any other type of diabetes, except T2DM	–	✓
	History of diabetic ketoacidosis or hyperosmolar state/coma within 1 year before screening	–	✓
	History of severe hypoglycemia or hypoglycemia unawareness within 1 year before screening	–	✓

✓=criterion applies; –=not a criterion for the clinical trial; BMI=body mass index; GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinotropic polypeptide; HbA_{1c}=glycated hemoglobin; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus.
The order of inclusion and exclusion criteria reflect those applicable to both studies, then to KaiNETIC-1 only, and then to KaiNETIC-2 only. Other eligibility criteria apply. See ClinicalTrials.gov (NCT07284875 and NCT07284901) and the study protocols for further details.
[a] Participants can be treatment naive if they have an HbA_{1c} of 6.5% to 7.5%, inclusive.

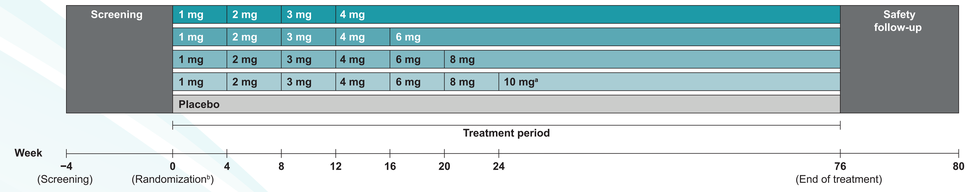
- The efficacy endpoints for both trials are summarized in **Table 2**. Safety and tolerability will be assessed throughout both trials.
  - Change in body weight will also be assessed in a predefined subgroup of participants with a baseline body mass index ≥35 kg/m² to evaluate treatment effects in participants with more severe obesity.

Table 2. Efficacy endpoints assessed in KaiNETIC-1 and KaiNETIC-2[a]

Primary endpoint	KaiNETIC-1	
Percent change in body weight for ribupatide 8 and/or 10 mg	✓	
Co-primary endpoints	**KaiNETIC-2**	
Percent change in body weight for ribupatide 8 and/or 10 mg	✓	
Change in HbA_{1c} for ribupatide 8 and/or 10 mg	✓	
Key secondary endpoints	**KaiNETIC-1**	**KaiNETIC-2**
Percent change in body weight for ribupatide 4 and/or 6 mg	✓	✓
Change in HbA_{1c} for ribupatide 4 and/or 6 mg	–	✓
Percentage of participants with ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% reduction in body weight	✓	✓
Change in waist circumference	✓	✓
Change in absolute body weight	✓	✓
Percentage of participants with HbA_{1c} targets of <7.0% and ≤6.5%	–	✓
Change in fasting blood glucose[b]	–	✓
Change in systolic blood pressure[b]	✓	✓
Percent change in fasting triglycerides, non-HDL-cholesterol, and HDL-cholesterol[b]	✓	✓
Change in IWQOL-Lite-CT physical function composite score[b]	✓	✓
Percent change in body weight in participants with BMI ≥35 kg/m² for ribupatide 8 and 10 mg (subgroup analysis)	✓	✓

✓=endpoint will be assessed; –=endpoint will not be assessed; BMI=body mass index; HbA_{1c}=glycated hemoglobin; HDL=high-density lipoprotein; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials.
Note: Other secondary efficacy outcomes include: percentage change in insulin, total cholesterol, and low- and very low-density lipoprotein cholesterol; change in BMI, Control of Eating Questionnaire scores, diastolic blood pressure, blood glucose, and Food Noise Questionnaire score; and proportion of participants with ≥30% reduction in body weight and with HbA_{1c} <5.7%. Other secondary non-efficacy outcomes include: safety and tolerability (including treatment-emergent adverse events, clinical laboratory parameters, electrocardiograms, and vital signs), immunogenicity (including anti-drug antibodies and neutralizing antibodies), population pharmacokinetics, and exposure–response analyses. Change and percent change from baseline in total body fat mass and total body lean mass, as measured by dual-energy X-ray absorptiometry, will be assessed in KaiNETIC-1 as exploratory endpoints. Sit-to-stand will be an additional assessment in both trials.
[a] Endpoints assessed at Week 76, and participants will attend clinic visits in a fasted state.
[b] All ribupatide doses combined.

Figure 2. Study design and treatment allocation in KaiNETIC-1 (without T2DM) and KaiNETIC-2 (with T2DM)



T2DM=type 2 diabetes mellitus.
Treatment begins at 1 mg, followed by a dose-titration period of up to 24 weeks and a maintenance period, for a total treatment duration of up to 76 weeks.
[a] The 10 mg dose is included because higher body weights in non-Chinese participants are expected to require a modestly higher dose to achieve plasma exposure similar to that observed with the 8 mg dose evaluated in Phase 2 studies in China.
[b] Randomization stratified by sex, geographic region, and baseline body mass index (<35 or ≥35 kg/m²) in both KaiNETIC-1 and KaiNETIC-2. Randomization in KaiNETIC-2 will also be stratified by type of oral therapy for T2DM based on potential body weight effect.

Statistical analyses

- Efficacy analyses will be conducted using the Full Analysis Set (all randomized participants), and safety analyses will be conducted using the Safety Analysis Set (all randomized participants who receive ≥1 dose of study treatment).
- Treatment effects will be evaluated using two prespecified estimands (primary treatment policy estimand; supplemental efficacy estimand).

Lifestyle and nutrition support

Lifestyle support throughout the study

Participants receive lifestyle support comprising **nutritional counseling** and **diet** and **physical activity** recommendations

Nutritional counseling visits

Day 1 | Week 8 | Week 12 | Week 20 | Week 28 (Optional) | Week 40 (Optional)

Participants are advised to complete diet and activity logs ≥3 days before counseling visits, to be reviewed during the session

Additional counseling on dietary behavior and GI symptom management will be provided as requested

Diet recommendations

Participants are encouraged to maintain a **reduced-calorie, high-quality diet** by:

- decreasing overall calorie intake
- restricting greasy/fried and high-added-sugar foods to reduce GI side effects
- prioritizing small, nutrient-dense, frequent meals
- incorporating adequate lean protein, fiber, and hydration

Physical activity recommendations

Participants are advised to engage in weekly **physical activity** including:

- ≥150 minutes a week of moderate-to-vigorous activity
- resistance training ≥2 times a week

Participants will receive guidance for safe physical activity

Conclusions

- KaiNETIC-1 and KaiNETIC-2 are international Phase 3 trials evaluating the efficacy and safety of once-weekly ribupatide at doses up to 10 mg in adults living with overweight or obesity, without and with T2DM respectively.
- Approximately 3800 participants have been enrolled across more than 280 trial locations in 10 countries, providing a broad international evaluation of ribupatide.
- KaiNETIC-1 and KaiNETIC-2 incorporate structured lifestyle support programs comprising nutritional counseling, dietary and activity self-monitoring, physical activity recommendations, and additional counseling when clinically indicated.
- In addition to body weight, the KaiNETIC programs will evaluate glycemic control, cardiometabolic measures, physical function, quality of life, patient-reported outcomes, and safety and tolerability, enabling a comprehensive evaluation of ribupatide.

Abbreviations

BMI=body mass index; GI=gastrointestinal; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; HbA_{1c}=glycated hemoglobin; HDL=high-density lipoprotein; IWQOL-Lite-CT=Impact of Weight on Quality of Life-Lite Clinical Trials; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus.

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