Rationale and design of the KaiNETIC-3 trial of ribupatide in people with obesity and no diabetes

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Objective

- To describe the rationale and design of KaiNETIC-3, an international Phase 3 trial evaluating the efficacy and safety of ribupatide 8 mg or 10 mg weekly versus semaglutide 2.4 mg and placebo in adults living with obesity who do not have diabetes.

Introduction

- Overweight and obesity are associated with increased risk of metabolic and long-term comorbidities.[1]
  - Higher levels of obesity (BMI ≥35 kg/m^2) are associated with a reduced life expectancy of 6.5 to 13.7 years.[2,3]
- There is an expanding role for glucagon-like peptide-1 (GLP-1) receptor-based agonists in chronic weight management.[4,5]
- 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.[6]
- 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).[7–9]
- Ribupatide has now advanced to Phase 3 investigation in the international KaiNETIC clinical trial program; the design of the KaiNETIC-3 trial is described here.
  - Clinical trial site locations are shown in **Figure 1**.

Figure 1. KaiNETIC-3 clinical trial site locations



Trial site locations updated August 2026.

Methods

Study design and participants

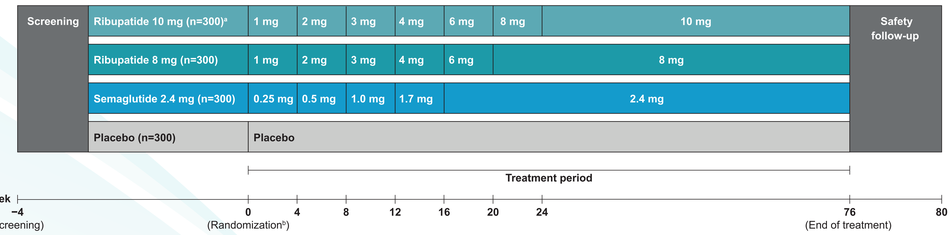
- KaiNETIC-3 (NCT07284979) is a Phase 3, multicenter, international, randomized, partially blinded, active- and placebo-controlled trial in adults ≥18 years old living with obesity without diabetes.
- The study inclusion and exclusion criteria are presented in **Table 1**.
- KaiNETIC-3 has enrolled ~1270 participants at ~60 locations.[1]
- After ≤4 weeks of screening, participants are randomized to once-weekly self-administered subcutaneous ribupatide 8 mg or 10 mg, semaglutide 2.4 mg, or placebo (**Figure 2**).

Table 1. Key inclusion and exclusion criteria for KaiNETIC-3

Key eligibility criteria	
Inclusion criteria	BMI ≥35 kg/m^2
	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
Exclusion criteria	Current diagnosis or history of diabetes mellitus, including T1DM or T2DM, history of diabetic ketoacidosis, or hyperosmolar state/coma
	Laboratory evidence of diabetes including HbA_{1c} ≥6.5%
	Received semaglutide, tirzepatide, GLP-1 receptor agonist, GLP-1/GIP agonist, or glucagon receptor agonist within 3 months before screening

BMI=body mass index; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; HbA_{1c}=glycated hemoglobin; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus.
Other eligibility criteria apply. See ClinicalTrials.gov (NCT07284979) and the study protocol for further details.

Figure 2. Study design and treatment allocation in KaiNETIC-3 without diabetes



Treatment begins with a dose-titration period (16 weeks for semaglutide and up to 24 weeks for ribupatide), followed by maintenance through Week 76.
[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 exposures similar to that observed with the 8 mg dose evaluated in Phase 2 studies in China.
[b] Randomization stratified by sex and geographic region (Europe and UK, North America, or Oceania).

- The efficacy endpoints assessed in KaiNETIC-3 are summarized in **Table 2**. Safety and tolerability will be assessed throughout the trial.
  - Change in body weight will also be assessed in predefined participant subgroups (e.g. age, sex, and geographic region) to evaluate the treatment effects across subgroups.

Table 2. Efficacy endpoints assessed in KaiNETIC-3[a]

Primary endpoint
Percent change in body weight[b,c]
Key secondary endpoints
Percentage of participants with ≥5% reduction in body weight[c]
Percentage of participants with ≥10%, ≥15%, ≥20%, and ≥25% reduction in body weight[b,c]
Change in waist circumference[b,c]
Change in absolute body weight[b,c]
Change in systolic blood pressure[c,d]
Percent change in fasting triglycerides, non-HDL-cholesterol, and HDL-cholesterol[c,d]
Change in IWQOL-Lite-CT physical function composite score[c,d]

BMI=body mass index; HDL=high-density lipoprotein; IWQOL-Lite CT=Impact of Weight on Quality of Life-Lite Clinical Trials.
Note: Other secondary efficacy outcomes include: proportion of participants with ≥30% reduction in body weight, change in BMI, Control of Eating Questionnaire scores, and Food Noise Questionnaire score. 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. Sit-to-stand will be an additional assessment.
[a] Endpoints assessed at Week 76, and participants will attend clinic visits in a fasted state.
[b] Compared with semaglutide.
[c] Compared with placebo.
[d] All ribupatide doses combined.

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-3 is an international Phase 3 trial evaluating the efficacy and safety of once-weekly ribupatide at doses of 8 mg and 10 mg versus semaglutide 2.4 mg and placebo in adults living with obesity (BMI ≥35 kg/m^2) without diabetes.
- Approximately 1270 participants have been enrolled across approximately 60 trial locations in 5 countries, providing a broad international evaluation of ribupatide.
- KaiNETIC-3 incorporates 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 program will evaluate 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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