STUDY SYNOPSIS

Protocol Title: A Randomized, Double-blind, Placebo-controlled Parallel Group Phase 2a Study to Evaluate the Efficacy and Safety of HPG1860 in Subjects with Nonalcoholic Steatohepatitis

Study Number: HPG1860-201

Study Name: Rise

Clinical Phase: 2A

Investigators/Study Centers: This study will be conducted at approximately 20 study centers, with approximately 20 investigators, located in the United States. Worldwide Clinical Trials, a contract research organization, will oversee operational aspects of this study on behalf of Hepagene (Shanghai) Co., Ltd., the Sponsor of the study.

Primary Objectives and Endpoints

Objective	Endpoint
• To investigate the safety and tolerability profile of HPG1860 3 mg, 5 mg, and 8 mg versus placebo in subjects with nonalcoholic steatohepatitis (NASH).	Primary Safety Endpoint Safety and tolerability of 12 - week treatment of HPG1860 3 mg, 5 mg, and 8 mg in subjects with NASH as assessed by: • Treatment-emergent adverse events (TEAEs) • Adverse events of special interest (AESI) • Serious adverse events (SAEs) • Changes in clinical safety laboratory values • Vital signs • Electrocardiogram (ECG)

Secondary Objectives and Endpoints

• To evaluate the efficacy of HPG1860 compared to placebo.	Key Secondary Efficacy Endpoint • Change from baseline (CFB) in liver fat content (LFC) measured by magnetic resonance

	imaging-proton density fat fraction (MRI-PDFF) at Week 12 Other Secondary Endpoints: • Percentage of subjects with ≥30% reduction in LFC from baseline measured by MRI-PDFF at Week 4 and Week 12 • CFB in LFC as measured by MRI-PDFF at Week 4
• To evaluate the pharmacokinetic (PK) profile of HPG1860 in NASH patients	PK Endpoints including: • Area under the curve from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of the last quantifiable concentration (AUC_{0-t}), AUC during the 24- hour dosing interval (AUC_{0-24h}), maximum observed concentration (C_{max}), time to maximum plasma concentration (T_{max}), half-life ($T_{½}$), apparent total clearance of the drug from plasma after oral administration (CL/F), and apparent volume of distribution during terminal phase after extravascular administration (Vz/F) • Trough concentration (C_{trough}) • Accumulation ratio (R_{ac}) based on C_{max} and AUC
• To evaluate the effect of HPG1860 compared to placebo on biomarkers of interest	• CFB in insulin, fasting plasma glucose (FPG) and homeostatic model assessment of insulin resistance (HOMA-IR) at Weeks 8, 12, and 16. Note:

	FPG and insulin will be measured as clinical safety laboratory assessments • CFB in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) at Weeks 12 and16. Note: ALT, AST, and GGT will be measured as clinical safety laboratory assessments • CFB in non-invasive biomarkers of liver injury and apoptosis: cytokeratin-18 (CK-18; M30 and M65 fractions), fibrosis-4 (FIB- 4), AST to platelet ratio index (APRI), and N- terminal propeptide of type III collagen (Pro-C3) at Weeks 12 and 16 • CFB in enhanced liver fibrosis (ELF), a non- invasive biomarker of fibrosis, hyaluronic acid, procollagen III N-terminal peptide (PIIINP) and tissue inhibitor of metalloproteinase- 1 (TIMP- 1) at Weeks 12 and 16 • CFB in pharmacodynamic (PD) and cardiometabolic biomarkers: high- sensitivity C reactive protein (hs-CRP), 7α-hydroxy-4-cholesten-3-one (C4), alkaline phosphatase (ALP), total bile acids (BAs), non-high density lipoprotein cholesterol (non-HDL-C), low-density lipoprotein cholesterol (LDL-C), total

		cholesterol (TC), and apolipoprotein B (apoB) at Weeks 2, 4, 8, 12, and 16. Note: HDL-C, LDL-C, and triglycerides (TG) will be measured as clinical safety laboratory assessments
Exploratory Objectives and Endpoints	• To collect reserve samples for future evaluation of the effect of HPG1860 compared to placebo on additional biomarkers, not otherwise described	• Assess biomarkers, not otherwise described, acquired from reserve samples
	• To characterize HPG1860 metabolites	• To measure HPG1860 metabolites
	• To characterize the relationship between PK values and study outcomes	• Explore correlations between PK concentration and LFC

Other Safety Measures:

- Physical examination (PE)
- Weight

Study Design:

This is a Phase 2a, randomized, double-blind, placebo-controlled, parallel group, multiple arm, multicenter study of 3 different doses of HPG1860 versus placebo in subjects with biopsy-confirmed or phenotypic NASH. Screening will occur up to 5 weeks prior to randomization; all eligible subjects will have baseline hepatic imaging during Screening, prior to randomization. Approximately 80 eligible subjects will be randomized 1:1:1:1 on Day 1/Week 0 (T1) to receive either HPG1860 3 mg (n = 20), or 5 mg (n = 20), or 8 mg (n = 20), or placebo (n = 20) for 12 weeks. Following a preplanned interim analysis, a dose cohort may be dropped and/or added.

Randomized subjects will return for clinic visits at Week 2 (T2), Week 4 (T3), Week 8 (T4), and Week 12 (T5) as well as Week 16 (T6). Imaging procedures will be completed during Screening, Week 4 (T3), and Week 12 (T5). A follow- up visit will be completed 4 weeks after last dose of investigational medicinal product (IMP) at Week 16 (Visit T6).

At selected PK sites, serial PK samples will be collected from approximately 6 to 8 subjects in each dose cohort; blood samples will be collected on Day 1 pre-dose (within 30 minutes prior to dosing) and at 1, 2, 4, 6, and 8 hours (±15 minutes) post-dosing and on Day 14 pre-dose (within 30 minutes before dosing) and at 1, 2, 4, 6, and 8 hours (±15 minutes) post-dosing, and at 24 hours

	(±30 minutes) prior to dosing on Day 15. For all subjects, PK samples will be taken within 30 minutes prior to dosing at Weeks 4, 8, 12, and 16. This study includes collection of reserve samples at Baseline (Day 1) and Week 12 for future biomarker analysis, unless prohibited by local law or regulations, and where approved by the Institutional Review Board (IRB).
Duration of Treatment:	Total study duration per subject: 21 weeks (approximate) Screening: up to 5 weeks Treatment: 12 weeks Follow-up: 4 weeks
Planned Sample Size and Treatment Groups:	Planned: Approximately 80 adult male and female subjects HPG1860 3 mg (n =20) HPG1860 5 mg (n = 20) HPG1860 8 mg (n = 20) Placebo (n = 20) Following a preplanned unblinded (comparative) interim analysis when 50% of randomized subjects have reached the Week 12 endpoint, an ongoing treatment group (3 mg, 5 mg, or 8 mg) may be dropped and/or a new treatment group of dose may be added.
Target Population:	Subjects with biopsy-confirmed or phenotypic NASH.
Eligibility Criteria:	**Inclusion Criteria:** 1. Provision of written informed consent prior to any study-specific procedure. 2. Males and females between 18 and 75 years of age; inclusive based on the date of Screening. 3. Nonpregnant, nonlactating women. Women must be either: a. Females who are postmenopausal must have cessation of menses for at least 12 months without an alternative medical cause and with screening FSH≥40, or. Note: females on hormone replacement therapy (HRT) and whose menopause status is in doubt will be required to use contraception methods described in exclusive criteria if they wish to continue their HRT during the study. Otherwise, they must temporarily stop HRT to enable confirmation of post

menopausal status before study enrollment.

b. Surgically sterile prior to Screening including hysterectomy, bilateral oophorectomy, or tubal ligation, or

c. Women of childbearing potential (WOCBP) willing to use at least 1 acceptable method of birth control. The minimal requirement for adequate contraception should be functional on Day 1, continuing during the study period and for at least 30 days after the last dose of IMP. Acceptable methods of birth control include:

   i. Oral, implantable, injectable, or topical birth control medications.

   ii. Placement of an intrauterine device with or without hormones.

   iii. Barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly.

   iv. Vasectomized male partner who is the sole partner for this subject.

   v. True abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

4. Male subjects must agree to utilize a highly effective method of contraception (condom) during heterosexual intercourse from the Screening through the study completion and for 90 days following the last dose of IMPs.

5. Body mass index (BMI) of ≥25 kg/m^2 (per MRI feasibility) at Screening.

6. Non-cirrhotic NASH subjects.

Presence of NASH is defined as at least 1 of the following at screening:

- Biopsy-confirmed NASH and F1-F3 fibrosis (Clinical Research Network [CRN]) , historical data of biopsy procedure obtained 24 months prior to randomization can be used OR

- Phenotypic diagnosis based on the following: liver stiffness ≥8.0 kPa and controlled attenuation parameter (CAP) >300 dB/m on transient elastography (TE) OR

- Elevated ALT (males >40 IU/L, females>30 IU/L), BMI ≥27 kg/m^2, and diagnosis of type 2 diabetes mellitus (T2DM).

7. Subjects will have CAP >300 dB/m on TE at screening and hepatic fat assessed by a central reader of MRI- PDFF ≥10% during Screening.
8. Male subjects must refrain from sperm donation from Screening through at least 90 days following the last dose of IMPs.
9. Female subjects must refrain from egg donation or harvest for 30 days after last dose of IMPs.
10. Willing and able to adhere to study restrictions and agree to comply with study protocol.

Exclusion Criteria:

1. Pregnant or lactating females; lactating females must agree to discontinue nursing before the IMPs are administered. WOCBP must have a negative pregnancy test at Screening and Day 1.
2. Past 2 years history of alcohol abuse or current significant alcohol consumption (>7 drinks per week for males or female; 1 drink = 12 ounces of beer (5% alcohol); 5 ounces of wine (12% alcohol), and 1.5 ounces of 80 proof distilled spirits (40% alcohol)).
3. LDL-C ≥190 mg/dL and already on a stable dose of statin and/or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for ≥30 days at Screening.
4. Renal dysfunction or nephritic syndrome or a history of nephritis or chronic kidney disease, including estimated glomerular filtration rate (eGFR) (using central laboratory determined Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) <60 mL/min/1.73 m^2 at Screening.
5. Recent (within 6 months prior to Screening or between Screening and Randomization) myocardial infarction (MI), unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of Screening), coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease, or plans to undergo a major surgical or interventional procedure (e.g., PCI, CABG, carotid or peripheral revascularization). Subjects with

implantable pacemakers or automatic implantable cardioverter defibrillators may not be considered.

6. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥100 mmHg after sitting quietly for 5 minutes at Screening.

7. Type 1 diabetes or uncontrolled T2DM including HbA_{1C} ≥9.5% at Screening.

8. Uncontrolled hypothyroidism, including thyroid stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Screening.

9. Liver transplant and/or other significant liver disease or dysfunction including:

    a. History of hepatic decompensation (such as ascites, variceal hemorrhage, hepatic encephalopathy, jaundice, and hepatorenal syndrome).

    b. ALT or AST >5 × ULN, ALP >2 × ULN, or total bilirubin (TB) >1.2 × ULN at Screening. If TB is >1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and if consistent with Gilbert's disease, in the opinion of the investigator, the subject may be enrolled in the study.

    c. Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C virus antibodies (HCV Ab) at Screening.

Note: If test for hepatitis C antibody is positive, but optional unscheduled reflexive test for hepatitis C ribonucleic acid (RNA) is negative, subject can be enrolled.

    d. Presence or suspicion of other forms of chronic liver disease including alcoholic liver disease, hemochromatosis (ferritin >1000 μg/L and percent iron saturation >45%), Wilson's disease, known cirrhosis (i.e., historical liver biopsy with stage 4 fibrosis or equivalent, or any evidence of cirrhosis in the opinion of the investigator), autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, drug- induced liver injury, and/or alpha-1 antitrypsin deficiency.

10. Human immunodeficiency virus (HIV) antibody positive.

11. Known hypersensitivity to HPG1860, the metabolites, or formulation excipient.

12. Significant gastrointestinal inflammation and symptoms including inflammatory bowel disease; Gastrointestinal conditions or procedures (including weight loss surgery; e.g., Lap-Band® or gastric bypass) that may affect drug absorption; planned weight reduction surgery during the study.
13. Hematologic or coagulation disorders, hemoglobin (Hgb) level <10.0 g/dL (100 g/L), platelet count <100,000 mm^3 or international normalized ratio (INR) ≥1.2 at Screening.
14. Unstable weight within the last 3 months of (>5% change) at Screening.
15. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed.
16. Unexplained creatine kinase (CK) >3 × ULN at Screening up to randomization (i.e., not associated with recent trauma or physically strenuous activity). Subjects with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization.
17. History within the last 2 years of drug abuse including but not limited to, amphetamine and derivatives, or cocaine. Subjects with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the investigator.
18. Blood donation, blood transfusion, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization and throughout the duration of study participation.
19. Use of any experimental or investigational drugs within 30 days prior to Screening.
20. Use of any of the following prior to Screening unless otherwise stated or a plan to use these drugs during the study is **prohibited**:
    a. High-dose vitamin E (>400 IU/day) (1 month prior to Screening).
    b. Pioglitazone (3 months prior to Screening).
    c. Medications associated with increased hepatic steatosis including mipomersen, lomatipide, amiodarone, methotrexate, tamoxifen, antiretrovirals, oral glucocorticoids at doses ≥5 mg

per day and/or valproic acid (3 months prior to Screening).

d. Substrates for P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP) including rosuvastatin (1 month prior to Screening) (Appendix 13).

21. Starting or adjusting the dose of the following permitted drugs within 5 weeks prior to Screening. These drugs are **allowed as long as stable** at least 5 weeks prior to Screening unless otherwise noted:

    a. Lipid regulating medications (except for rosuvastatin, which is prohibited) may be included; however, those that may affect liver steatosis or may have a potential drug-drug interaction risk are excluded per principal investigator (PI) discretion.

    b. Hormone replacement.

    c. Thyroid replacement.

    d. Obesity medication (if dose is stable 6 months prior to Screening).

    e. Diabetes medications (if dose is stable 3 months prior to Screening).

22. Unable to undergo or contraindication to MRI procedure (i.e., extensive tattoos, pacemaker, shrapnel injury, severe claustrophobia, ear (cochlea) implant).

23. History of intestinal resection or malabsorptive condition that may limit the absorption of HPG1860.

24. A medical or situational (i.e., geographical) finding that in the investigator's opinion may compromise the subject's safety or ability to complete the study.

25. An employee or contractor of the facility conducting the study, or a family member of the PI, co- investigator, or Sponsor.

26. Suspected Coronavirus Disease-19 (COVID-19) infection at Screening in the opinion of the investigator. COVID-19 screening is not required. During the study, if subjects have infections, the subjects may continue the study at the discretion of the PI. Subjects who receive COVID-19 vaccinations during the study are not excluded.

27. Any condition or finding that in the opinion of the PI or designee

would put the subject or study conduct at risk if the subject were to participate in the study.

28. Past 5 years history of bone disease disorder including osteoporosis

Investigational Medicinal Products

- HPG1860 3 mg, 5 mg, and 8 mg capsules
  - Chemical name: (R)-2-(4-((5-cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl)methyl)-2-methylpiperazin-1-yl)-4-methoxybenzo[d]thiazole-6-carboxylic acid
- Matching placebo capsules

All IMP will be ingested once daily at a similar time with or without food.

Statistical Procedures:

Sample Size

A sample size of 17 in each group will provide 90% power to detect an absolute difference in mean CFB of 7.0% (a 33% reduction from baseline assuming a percent LFC value of 21.5% at baseline and 14.5% at Week 12) in at least 1 of the HPG1860 treatment groups compared to placebo using Dunnett's multiple comparisons test with a 2-sided significance level of 0.05 and assuming a common standard deviation of 6.8%. To account for a 15% dropout rate, approximately 20 subjects per group will be randomized.

Analysis Populations

The Intent-to-Treat (ITT) Population, used for all of the efficacy analyses, is defined as all randomized subjects. Subjects will be reported according to randomized study treatment.

The Per-Protocol (PP) Population, used for sensitivity analyses on the primary endpoint, is defined as all randomized subjects who received at least 80 to 120% of randomized treatment and had no major protocol deviations. Subjects will be reported according to randomized study treatment.

The Safety Population (SP), used for all of the safety summaries, is defined as all randomized subjects who received at least 1 dose of blinded IMP. Subjects will be reported according to actual treatment received at the first dose.

The PK Analysis Set (PKS), used for all of the PK-related summaries, is defined as all subjects in the SP who have at least 1 resulted PK assessment. Subjects will be reported according to actual treatment received at the first dose.

Primary Safety Analysis

Descriptive statistics will be used to assess the safety and tolerability

of 12-week treatment of HPG1860 3 mg, 5 mg, and 8 mg in subjects with NASH during the study. Safety assessments will include TEAEs including TEAEs of special interest, SAEs, changes in clinical safety laboratory values, 12-lead ECGs, and vital signs.

Efficacy Criteria for Evaluation

Liver fat content and liver stiffness: Changes in LFC from baseline to Weeks 4 and 12 will be assessed by MRI-PDFF. All images will be approved by the central reader.

Key Secondary Efficacy Analysis

The change in LFC measured by MRI-- PDFF from baseline to Week 12 will be analyzed using analysis of covariance (ANCOVA) adjusted for baseline LFC and treatment group. To control for multiple comparisons, Dunnett's test will be used to test if any of the treatment groups are significantly different from the placebo group.

Other Secondary Efficacy, Pharmacokinetic, and Pharmacodynamic Analyses

The proportion of subjects with ≥30% reduction in LFC from baseline to Week 4 and Week 12 will separately be compared across treatment groups using a chi-square test.

The change in LFC measured by MRI-PDFF from baseline to Week 4 will be compared using ANCOVA as proposed for the primary efficacy analysis.

PK parameters including $AUC_{0-\infty}$, AUC_{0-t}, AUC_{0-24h}, C_{max}, T_{max}, $T_{½}$, CL/F, Vz/F, R_{ac}, and C_{trough} of HPG1860 in subjects with NASH will be reported by dose group and study day.

Biomarkers for liver injury and apoptosis, fibrosis, metabolism/cardiometabolic, and other biomarkers will be summarized by the value and by CFB in the value (where appropriate) at each postbaseline time point.

Other Safety Analyses

PE findings and weight measured throughout the trial will be reported using descriptive statistics.

Exploratory Analyses

Metabolites of HPG1860 may be reported. The correlation of PK values and study outcomes may be explored, specifically the correlation between PK concentration measures and LFC.