Clinical Study Synopsis

Synopsis Title:	A Phase 1 Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Cyclo (His-Pro) (CHP) following Single and Multiple, Ascending Oral Dose Administration to Healthy Volunteers
Synopsis Number:	CHP-001
Date of Synopsis/Version:	07 April 2025 / Version 0.3
Product:	Cyclo (His-Pro) (referred to as "CHP")
IND No.:	n/a
Study Phase:	1
Corporate Sponsor:	NovMetaPharma Co., Ltd. 13th Floor, Trees Bldg. 727, Eonju-ro, Gangnam-gu, Seoul, Korea Phone: +82-2-538-1893
CRO (Local Sponsor)	n/a

Synopsis Version and Amendment Tracking

Version Number/Amendment	Date
0.1	31 March 2025
0.2	04 April 2025
0.3	07 April 2025

PROTOCOL SYNOPSIS

Study Title	A Phase 1 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of CHP following Single and Multiple, Ascending Oral Dose Administration to Healthy Volunteers
Prepared By	Kylie O'Keefe
Protocol Number	CHP-001
Sponsor	NovMetaPharma
Local Sponsor	NovMetaPharma
Study Hypothesis	Administration of single and multiple ascending oral doses of CHP to healthy human volunteers will be safe and well tolerated.
Primary Objectives	1. To evaluate the safety and tolerability of ascending single and multiple, oral doses of CHP when administered to healthy volunteers.
Secondary Objectives	1. To evaluate the pharmacokinetics (PK) of single and multiple, oral doses of CHP when administered to healthy volunteers. 2. To evaluate the relative bioavailability of CHP in the fed and fasted state following a single oral dose of CHP in healthy volunteers.
Study Design	This is the first-in-human study for CHP. A double blind, placebo-controlled, randomized, ascending single and multiple dose study to determine the safety, tolerability and pharmacokinetics of CHP. In the single ascending dose (SAD) component each participant will be randomized to receive either a single dose of CHP or a single dose of placebo under fasted conditions. Eight participants (6 active, 2 placebo) will be enrolled into each of 4 cohorts, as required. In SAD cohort 1 participants will be treated with CHP in both the fed and fasted state. The fed state will occur after a 7-day wash-out or 5 half-lives, whichever comes later, to assess food effect. Following the completion of each of the SAD cohorts 1 and 2, all available safety and tolerability data to Day 8, from evaluable participants, will be reviewed by the Safety Review Committee (SRC), before enrolment into the next cohort is commenced. However, on completion of SAD Cohort 3, in addition to the available safety and tolerability data to Day 8, from evaluable participants, all PK data from all participants in SAD Cohorts 1 – 3 will also be reviewed by the SRC before enrolment into the first cohort of the MAD component and Cohort 4 of the SAD component. It is anticipated that a total of 4 dose level cohorts will be recruited for the SAD component, however based on the SRC review of each individual

	cohort, if the maximum tolerated dose (MTD) is not reached after completing the planned sequential groups, additional groups may be included up to a maximum of 4 sequential groups in total. The multiple ascending dose (MAD) component, will commence on completion of the third dose cohort in the SAD component, following approval from the SRC and at the same time as the commencement of the fourth dose cohort in the SAD component. In the MAD component each participant will be randomized to receive either a single dose of CHP or a single dose of placebo once daily for 7 days under fasted conditions. Eight participants (6 active, 2 placebo) will be enrolled into each of 4 cohorts, as required. Recruitment into a MAD Cohort will not commence until the dose/concentration for that cohort has been deemed safe by the SRC, following their safety review of the dose/concentration in the equivalent SAD Cohort. Following the completion of each MAD cohort, all available safety and tolerability data to Day 7, from evaluable participants, will be reviewed by the SRC, before enrolment into the next cohort is commenced. It is anticipated that a total of 4 dose level cohorts will be recruited for the MAD component, however based on the SRC review of each individual cohort, if the maximum tolerated dose (MTD) is not reached after completing the planned sequential groups, additional groups may be included up to a maximum of 4 sequential groups in total.
Study Medication	**CHP hard gel capsules:** CHP for oral administration is a size 1 hard gel capsule. **Vehicle hard gel capsules:** The vehicle hard gel capsules provided will be identical to the CHP hard gel capsules except for the active drug.
Treatment Duration	The following treatment regimens will be utilized in the study: SAD cohorts: a single oral dose MAD cohorts: an oral dose given once daily for 7 days
Number of Planned Participants	The study is planned to enrol approximately 64 healthy volunteers (participants). However, based on the SRC review of each individual SAD and MAD cohort, the total number of healthy volunteers may be revised. Up to four (4) sequential SAD cohorts, each will include 8 participants, with 6 participants to receive active drug and 2 participants to receive placebo per the randomization. Each cohort should include at least 2 females. Additional participants (8 per cohort) may be enrolled in the SAD component if it is deemed appropriate or necessary by the SRC to repeat a dose level in a

	new cohort of participants or to study an interim dose level or to add additional higher dose cohorts. Up to four (4) sequential MAD cohorts, each will include 8 participants, with 6 participants to receive active drug and 2 participants to receive placebo per the randomization. Each cohort should include at least 2 females. Additional participants (8 per cohort) may be enrolled in the MAD component if it is deemed appropriate or necessary by the SRC to repeat a dose level in a new cohort of participants or to study an interim dose level or to add additional higher dose cohorts.

Participant Selection Criteria	**Inclusion Criteria** Participants are eligible to be included in the study if all the following criteria apply: 1. Healthy male and female, non-smoking, participants between the ages of 18 and 55 years, inclusive, at the time of screening. 2. Have a body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive and weigh at least 50 kg and no more than 100 kg inclusive. 3. Good general health, as determined by an experienced physician based on a medical evaluation including detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead electrocardiogram (ECG) and clinical laboratory tests. 4. Male participants and their female spouse/partner(s) who are of childbearing potential: o Must agree to stay abstinent (where abstinence is the preferred and usual lifestyle of the participant), starting at screening and continuing throughout the clinical study period, and for 90 days after last study drug administration. o Or o Must be using highly effective contraception consisting of 2 forms of birth control (1 of which must be a barrier method) starting at screening and continuing throughout the clinical study period, and for 90 days after last study drug administration. o These requirements do not apply to participants in a same sex relationship. 5. Male participants must agree not to donate sperm starting at screening and continuing throughout the clinical study period, and for 90 days after last study drug administration. 6. Female participants of childbearing potential: o Must agree not to become pregnant during the clinical study period and for 30 days after last study drug administration. o Must have a negative serum pregnancy test at screening. o If heterosexually active, must agree to consistently use a form of highly effective birth control, in combination with a barrier method starting at screening and continuing

	throughout the clinical study period, and for 30 days after last study drug administration. o Or o Must agree to stay abstinent (where abstinence is the preferred and usual lifestyle of the participant), starting at screening and continuing throughout the clinical study period, and for 30 days after last study drug administration. o These requirements do not apply to participants in a same sex relationship. 7. Female participants of non-childbearing potential: o Must have a confirmed clinical history of sterility o Or o Must be postmenopausal as defined as: amenorrhea for at least 1 year prior to screening and a laboratory confirmed serum follicle stimulating hormone (FSH) level ≥ 40mIU/mL. 8. Female participants must agree not to breastfeed starting at screening and continuing throughout the clinical study period, and for 90 days after last study drug administration. 9. Female participants must agree not to donate ova starting at screening and continuing throughout the clinical study period, and for 90 days after last study drug administration. 10. Participant must be competent to understand the nature of the study & capable of giving written informed consent. Be willing to report for the scheduled study visits and communicate to study personnel about adverse events and concomitant medication use. 11. Participant must abstain from the following foods from 1 week prior to study drug administration until the last PK sample has been obtained: grapefruit juice or products, pomegranate juice or products, foods containing poppy seeds, and/or drinks or foods containing quinine (e.g., tonic water) or Seville oranges (e.g., orange marmalade). 12. Participant agrees not to participate in another interventional study while participating in the present clinical study. **Exclusion Criteria**

	Participants are excluded from the study if any of the following criteria apply: 1. Female participant who has been pregnant within the 6 months prior to screening or breastfeeding within the 3 months prior to screening. 2. Evidence or history of clinically significant haematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies and childhood asthma) at time of screening or study drug administration. 3. Current or chronic history of gastrointestinal illness or conditions interfering with normal gastrointestinal anatomy or motility. Examples include gastrointestinal bypass surgery, cholecystectomy, partial or total gastrectomy, small bowel resection, vagotomy, malabsorption, Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS) or celiac sprue. 4. Current treatment with any anti-platelet and/or anticoagulant medication. 5. Evidence or history of specific food intolerance. Examples include gluten intolerance, lactose intolerance, or dairy food intolerance or any food/ingredient included in the standard protein breakfast. 6. Any positive result, on screening, for serum hepatitis B surface antigen (HBsAg), hepatitis A virus antibodies (HAV), hepatitis C virus antibodies (HCV) or antibodies to human immunodeficiency virus type 1 (HIV-1) and/or type 2 (HIV-2). 7. A positive pre-study drug/alcohol screen. However, there is the option to re-screen during the screening period at the discretion of the PI or delegate in the case of a positive pre-study drug screen for a prescribed medication e.g., codeine. 8. Participant has a history of drinking > 21 units of alcohol/week for male patients or > 14 units of alcohol/week for female patients within the 3 months prior to screening. 9. Participant has a history of regular smoking (daily or most days in a week) or the use of nicotine products (3 or more nicotine-containing products) within the 6 months prior to screening. 10. Participant has used any recreational drugs of abuse within the 3 months prior to screening. 11. Participant has a pulse rate <40 or > 100 bpm; mean systolic blood pressure (SBP) > 140 mmHg; mean diastolic blood pressure (DBP) > 90 mmHg at screening. Repeat measurements are allowed at the

	discretion of the PI or delegate. 12. Participant has any clinically significant abnormalities at screening in rhythm, conduction or morphology of the resting ECG and any clinically significant abnormalities in the 12-lead ECG, as considered by the Investigator, that may interfere with the interpretation of QTc interval changes including abnormal ST-T wave morphology. 13. Participant has prolonged QTcF (QT interval corrected for heart rate using Fridericia's formula) > 450 ms for male patients or > 470 ms for female patients, or a shortened QTcF < 300 ms or a family history of prolonged QT syndrome, at screening. 14. Participant has any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis at screening as judged by the Investigator, including: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT) or Total bilirubin (TBL) up to 1.5 times above the Upper Limit of Normal (ULN). 15. Plasma donation within the 14 days prior to screening or any whole blood donation/significant blood loss > 500 mL during the 3 months prior to screening. 16. Treatment with any Investigational Drug or Device/Treatment within the 60 days prior to the first administration of study drug. 17. Use of any prescribed or non-prescribed medication including herbal and dietary supplements, antacids, analgesics (other than oral contraceptives, paracetamol or multi-vitamins) during the two weeks prior to the administration of the study drug, or up to a minimum of 5 times the half-life of the medication if it has a long half-life. 18. Exposure to more than four new chemical entities within the 12-month period prior to the administration of the study medication. 19. Known allergy or adverse reaction history to any of the oral dose formulation components e.g., mannitol. 20. Inability to chew the hard gel capsule.
Study Duration	It is estimated that from first participant-first visit to last participant-last visit, the study will take approximately 9 months to complete. Each individual participant/patient will participate in the study for up to: • SAD participants – 5 weeks, including the screening visit, confinement period and follow-up visits • MAD participants – 5 weeks, including the screening visit, confinement periods and follow-up visits

Mode of Administration	Oral
Treatment Groups	**SAD cohorts:** Participants will be randomized to receive a single oral dose of CHP or matching placebo. All participants will receive a single dose of CHP as hard gel capsules or placebo capsules, according to the cohort they have been assigned to. Four cohorts of 8 eligible participants will be studied, as required. **MAD cohorts:** Participants will be randomized to receive a single oral dose of CHP or matching placebo once daily for 7 days. All participants will receive a single dose of CHP as hard gel capsules or placebo capsules, according to the cohort they have been assigned to. Four cohorts of 8 eligible participants will be studied, as required.
Randomization Procedure	**SAD and MAD cohorts:** Up to 32 participants in both the SAD and MAD components of the study will be enrolled into 4 cohorts. Each cohort will include 8 participants. Each Cohort will be randomized such that 6 participants will receive active medication, and 2 participants will receive placebo medication.
Screening Procedures	**Healthy Volunteer SAD and MAD cohorts:** Within 14 days prior to randomization into the study, participants will attend the clinic for screening. They will be advised to avoid strenuous exercise during the 48-hour period prior to the screening day, and to cease all alcohol, xanthine and caffeine consumption 24 hours prior to screening. Participants will be required to sign an Informed Consent Form (ICF), after which screening assessments will be carried out as follows: • Review of medical history. • Review of inclusion and exclusion criteria. • Measurement of height and weight. • Physical examination. • 12-Lead ECG recording • Vital signs measurements (blood pressure, heart rate, respiration rate and temperature). • Review of GI symptomatology. • Fasting (minimum of 8 hours) clinical laboratory testing (hematology, coagulation, serum chemistry and routine urinalysis). • HIV, Hepatitis A, B and C screen. • Urine drug screen and alcohol breath test. • Serum pregnancy test (in women of child-bearing potential only). • FSH (in postmenopausal women only). • Review of concomitant medication/treatment
Dosing Procedure	**SAD cohorts**

	It is planned that there will be a 3-fold increase from the first dose level (200mg/kg) to the second dose level. The dose levels of the following groups will be increased by approximately 2-fold from the previous dose level, until the dose exceeds 1920mg, which is the human equivalent dose (HED) corresponding to the no observable adverse effect level (NOAEL) in the rat. Thereafter, there will be a 50% increase up to the last dose. **Cohort 1 (Dose 200mg):** The first 2 eligible participants will be dosed 1 day (24 hours) prior to the remaining 6 in the cohort. One sentinel participant will be randomized to receive CHP and the other to receive placebo. A review of the sentinel participants will occur, by either the PI or delegate, 23 hours after their dosing. If no safety concerns are reported, then the remaining 6 participants will be dosed approximately 24 hours after the sentinel participants (5 will receive CHP and 1 will receive a matching placebo). **Fasted:** Study drug will be administered in a fasted condition with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. **Fed:** Study drug will be administered 30 minutes after the high-fat and high-calorie meal with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Dose-escalation to Cohort 2 will occur following a review of all the available safety and tolerability data to Day 8 from evaluable participants in Cohort 1 by the SRC. **Cohort 2 (Dose 600mg):** Six of the participants will receive CHP and 2 will receive a matching placebo on Day 1. Dose-escalation to Cohort 3 will occur following a review of all the available safety and tolerability data to Day 8 from evaluable participants in Cohort 2 by the SRC. **Cohort 3 (Dose 1200mg):** Six of the participants will receive CHP and 2 will receive a matching placebo on Day 1. Dose-escalation to Cohort 4 will occur following a review of all the available safety and tolerability data to Day 8 from evaluable participants in Cohort 3 and in addition all the PK data from Cohorts 1-3, to check for dose proportionality, by the SRC. **Cohort 4 (Dose 2400mg):** Six of the participants will receive CHP and 2 will receive a matching placebo on Day 1. Additional cohorts will be included as if needed and as recommended, following the advice of the SRC. **MAD cohorts**

	Cohort 1 (Dose 200mg): Following review of the available safety and tolerability data for SAD cohorts 1 to 3, including PK data, and approval to escalate by the SRC, the first 2 eligible participants will be dosed separately to the remaining 6 in the cohort. One sentinel participant will be randomized to receive CHP and the other to receive placebo. A review of the sentinel participants will occur, by either the PI or delegate, 23 hours after their last dose. If no safety concerns are reported, then the remaining 6 participants will be dosed (5 will receive CHP and 1 will receive a matching placebo). Study drug will be administered in a fasted condition with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Dose-escalation to Cohort 2 will occur following a review of all the available safety and tolerability data up to and including Day 28 from all evaluable participants in Cohort 1 by the SRC. **Cohort 2 (Dose 600mg):** Six of the participants will receive CHP and 2 will receive a matching placebo on Day 1. Dose-escalation to Cohort 3 will occur following a review of all the available safety and tolerability data up to and including Day 28 from all evaluable participants in Cohort 1 by the SRC. **Cohort 3 (Dose 1200mg):** Six of the participants will receive CHP and 2 will receive a matching placebo on Day 1. Dose-escalation to Cohort 4 will occur following a review of all the available safety and tolerability data up to and including Day 28 from all evaluable participants in Cohort 1 by the SRC. **Cohort 4 (Dose 2400mg):** Six of the participants will receive CHP and 2 will receive a matching placebo on Day 1. Additional cohorts will be included as if needed and as recommended, following the advice of the SRC.

Outcome Measures	**<u>Primary Endpoints</u>**:
	The primary endpoints of the study are:
	
	• The safety and tolerability of ascending single and multiple, oral doses of CHP when administered to healthy volunteers.
	
	As assessed by:
	
	• Adverse events monitoring:
	  o Solicited treatment-emergent AE's relating to GI symptomatology
	  o Non-solicited AE's that would include all AE's, including emergent clinical chemistry abnormalities
	• Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR) & body temperature
	• 12 lead ECG
	• Physical examination
	• Laboratory assessments:
	  o Clinical chemistry
	  o Hematology
	  o Coagulation
	  o Routine urinalysis
	
	<u>Secondary Endpoints</u>:
	
	• The pharmacokinetics (PK) of single and multiple, oral doses of CHP when administered to healthy volunteers, as assessed by the rate and extent of absorption of CHP into plasma.

Study Assessments for all cohorts	**Clinical:** • Medical history including: ▪ Evaluation of any on-study adverse events ▪ Concomitant medication use ▪ Height and weight ▪ Physical examination ▪ Vital signs (Body temperature, heart rate, respiratory rate, blood pressure) ▪ Review of GI symptomatology ▪ 12-lead ECG recording **Laboratory testing:** Hematology including: ▪ Hemoglobin, hematocrit, erythrocyte count (RBC's), thrombocyte count, (platelets), reticulocytes, leukocyte count (WBC's) with differential (including eosinophils, neutrophils, basophils, lymphocytes, and monocytes). Coagulation including: ▪ Prothrombin time (PT), activated partial thromboplastin time (APPT), fibrinogen level. Serum Chemistry including: ▪ Blood urea nitrogen (BUN), creatinine, total and direct bilirubin, uric acid, albumin, alkaline phosphatase, creatine kinase (CK), aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), gamma-glutamyl transferase (GGT) total protein, lactate dehydrogenase (LDH), lipids, glucose, sodium, potassium, calcium, chloride, phosphorus (phosphate), bicarbonate. Routine urinalysis including: ▪ pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocytes. Serology: ▪ HIV, Hepatitis A, Hepatitis B and Hepatitis C testing will be performed at the Screening visit. Pregnancy testing: ▪ A serum pregnancy test for women of child-bearing potential will be performed at the Screening visit. ▪ A urine pregnancy test for women of child-bearing potential will be performed at the Day -1 visit. Serum FSH determination: ▪ FSH level for postmenopausal women will be performed at the Screening visit. Urine drug screen: ▪ A urine drug screen will be performed at the screening visit, and at the Day -1 visit. Alcohol Breath Test: ▪ An alcohol breath test will be performed at the screening visit and at the Day -1 visit.

Safety and Tolerability Assessments	Specific assessments to evaluate treatment safety at each follow-up visit will include the following:
	• The frequency and type of adverse events:
	  o Solicited treatment-emergent AE's relating to GI symptomatology
	  o Non-solicited AE's that would include all AE's including treatment-emergent clinical chemistry abnormalities
	• Clinical laboratory testing
	• 12-lead ECG's
	• Physical examination
	• Vital signs

Pharmacokinetics	Blood will be collected for pharmacokinetic analysis as follows: **SAD:** PK blood samples will be collected within 10 minutes (min) prior to dosing and at 15 min, 30 min, 45 min, 1 hour (h), 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, and 24h after dosing. **MAD:** PK blood samples will be collected within 10 minutes (min) prior to dosing and at 15 min, 30 min, 45 min 1 hour (h), 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, and 24h after dosing on Day 1 and Day 7 & 8.
Visit Schedule	**SAD:** Screening (up to 4 weeks prior to Day 1), Day -1, Day 1 & 2, Day 8, Day 22 **MAD:** Screening (up to 4 weeks prior to Day 1), Day -1, Day 1 & 2, Day 5, Day 7 & 8, Day 22

Statistical Considerations	The following analyses will be performed. Safety will be assessed in the Safety Analysis Set (SAS). The placebo subjects from all cohorts within SAD and MAD will be pooled into a single placebo group, respectively, for all summaries and presentations. Data from the SAD and MAD portion of the study will be summarized separately. In general, disposition, demographics, baseline characteristics, medical history, safety data, and PK variables will be summarized using descriptive statistics by treatment group. For continuous variables, the descriptive statistics include: the number of observations (n), means, standard deviation (SD), median, minimum and maximum. For categorical variables, the summaries will contain the number and percentage of subjects falling into each category. Individual subject data will be presented in data listings. All analyses, summaries, and listings will be generated using SAS® software version 9.4 or higher. Adverse Events: Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 28.0. A by-subject AE data listing, including verbatim term, preferred term, system organ class, treatment, severity, seriousness criteria, relationship to drug, and action taken, will be provided. The number and percentage of subjects experiencing treatment-emergent adverse events (TEAEs) and number of TEAEs will be summarized by treatment group using frequency counts. Medical History and Physical Examination: Medical history will be listed by subject. The number and percentage of subjects with changes in physical examinations will be summarized by treatment group. Clinical Laboratory Results, Electrocardiograms, and Vital Signs Measurements: All clinical laboratory results, 12-lead ECGs, vital signs measurements, and their changes from baseline for these results, will be summarized by treatment group and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. Concomitant Medications: Concomitant medications will be coded using the most current WHO drug dictionary will be summarized and listed by treatment group. Pharmacokinetics data will be assessed in the Pharmacokinetic Analysis Set, consisting of all subjects who received at least one dose of study medication, have measurable plasma concentrations of CHP and without any major protocol deviation. Pharmacokinetics: The following parameters will be computed from plasma concentration data

	for CHP, if deemed appropriate: C_{max}, t_{max}, $t_{1/2}$, λ_z, $AUC_{(0-t)}$, $AUC_{(0-24)}$, AUC_{inf}, MRT, CL/F, and Vz/F Individual PK blood sample collection times and concentration-time data will be listed by dose level (cohort) and subject. Individual PK parameters will be listed by dose level and subject. Plasma concentration will be summarized by dose level, study day, and scheduled time. Concentration values reported as below the limit of quantification will be set to zero for calculation of descriptive statistics. The PK parameters will be summarized by dose level and study day. Descriptive statistics include: n, arithmetic mean, median, SD, minimum, maximum, geometric mean, and coefficient of variation (CV%). For t_{max}, only n, minimum, median, and maximum will be reported. Figures of individual and mean (SD) concentration-time data at different dose levels on Day 1 and Day 7 will be depicted on linear and semi-logarithmic scales. Attainment of steady state will be evaluated by visual assessments of pre-dose concentrations collected over the 7-day dosing period. <u>Food effect on Single Dose Phase (Fasted vs. Fed)</u>: To assess the food effect on the CHP, the following statistical comparisons of the relevant PK parameters will be made: the values of AUC and C_{max} calculated for the two diet regimens [Fasted (FA) and Fed (FE)] will be compared by the ANOVA for the log-transformed data at 0.05 level of significance. The 90% CI for the ratio of the geometric means for AUC and C_{max} obtained for the FA and FE condition will be calculated, the absence of a food effect will be concluded when the 90% CI for the ratio of means (geometric means based on log-transformed data) of FA and FE treatments fall within 80% – 125% for both AUC and C_{max}. The value of t_{max} obtained under FA and FE conditions will be compared by the non-parametric Friedman test (non-transformed data). The mean plasma levels with SD of CHP exposures of FA and FE subjects will be displayed as a figure format. <u>Comparison single dose vs. multiple dose treatments (Fasted)</u>: Dose proportionality following single and multiple dose administration will be assessed using a power model with the logarithm of exposure [$AUC_{(0-24)}$, C_{max}] on respective Day 1 and Day 7 as the dependent variable and the logarithm of dose as the independent variable. Point estimates and 90% confidence intervals of the slope and intercept will be presented for each of the single- and multiple-dose exposure parameters. An ANOVA model will be used to explore the degree of accumulation after repeated dosing by comparing log transformed C_{max} on Day 7 with Day 1, and log transformed $AUC_{(0-24)}$ on Day 7 with Day 1. C_{max} values will be compared based on the ANOVA at 0.05 level of significance with study treatment (single dose vs. multiple dose) as covariate and the 90% CI for log-transformed data.

	The comparison of mean plasma levels with SD of CHP exposures measured after single and multiple daily administration under FA condition will be displayed as a figure format.

Schedule of Assessments for SAD

	Study Day (Fasted)						Study Day (Fed)*					
Study Procedures	**Screen -14 Days**	**Day -1**	**Day 1**	**Day 2**	**Day 8**	**End-of-Study Day 22**	**Wash-out**	**Day -1**	**Day 1**	**Day 2**	**Day 8**	**End-of-Study Day 22**
Visit window	**± 3 days**						**7 ± 3 days**					
Informed consent	×											
Inclusion/exclusion criteria	×	×						×				
Medical history	×	×						×				
Physical exam[1]	×	×				×						×
Vital signs[2]	×	×	×	×	×	×		×	×	×	×	×
Electrocardiogram	×		×	×	×	×			×	×	×	×
Concomitant medications	×	×	×	×	×	×		×	×	×	×	×
Randomization		×	×									
Study drug administration			×						×			
Adverse events		×	×	×	×	×		×	×	×	×	×
Pharmacokinetic assessments**												
Blood			×	×		×			×	×		×
Clinical laboratory evaluations												
Hematology	×	×	×	×		×		×	×	×	×	×
Chemistry	×	×	×	×		×		×	×	×	×	×
Lipid panel (fasting)			×			×						×
Serology	×	×	×	×		×		×	×	×	×	×
Viral screen (HIV, HCV, HBV)	×											
Coagulation	×	×	×	×		×		×	×	×	×	×
Urinalysis	×	×	×	×		×		×	×	×	×	×
Urine drug screen and alcohol breath test	×	×[3]						×				
Serum pregnancy test (for women of childbearing potential only)	×											
Urine pregnancy test (for women of childbearing potential only)		×						×				
FSH (for women only, if needed)	×											

** For one SAD cohort only, following approximately 7-day washout*

** Day 1: PK blood samples will be collected within 10 minutes (min) prior to dosing and at 15 min, 30 min, 45 min, 1 hour (h), 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, and 24h after dosing

Note: If there are any discrepancies between the schedule of events and body text, the schedule of events will prevail. When more than one procedure is scheduled at a specific time point, PK blood sampling should be performed on time. These procedures should be performed in the following order: vital signs, ECG, blood sampling for safety testing, and physical examination. Other procedures should be performed as close as possible to the scheduled time point.

The time windows for study procedures are as follows:

PK sampling: 0-4 hours: ±5 minutes; and 6-24 hours: ±10 minutes

All other procedures: Dose to 1 hour post dose: ± 3 mins; >1 to 4 hours: ± 5 mins; > 4 to 24 hours: ± 10 mins; and >24 hours: up to ± 60 mins

1. Target PE if ≥ 1 week since Screening.
2. Height at Screening Visit only. Weight in the morning before study drug administration.
3. Repeat if ≥ 1 week since screening.

Schedule of Assessments for MAD

	Study Day (Fasted)									
Study Procedures	**Screen -14 Days**	**D -1**	**D 1**	**D 2**	**D 3**	**D 4**	**D 5**	**D 7**	**D 8**	**End-of-Study Day 22**
Visit window	**± 3 days**									
Informed consent	×									
Inclusion/exclusion criteria	×	×								
Medical history	×	×								
Physical exam	×	×[1]								×
Vital signs[2]	×	×	×	×	×	×	×	×	×	×
Electrocardiogram	×		×	×	×	×	×	×	×	×
Concomitant medications	×	×	×	×	×	×	×	×	×	×
Randomization		×	×							
Study drug administration			×	×	×	×	×	×	×	
Adverse events		×	×	×	×	×	×	×	×	×
Pharmacokinetic assessments*										
Blood			×	×	×	×	×	×	×	×
Clinical laboratory evaluations										
Hematology	×	×	×			×		×	×	×
Chemistry	×	×	×			×		×	×	×
Lipid panel (fasting)			×							×
Serology	×	×	×			×		×		
Viral screen (HIV, HCV, HBV)	×									
Coagulation	×	×	×	×			×		×	×
Urinalysis	×	×	×	×			×		×	×
Urine drug screen and alcohol breath test	×	×[3]								
Serum pregnancy test (for women of childbearing potential only)	×									
Urine pregnancy test (for women of childbearing potential only)		×								
FSH (for women only, if needed)	×									

* Day 1: PK blood samples will be collected within 10 minutes (min) prior to dosing and at 15 min, 30 min, 45 min 1 hour (h), 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, and 24h after dosing
* Day 7/8: PK blood samples will be collected within 10 minutes (min) prior to dosing and at 15 min, 30 min, 45 min 1 hour (h), 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, and 24h after dosing

Note: If there are any discrepancies between the schedule of events and body text, the schedule of events will prevail. When more than one procedure is scheduled at a specific time point, PK blood sampling should be performed on time. These procedures should be performed in the following order: vital signs, ECG, blood sampling for safety testing, and physical examination. Other procedures should be performed as close as possible to the scheduled time point.

The time windows for study procedures are as follows:

PK sampling: 0-4 hours: ±5 minutes; and 6-24 hours: ±10 minutes

All other procedures: Dose to 1 hour post dose: ± 3 mins; >1 to 4 hours: ± 5 mins; > 4 to 24 hours: ± 10 mins; and >24 hours: up to ± 60 mins

1. Target PE if ≥ 1 week since Screening.
2. Height at Screening Visit only. Weight in the morning before study drug administration.
3. Repeat if ≥ 1 week since screening.