Clinical Study Protocol

Study Title:	A phase 1, first-in-human, randomized, double-blind, placebo-controlled, single and multiple ascending dose study to evaluate the safety, tolerability, and pharmacokinetics (PK) of orally administered IPG1094 in healthy adult participants
Study Number:	IPG1094-A001
Study Phase:	1
Product Name:	IPG1094
Sponsor:	NANJING IMMUNOPHAGE BIOTECH CO., LTD.
Local Sponsor:	
Local Sponsor Contact:	[redacted]

Issue Date:

Version	V3.0
Date	31 Mar 2022

Confidentiality Statement

Protocol Signature Page

Sponsor Agreement

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol (Protocol No.: IPG1094-A001, Version/Date: V3.0/31 Mar 2022) and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization (ICH) E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws and regulations.

[redacted]

Protocol Signature Page

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Protocol Signature Page

Investigator Agreement

I confirm that I have read and that I understand this protocol (Protocol No.: IPG1094-A001, Version/Date: V3.0 /31 Mar 2022), the Investigator's Brochure and any other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and protect the rights, safety, privacy and well-being of study participants in accordance with guidelines and all applicable governments' regulations. These guidelines include but not limited to:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.

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SYNOPSIS

Study Title:

A phase 1, first-in-human, randomized, double-blind, placebo-controlled, single and multiple dose escalation study to evaluate the safety, tolerability, and pharmacokinetics (PK) of orally administered IPG1094 in healthy adult participants

Protocol Number:

IPG1094-A001

Version Number:

3.0

Study Phase:

1

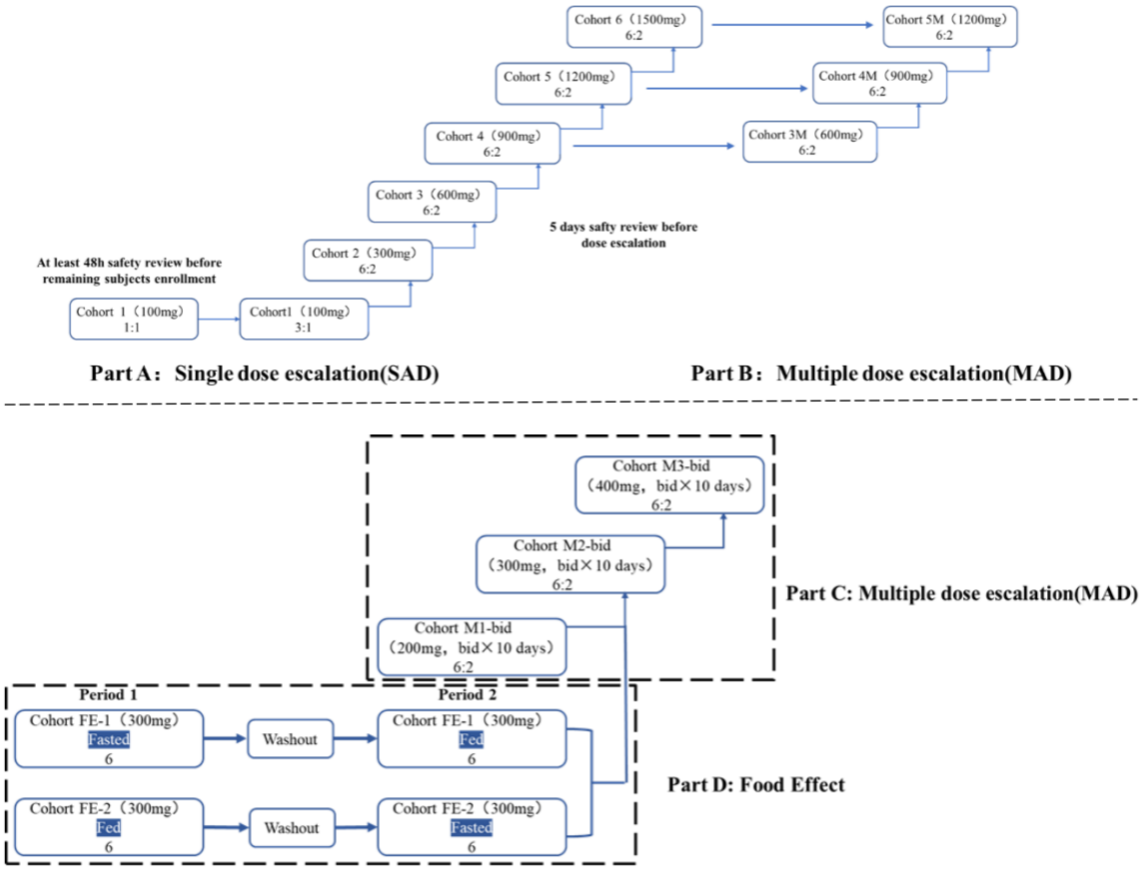
Objectives and Endpoints:

Objectives	Endpoints
Primary	
Part A-Single ascending dose (SAD) To assess the safety and tolerability of IPG1094 after ascending single oral doses.	- Assessment of Adverse events (AEs) - Clinical laboratory evaluations (hematology, clinical chemistry, coagulation, urinalysis). - Vital signs (blood pressure, heart rate, body temperature, respiratory rate) - Electrocardiogram (ECG) (heart rate, PR, QRS, QT, QTcF)
Part B and Part C-multiple ascending dose (MAD) To assess the safety and tolerability of IPG1094 after ascending multiple oral doses.	-
Part D- To evaluate the effect of food on the PK of IPG1094	- Ratio fed/fasted on C_{max}, AUC_{0-t}, AUC_{0-inf}
Secondary	
Part A-Single ascending dose (SAD) To assess the PK parameters of IPG1094 after ascending single oral doses.	- Part A: plasma PK parameters: at least maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the curve from time 0 to the last measurable concentration (AUC_{0-t}), and if possible, area under the curve from time 0 extrapolated to infinite time (AUC_{0-inf}), half-life ($t_{1/2}$), clearance (CL/F);
Part B and Part C- Multiple ascending dose (MAD) To assess the PK parameters of IPG1094 after ascending multiple oral doses	- Part B and Part C: plasma PK parameters: at least maximum plasma concentration at steady state ($C_{ss,max}$), time to $C_{ss,max}$ ($T_{ss,max}$), dose interval AUC ($AUC_{0-\tau}$), clearance at steady state (CL_{ss}/F), accumulation ratio calculated using AUC ($Rac_{(AUC)}$), accumulation ratio calculated using C_{max} ($Rac_{(Cmax)}$).

Part D-To assess the safety and tolerability of IPG1094 after 300 mg single oral dose under fasted and fed conditions	- Assessment of Adverse events (AEs) - Clinical laboratory evaluations (hematology, clinical chemistry, coagulation, urinalysis). - Vital signs (blood pressure, heart rate, body temperature, respiratory rate） - Electrocardiogram (ECG) (heart rate, PR, QRS, QT, QTcF)

Overall Design:

This is a phase 1, first-in-human, randomized, double-blind, placebo-controlled, single and multiple dose escalation study to evaluate the safety, tolerability, PK and food effect of orally administered IPG1094 in healthy adult participants. The study will involve four parts: a single ascending dose (SAD) period (Part A) followed by two multiple ascending dose (MAD) period (Part B and Part C) and a food effect study (Part D)



Part A

Dose escalation will start from 100 mg. Currently, the 6 dose cohorts are Cohort 1 (100 mg), Cohort 2 (300 mg), Cohort 3 (600 mg), Cohort 4 (900 mg), Cohort 5 (1200 mg) and Cohort 6 (1500 mg). About 46 healthy adult participants are being sequentially enrolled in 6 cohorts. There are 6 participants in Cohort 1. 4 participants will receive IPG1094 and 2 participants will receive the placebo as per the randomization code. Approximately 8 participants will be enrolled in Cohort 2 to Cohort 6 respectively; in each cohort, 6 participants will receive IPG1094 and 2 participants will receive the placebo as per the randomization code.

In Cohort 1, 2 sentinel participants will be dosed at least 48 hours prior to the remaining participants. One sentinel will be dosed with IPG1094 and the other with a matching

placebo. The remaining 4 participants will be dosed only if no significant safety issues are identified in the sentinel participants. Doses and sampling intervals may be modified based on the PK and safety data that emerges throughout the study.
Healthy participants will be screened within 28 days prior to dosing. Participants will be admitted to the study site on Day -1 for up to 6 days. Administration of a single dose of IPG1094 or the placebo will occur on Day 1 under the fasted conditions. Participants will be discharged on Day 5 following the obtainment of samples for PK analyses and the completion of safety assessments. A follow-up visit will occur on Day 8.
On Day 5, after each dose cohort has been administered the investigational medical products (IMP) and completed evaluation, the Safety Monitoring Committee (SMC) will review cumulative blinded safety data (including follow-up visit data from preceding cohorts) and available PK data to determine the safety and tolerability of the study drug. If the dose level is determined to be safe and well-tolerated, the next dose cohort will be enrolled and randomized in preparation to receive the next dose level of IPG1094 or the placebo.

Part B - QD
Three dose levels (600mg, 900mg and 1200mg) are anticipated to be evaluated in the MAD, once daily. There will be approximately 8 subjects per cohort, 6 subjects will receive IPG1094 and 2 subjects will receive placebo per the randomization code.
For Cohort 3M (600mg), the MAD phase will commence following the establishment of the safety and tolerability of Cohort 4 (900mg) in the SAD. The SMC will evaluate the safety and tolerability data obtained from the participants of cohort 4 in the SAD to determine if the Cohort 3M will be enrolled and randomized to receive the 600mg multiple dose levels of IPG1094 or placebo.
For Cohort 4M (900 mg), the SMC will evaluate the safety and tolerability data obtained from the participants of cohort 5 (1200mg) in the SAD as well as the safety and PK data from Cohort 3M to determine if the Cohort 4M will be enrolled and randomized to receive the 900mg multiple dose levels of IPG1094 or placebo. Cohort 5M will follow the same procedure.
All subjects will be screened within 28 days prior to dosing and will be admitted to the study site on Day -1. Dosing will start on the morning of Day 1 and will extend over a 10-day period at each dose level. Blood draws will be collected for the assessment of PK parameters. Participants will be discharged on Day 14 following the completion of all PK sample collection and safety assessments. There will be a follow-up visit 7 days after the last dose.
After each MAD dose cohort has completed the administration of the study drug and evaluation on Day 14, the SMC will review blinded cumulative safety data (including the follow-up visit data) and available PK data to determine the safety and tolerability of the study drug.

Part C - BID
Three dose levels (200mg BID, 300mg BID and 400mg BID) are anticipated to be evaluated in the Part C MAD. There will be approximately 8 subjects per cohort, 6 subjects will receive IPG1094 and 2 subjects will receive placebo per the randomization code
For Cohort M1-bid (200mg, twice daily), the MAD bid phase will commence following the establishment of the safety and tolerability data obtained from the participants of Part A and Part B. The SMC will evaluate the safety and tolerability data obtained from the participants of Part A and Part B to determine if the Cohort M1-bid will be enrolled and

randomized to receive the 200mg BID multiple doses of IPG1094 or placebo.
For Cohort M2-bid (300 mg, twice daily), the SMC will evaluate the safety and tolerability as well as PK data obtained from the participants of cohort M1-bid (200 mg BID) and Food effect cohort (Cohort FE-1 and Cohort FE-2) to determine if the Cohort M2-bid will be enrolled and randomized to receive the 300mg BID multiple dose levels of IPG1094 or placebo.
For Cohort M3-bid (400 mg, twice daily), the SMC will evaluate the safety and tolerability as well as PK data obtained from the participants of cohort M2-bid (300 mg BID) to determine if the Cohort M3-bid will be enrolled and randomized to receive the 400mg BID multiple dose levels of IPG1094 or placebo.
All subjects will be screened within 28 days prior to dosing and will be admitted to the study site on Day -1. Dosing will start on the morning of Day 1. The AM dose will be administered following an overnight fast of at least 10 hours on Day 1. From Day 2 to Day 10, participants will be required to fast for at least 2 hours prior to study drug administration. The PM dose will be administrated at 12 hours(±1h) interval after the AM dose and it will be under a fasted condition at 2 hours (±15mins) post meal. The Fed or Fasted condition of Cohort M2-bid and Cohort M3-bid will be based on the result of FE study. The dosing will be extended over a 10-day period at each dose level. Blood draws will be collected for the assessment of PK parameters. Participants will be discharged on Day 13 following the completion of all PK sample collection and safety assessments. There will be a follow-up visit 7 days after the last dose of the study drug. After the last administration of the study drug and the follow-up visit on Day 17 of each MAD dose cohort, the SMC will review blinded cumulative safety data (including the follow-up visit data) and available PK data to determine the safety and tolerability of the study drug.

Part D
The food effect study is an open-label, randomized, single oral dose, two-way cross-over study to investigate the effect of food on the pharmacokinetics of IPG1094 in healthy participants.

300 mg will be selected to assess the effect of food on the pharmacokinetic parameters and referred to as the food effect (FE) cohort (Cohort FE-1 and Cohort FE-2).

A total of 12 subjects will be randomized in 2 groups (Cohort FE-1 and Cohort FE-2) with ratio 1:1.

Participants in the FE cohort will be admitted to the study site for 6 days at a time for the 2 admissions. A washout of $\geqslant$ 3 days ($> 5 \times T_{1/2}$ of IPG1094) will be included between investigational product (IP) administrations.

For Cohort FE-1, administration of a single dose of IPG1094 will occur on Day 1 of Period 1 under the fasted condition, and Day 5 (anticipated) of Period 2 under the fed condition. Following the completion of all safety assessments and sampling for PK analyses, subjects will be discharged on Day 8 (anticipated) after Period 2.

For Cohort FE-2, administration of a single dose of IPG1094 will occur on Day 1 of Period 1 under the fed condition, and Day 5 (anticipated) of Period 2 under fasted condition. Following the completion of all safety assessments and sampling for PK analyses, subjects will be discharged on Day 8 (anticipated) after Period 2.

Mode(s) of Administration for FE cohort (Part D)

Fasted Conditions: Following an overnight fast of at least 10 hours, subjects will receive a single dose of IPG1094 with 240 mL water. No foodwill be allowed for at least 4 hours post-dose. Water can be ingested as desired except for 1 hour pre-dose until one hour post dose. There will be a follow-up visit 7 days after the last dose.
After the FE cohort completed the administration of the study drug, the SMC will review the cumulative safety data (including the follow-up visit data) and available PK data to determine the safety and tolerability of the study drug under fasted/fed condition at 300 mg dose level.

Fed Conditions: Following an overnight fast of at least 10 hours, subjects will start a high-fat breakfast. Subjects should eat breakfast in 30 minutes or less. Subjects will receive a single dose of IPG1094 with 240 mL water 30±5 minutes after the start of the breakfast. No food will be allowed for at least 4 hours post-dose, except for the day 1 breakfast in each period, subjects will receive standardized meals scheduled at the same time during the stay at the clinical unit. Water can be ingested as desired except for 1 hour pre-dose until one hour post-dose.

The high-fat meal will be based on that recommended by the FDA (the breakfast will consist of a high-fat (approximately 50% of the total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal with approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively (eg, 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz. of hash brown potatoes, and 8 oz. of whole milk).

The Rationale for Starting Dose Selection

[redacted]

Dose Escalation and Stopping Rules:

The decision to escalate to subsequent dose levels in Part A, Part B and Part C will be based on the review of all available safety information, including AEs, ECGs, vital signs, and clinical laboratory test results from a minimum of 6 volunteers in each cohort, and available PK data. Doses may be adjusted based on safety and PK data that emerges during the study. Additional incremental dose levels (either increased or decreased) may be investigated (250 mg bid in Part C for example). Dose escalation from Cohort 1 to 2 only will be based solely on safety and tolerability data.

The decision to escalate doses will be made by the SMC. All dose escalation meetings and dose escalation decisions will be formally documented.

Criteria for stopping rules:

1. AE of at least Grade 3 intensity, according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), unless the event is clearly determined to be unrelated to IPG1094.
2. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × upper limit of normal (ULN), and total bilirubin ≥ 2× ULN
3. QTcF ≥ 500 ms (confirmed by a device re-reading and by manual reading by the Investigator, or a physician delegated by the Investigator, using the Fridericia formular for correcting QT)

One of the above criteria occurring in a participant will lead to investigational medical product (IMP) discontinuation in this participant (only for the participant in Part B and Part C). If any one of the above criteria is met by 2 or more participants within a dose cohort (in the instance of AEs, if they experience the same medical conditions), the double-blind will be broken by the Sponsor for the concerned participants:

- If 2 or more participants were given IPG1094 and no participant was given the placebo, drug administration will cease for all other participants in that dose level (for the participant in Part A); If 2 or more participants were given IPG1094 and no participant was given a placebo, drug administration will be stopped for these participants and all other participants in that dose level (for the participant in Part B) and either:
  - only if, after reviewing all data, the Investigator and the Sponsor agree that it is safe to do so, or
  - Part A or B may be stopped.
- Otherwise, drug administration as per protocol may either continue as planned or be reconsidered if, after reviewing all data, the Investigator and the Sponsor agree that it is safe to do so; and
  - The current dose may be continued, or
  - Additional incremental dose(s) may be considered (either increased or decreased), or
  - The study may be stopped.

Number of Participants:

Approximately 106 healthy participants: with 46 in Part A (6 participants in Cohort 1 and 8 participants in Cohorts 2 to 6); with approximately 24 participants in Part B, with approximately 24 participants in Part C; with approximately 12 participants in Part D

Criteria for Inclusion and Exclusion

<Inclusion Criteria>

Participants must meet all of the following criteria to be included in the study:

Demography

1. Healthy adult male or female participants between 18 and 50 years of age (inclusive).
2. Body weight between 45 and 100 kg (inclusive) and body mass index (BMI) within 18~32 kg/m^2 (inclusive).

Health status

3. In good health as determined by screening tests. Good health is defined as having no clinically relevant abnormalities identified by a detailed medical history, full physical examination (including measurement of blood pressure and pulse rate), 12-lead ECG, and clinical laboratory tests.
   - Vital signs (measured after resting for 5 minutes supine position) within normal range, or outside the normal range and not considered clinically significant by the Investigator.
   - Standard 12-lead ECG parameters (recorded after resting for 5 minutes in supine position) in the following ranges; QTc (Fridericia algorithm recommended) ≤ 450 ms for males and 470 ms for females, and normal ECG tracing, or abnormal ECG tracing not considered clinically relevant by the Investigator.
   - Laboratory parameters demonstrating no clinically significant abnormalities, as determined by the Investigator. Total bilirubin outside the normal range may be acceptable if total bilirubin does not exceed 1.5 × ULN with normal conjugated bilirubin (with the exception of a participant with documented Gilbert syndrome).
4. A negative result on a urine drug screen and a repeat negative result on Day -1 (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).
5. Female participants must not be pregnant or breastfeeding and must use an effective contraception method (as described in Section 4.5.4), with the exception of participants who have undergone sterilization in the preceding 3 months, or who are postmenopausal.

   A woman of childbearing potential (WOCBP) must undergo pregnancy testing prior to the first dose of the IMP. The participant must be excluded from the study if the serum pregnancy test is positive.

   A postmenopausal state is defined as 12 months of amenorrhea without an alternative medical cause. In the absence of 12 months of amenorrhea, menopause may be confirmed by FSH measurement (> 40 IU/L or mIU/mL).

   Females on HRT (Hormonal Replacement therapy), where menopausal status is indeterminate, will be required to use a non-estrogen hormonal contraceptive method if they wish to continue their HRT during the study. Participants must otherwise discontinue HRT to allow for confirmation of postmenopausal status prior to enrollment in the study.

Regulation

6. Provide written informed consent prior to undertaking any study-related procedures.
7. Must not be under any administrative or legal supervision or under institutionalization as per a regulatory or juridical order.

<Exclusion Criteria>

Participants who meet any of the following criteria will be excluded from the study:

Medical history and clinical status

1. Any history or presence of clinically relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, musculoskeletal, rheumatological, psychiatric, systemic, ocular, or infectious disease, or signs of acute illness.
2. Frequent severe headaches and/or migraines, recurrent nausea and/or vomiting (defined as vomiting more than twice a month).
3. Made a blood donation of any volume within 2 months prior to the first dose.
4. Demonstrated clinically significant (required intervention, e.g., emergency room visit, epinephrine administration) allergic reactions, which in the opinion of the Investigator, would interfere with the volunteer's ability to participate in the trial.
5. Known hypersensitivity to any component of the IMP formulation.
6. History or presence of drug or alcohol abuse (defined as alcohol consumption of more than 2 units per day on a regular basis).
7. Regular smoking (defined as more than 5 cigarettes or equivalent per week), or unable to stop smoking during the study. Occasional smokers may be enrolled.
8. Excessive consumption of beverages containing xanthine bases (defined as more than 4 glasses per day).

Interfering substances

9. Any medication, including St John's Wort, within 14 days prior to administration of the first dose or within 5 times the elimination half-life or pharmacodynamic half-life of the medication, with the exception of hormonal contraception, menopausal hormone replacement therapy, or occasional paracetamol at doses up to 2g/day.
10. Any consumption of grapefruit or products containing grapefruit within 5 days prior to the first dose administration.
11. Any vaccination in the 2 weeks prior to administration of the first dose.

General conditions

12. Any participant who, in the judgment of the Investigator, is likely to be non-compliant during the study, or to be unable to cooperate due to language problems or poor mental development.
13. Any participant who enrolled in or participated in any other clinical study involving an investigational medicinal product, or in any other type of medical research within 1 month or within 5 times the elimination half-life prior to administration of the first dose.
14. Any participant who cannot be contacted in the case of an emergency.
15. Any participant who is the Investigator or any subinvestigator, research assistant, pharmacist, study coordinator, or other staff thereof directly involved in conducting the study or any person dependent on (employees or immediate family members) the study site, the Investigator or the Sponsor.

Biological status

16. Positive result on any of the following tests: hepatitis B surface antigen (HbsAg), hepatitis B core antibodies (HbcAb), anti-hepatitis C virus antibodies (anti-HCV), anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti-HIV2 Ab).

17. Positive alcohol test at Day -1 .
18. Any participant in whom venous blood collection is difficult.

Investigational Medical Products:
IPG1094
Activity: An inhibitor of macrophage migration inhibitory factor (MIF)
Dosage form: Tablet
Strength: 50mg and 100mg
Administration: IPG1094 tablets are orally administered with 240mL of water. Tablets should not be chewed or crushed.

IPG1094 PLACEBO
Placebo tablet: tablet identical to IPG1094 tablet

Duration of Study:

Part A: Up to 36 days (including a Screening Period of 28 days; a Single-dose Treatment Period of 1 day, and a Follow-up period of 7 days)

Part B: Up to 45 days (including a Screening Period of 28 days; a Multiple-dose Treatment Period of 10 days, and a Follow-up period of 7 days)

Part C: Up to 45 days (including a Screening Period of 28 days; a Multiple-dose Treatment Period of 10 days, and a Follow-up period of 7 days);

Part D: Up to 40 days (including a Screening Period of 28 days; a Period 1 [fasting or fed state] of 1 day; a washout period of ⩾3 days, a Period 2 [fasting or fed state] of 1 day and a Follow-up period of 7 days).

Pharmacokinetic Evaluation:

The pharmacokinetic parameters of IPG1094 will be compared between dose groups. Due to the absence of definitive clinical information on this novel drug, the time points for PK sampling may be modified based on the data obtained.

Blood samples: Plasma concentration of IPG1094

Part A:

0 h before administration (within 1h prior to administration), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48, 72, and 96 h after administration.

Part B:

Blood sample: Plasma concentrations of IPG1094

0 h before administration (within 1h before administration), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24 h after administration on Day 1 and Day 10.

0 h before administration (within 1h before administration) on Day 4, Day 6 and Day 8.

36, 48, 72, 96 h after the last administration on Day 10.

Part C:

Blood sample: Plasma concentrations of IPG1094

0 h before the AM administration (within 1h before administration), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12(within 1h before PM administration), 24 h(within 1h before AM administration) after AM administration on Day 1 and Day 10.

0 h before AM administration (within 1h before AM administration) on Day 3, Day 4, Day 5, Day 6 and Day 8.

36, 48, 72 h after the last AM administration on Day 10.

Part D:

0 h before administration (within 1h prior to administration), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24, 36, 48, 72 h after administration in each Period.

Safety Evaluation:

Adverse events (AEs), physical examination, vital signs (body temperature, pulse, respiration, sitting blood pressure), 12-lead ECG findings, clinical laboratory tests (hematology test, blood chemistry test, coagulation test and urinalysis).

Statistical Methods:

General analysis:

Clinical data will be summarized by the treatment group. Data for participants receiving the placebo will be pooled across cohorts. Descriptive summary statistics will be calculated for continuous variables such as the number of participants, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using participant counts and percentages.

Analysis of population:

Intention-To-Treat Set (ITT): All participants enrolled. This population will be used to analyze dropout rate, demographic data and baseline characteristics.

Safety Set (SS): Participants who have received at least one dose of IMP. This population will be used to analyze safety.

PK Concentration Set (PKCS): Participants who have received at least one dose of IPG1094 with at least one evaluable IPG1094 concentration value.

PK Parameters Set (PKPS): Participants who have received at least one dose of IPG1094 with at least one evaluable IPG1094 pharmacokinetic parameter.

Food Effect Set(FES): Participants who have received at least one dose of IPG1094 with at least one evaluable primary pharmacokinetic parameter (C_{max}、AUC_{0-t}、AUC_{0-inf}) from at least one period.

Safety

Safety analysis (AE, laboratory parameters, vital signs, ECGs, etc.) will be based on review of individual values and descriptive statistics.

Safety analysis will focus on adverse events (AE) occurring during the study period. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity will be graded according to NCI-CTCAE V5.0. The number of participants who experience AEs during the study period and the incidence of AEs will be recorded.

Vital sign measurement and 12-lead ECGs will be performed longitudinally, to calculate summary statistics by dose group and by sampling time point. Summary statistics will be calculated by dose group and by sampling time point using quantitative results from hematology tests, blood chemistry tests, coagulation tests and urinalyses. Data will be classified into three categories based on reference values and the frequency will be calculated. Category frequencies will be calculated by dose group and by sampling time point using qualitative results.

Pharmacokinetics

Part A:

Pharmacokinetic parameters will be summarized using descriptive statistics.

Dose proportionality in fasting conditions will be assessed using a power model on C_{max}, AUC_{0-t}, AUC_{0-inf}.

Part B and Part C:

Pharmacokinetic parameters will be summarized using descriptive statistics.

Steady-state will be assessed on C_{trough} using a non-linear model. Accumulation will be assessed using a linear model on log-transformed accumulation ratio. Dose proportionality will be assessed using a power model on C_{max} and AUC_{0-tau} on Day 1 and Day 10 separately. Variance components of log-transformed C_{max} and AUC_{0-tau} will be estimated using a linear model.

Part D

Food effect will be assessed using a linear mixed model on log-transformed C_{max}, AUC_{last} and AUC_{inf} in 300mg dose level cohort. Food effect on T_{max} will be tested using the nonparametric test.

Pharmacokinetics/Safety

The relationship between concentration and ECG changes will be evaluated with an exposure-response analysis based on changes from baseline in centrally read ECG intervals and corresponding drug concentrations. This will be performed using graphical tools and regression methods. The final model will be utilized to make projections for selected concentrations.

Study Duration:

The planned duration of the study; from Sep. 2021 to Jul. 2022

Schedule of Activities：SAD (Part A)

Evaluation	Screening	Check-in	Dosing day	Safety review				
Study Day	D-28~-2	D-1	D1	D2	D3	D4	D5[1]	D8/ Follow-up (-1/+2 days)
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Schedule of Activities: MAD (Part B)

Evaluation	Screening	Check-in	Dosing period	Safety review
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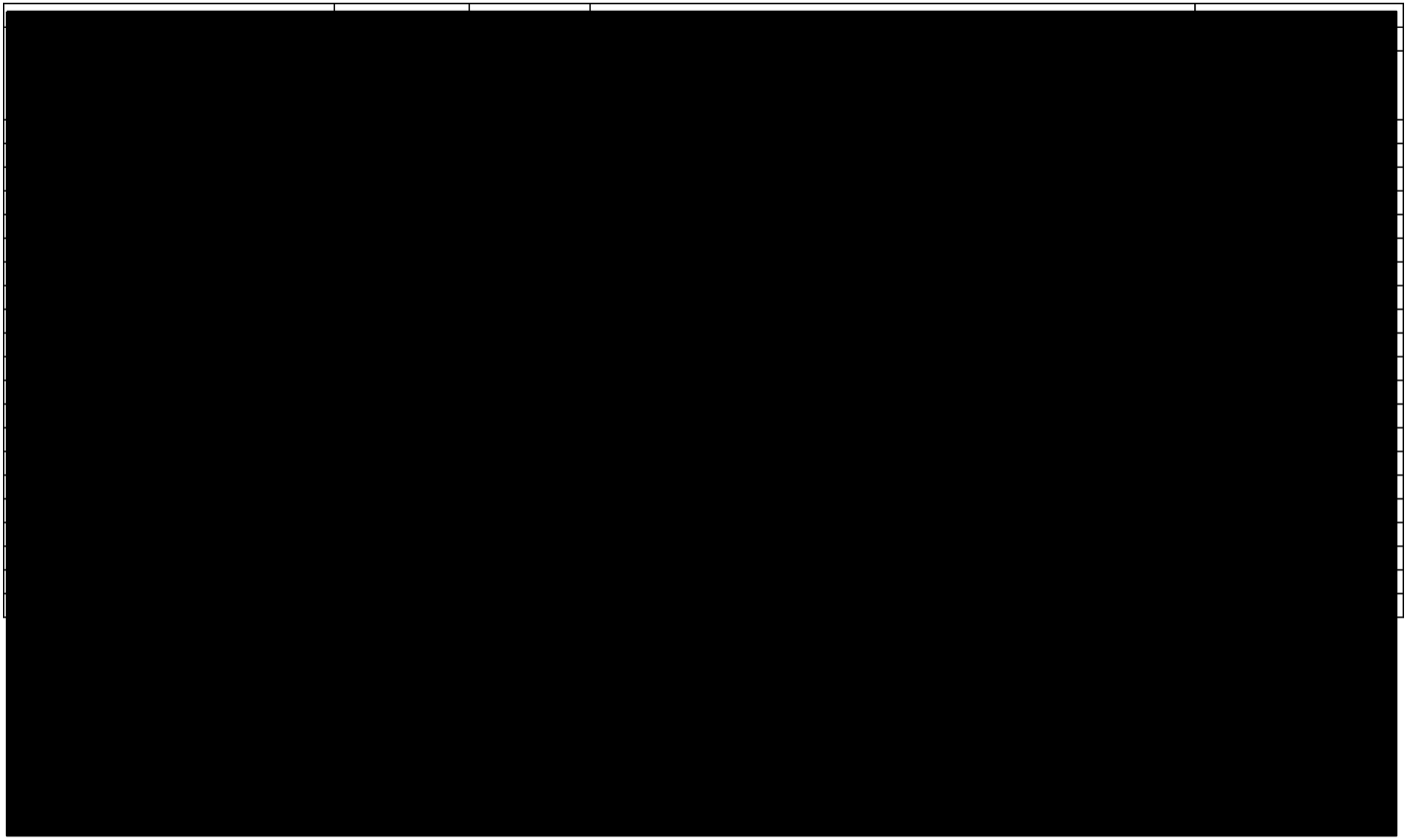
Schedule of Activities: MAD (Part C)



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Schedule of Activities: Food Effect Cohort (Part D)

Evaluation	Screening	Check-in	Period 1	Period 2	Follow-up
[redacted]					

1. COVID-19 PCR/RAT testing as required per the Investigator's discretion and if required can be done from Day -28 to Day -1 or any other time as required throughout

[redacted]