NANJING IMMUNOPHAGE BIOTECH CO., LTD.

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

IPG1094-A001

Statistical Analysis Plan

Version: 1.0

Date: 30Aug2022

Sponsor Approval Page

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Version: 1.0

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Signature: _____ Date: _____

Review Statistician: [redacted]

Company Name:

Signature: _____ Date: _____

Approved by Sponsor: [redacted]

Company Name:

Signature: _____ Date: _____

Modification History

Version	Version Date	Author	Description
1.0	30AUG2022	[redacted]	

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Abbreviation

Abbreviation	Specification
AE	adverse event
ALB	albumin
ALT	alanine aminotransferase
ALP	alkaline phosphatase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{0-inf}	area under the curve from time 0 extrapolated to infinite time
AUC_{0-t}	area under the curve from time 0 to the last measurable concentration
$AUC_{0-\tau}$	dose interval AUC
BID	twice daily
BMI	body mass index
Ca	calcium
CHO	cholesterol
CL/F	clearance
CL_{ss}/F	clearance at steady state
CK	creatine kinase
Cl	chloride
C_{max}	maximum plasma concentration
Cr	creatinine
$C_{ss,max}$	maximum plasma concentration at steady state
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of treatment
FDA	Food and Drug Administration
GCP	good clinical practice

Glu	glucose
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HGB	haemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
ITT	intention-to-treat set
K	potassium
LDH	lactate dehydrogenase
Max	Maximum
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Na	sodium
P	phosphate
PD	pharmacodynamic
PK	pharmacokinetic(s)
PKCS	PK concentration set
PKPS	PK parameters set
PLT	platelet count
PT	preferred term
Q1	lower quant
Q3	upper quant
QD	daily dose
Rac $_{(AUC)}$	accumulation ratio calculated using AUC
Rac $_{(Cmax)}$	accumulation ratio calculated using Cmax

RBC	red blood cell count
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SMC	Safety Monitoring Committee
SOC	system organ class
SS	safety set
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
Tbil	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time to C_{max}
TP	total protein
$T_{ss,max}$	time to maximum plasma concentration at steady state
U-BIL	urinary bilirubin
U-KET	urinary ketones
U-LEU	urinary leukocyte
ULN	upper limit of normal
U-NIT	urinary nitrites
U-PRO	urinary protein
U-RBC	urine erythrocytes
URO	urobilinogen
U-SG	urinary specific gravity
WBC	white blood cell count
WHO	World Health Organization

1. Introduction

This statistical analysis plan was drafted for the "*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*" (protocol No.: IPG1094-A001) of NANJING IMMUNOPHAGE BIOTECH CO., LTD.. In this document, the contents and methods of statistical analysis will be described in details.

This statistical analysis plan was based on protocol (version *3.0, 31Mar2022)* and Case Report Form (CRF, version *5.0, 22Apr2022*). It considered the intention-to-treat set (ITT) and safety set (SS) only.

2. Study Objectives and Endpoints

2.1. Primary Objectives

The primary objective of this study is:

Part A-Single ascending dose (SAD)
To assess the safety and tolerability of IPG1094 after ascending single oral doses.

Part B and Part C-multiple ascending dose (MAD)
To assess the safety and tolerability of IPG1094 after ascending multiple oral doses.

Part D-Food Effect
To evaluate the effect of food on the PK of IPG1094

The primary endpoints of Part A, Part B and Part C will be:

- Assessment of adverse events (AEs)
- Clinical laboratory evaluations (hematology, clinical chemistry, coagulation, urinalysis)
- Vital signs
- Electrocardiogram (ECG) (heart rate, PR, QRS, QT, QTcF)

The primary endpoints of Part D will be:

- Ratio fed/fasted on C_{max}, AUC_{0-t}, AUC_{0-inf}

2.2. Secondary Objectives

The secondary objectives of this study are:

Part A-Single ascending dose (SAD)
To assess the PK parameters of IPG1094 after ascending single oral doses.

Part B and Part C- Multiple ascending dose (MAD)
To assess the PK parameters of IPG1094 after ascending multiple oral doses

Part D-Food Effect
To assess the safety and tolerability of IPG1094 after 300 mg single oral dose under fast and fed conditions

The secondary endpoints will be:

- 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: 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-Food Effect: Assessment of adverse events (AEs); Clinical laboratory evaluations (hematology, clinical chemistry, coagulation, urinalysis); Vital signs; Electrocardiogram (ECG) (heart rate, PR, QRS, QT, QTcF)

3. Study Design

3.1. Study Type and Control Type

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

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

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. In each cohort, 2 sentinel participants will be dosed at least 48 hours prior to the other participants. One sentinel will be administered IPG1094 and the other the matching placebo. The remaining 6 participants will be dosed only if no significant safety issues are identified in the sentinel participants.

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 dose 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. Cohort M3-bid 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. The AM dose will be administrated under the fasted condition. For Day 1, participants will be required to fast overnight for at least 10 hours. For Day 2 to Day 10, participants will be required to fast for at least 2 hours prior to study drug The PM dose of

IPG1094 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. No food or beverage will be allowed for at least 2 hours post-dose for both AM and PM doses. Participants will not drink water for 1 hour pre-dose to 1 hour post dose, except for water with oral administration. 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.

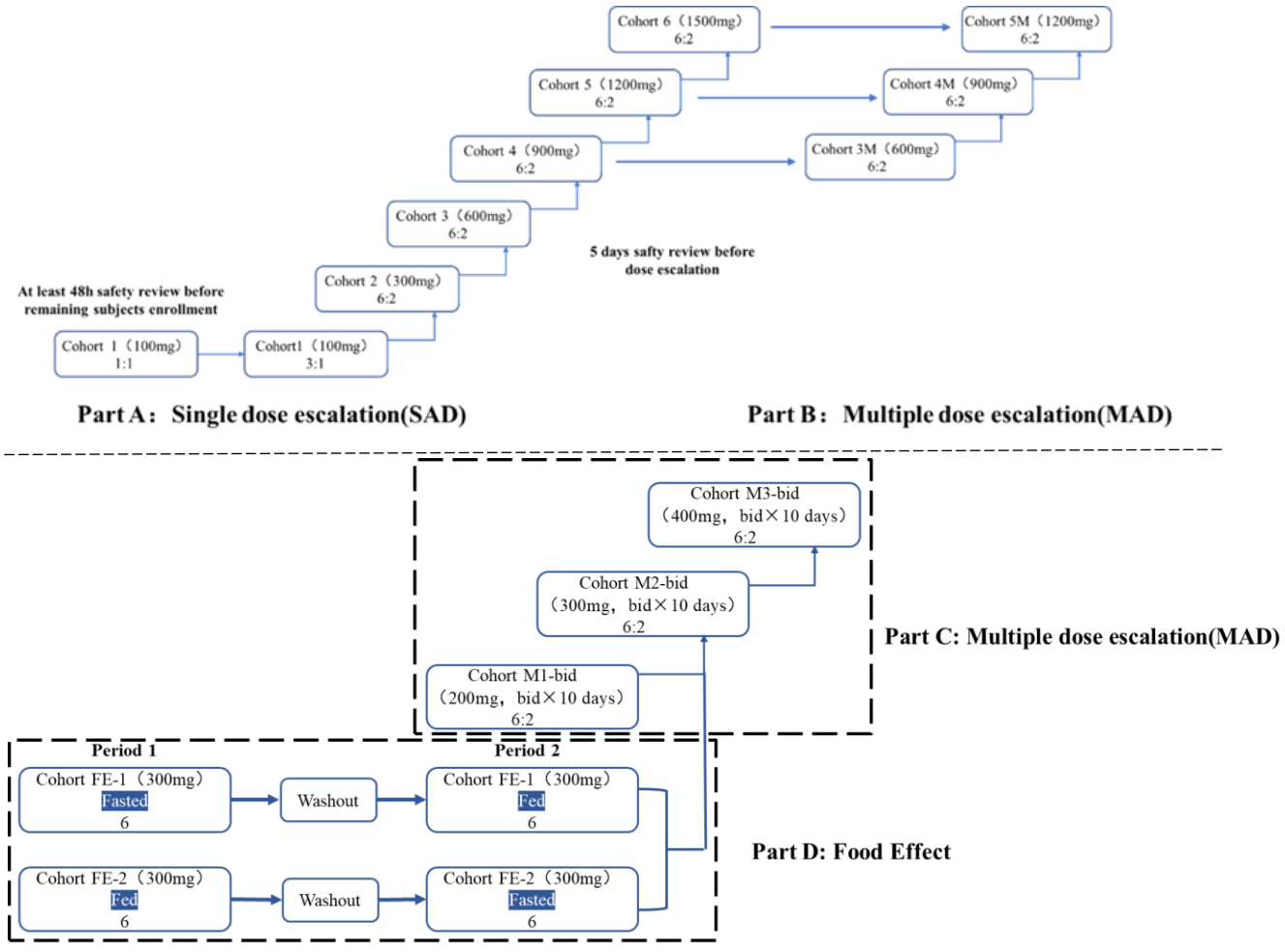
300 mg will be selected to assess the effect of food on the pharmacokinetic parameters and referred to as the food effect (FE) cohort (Cohort FE-1 and Cohort FE-2).

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 ≥ 3 days （＞5×T1/2 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 9 (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 9 (anticipated) after Period 2.

Mode(s) of Administration for FE cohort
Fasted Conditions: Following an overnight fast of at least 10 hours, subjects will receive a single dose of IPG1094 with 240 mL water. No food will 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.
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 minutes after the start of the breakfast. No food or beverage 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).

3.2. Study Flow Chart



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)**
[redacted]								
PK blood samples [9]			X					

Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X

Footnotes:

a) The test will not be repeated if performed within 7 days prior to check-in.
b) Will be performed pre-dose (-2-0h), 2h±30min and 6±1h post-dose.

1. For participants who prematurely withdraw from the study: if withdrawing after administration, Day 5 test items should be completed. If withdrawing before the first dose, the Investigator may determine whether the participants should undergo examinations for premature withdrawal based on their specific reasons for withdrawal.
2. Urine drug screening: amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates.
3. Clinical laboratory tests: Hematology, chemistry, coagulation and urinalysis.
4. Pregnancy test: (WOCBP only): Performed on serum (at screening) and urine (on Day -1 and Day 5). If a urine pregnancy test is positive or returns an ambiguous result, it must be confirmed by a serum pregnancy test.
5. Serum virology test: hepatitis B surface antigen (HbsAg), hepatitis B core antibodies (HbcAb), anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti HIV2 Ab). Results obtained within 28 days prior to the first dose may be accepted at the Investigator's discretion.
6. Randomization will be performed on Day -1 or Day 1 pre-dose.
7. Study drug administration: Participants will be administered with single dose of the assigned study drug (IPG1094 or the placebo) once daily while fasted.
8. Vital Signs (in a supine position): Blood pressure, pulse, respiratory rate, and temperature.
9. PK blood samples: Blood samples will be collected at 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. Samples should be obtained within 10% of the nominal time (e.g., within 6 minutes of a 60 minute sample) from dosing.
10. COVID-19 Swab testing is required as per the Investigator's discretion and if required can be done from Day -28 to Day -1 or any other time as required throughout the study

Schedule of Activities: MAD (Part B)

Evaluation	Screening	Check-in	Dosing period										Safety review	
Study Day(D)	D-28-2	D-1	D1~10										D11~17	
			D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D14[9]	D17/ Follow-up (-1/+2 days)
[redacted]														
P														X
[redacted]														

[redacted]

Footnotes:

a) The test will not be repeated if performed within 7 days prior to check-in.
b) Will be performed pre-dose (-2-0h), 2h±30min and 6±1h post-dose.
c) Pre-dose.

1. Urine drug screening: amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates.
2. Clinical laboratory tests: Hematology, chemistry, coagulation and urinalysis.
3. Pregnancy test: (WOCBP only): Performed on serum (at screening) and urine on Day-1 and Day 14). If a urine pregnancy test is positive or returns an ambiguous result, it must be confirmed by a serum pregnancy test.
4. Serum virology test: hepatitis B surface (HBs Ag) antigen, hepatitis B core antibodies (HBc Ab), anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti-HIV2 Ab). Results obtained within 28 days prior to the first dose may be accepted according to the Investigator's discretion.
5. Randomization will be performed on Day -1 or Day 1 pre-dose.
6. Study drug administration: Subjects will be administered with assigned study drug (IPG1094 or placebo) once daily while fasted from Day 1 to Day 10.
7. Vital Signs (In a supine position): Blood pressure, pulse, respiratory rate, and temperature.
8. PK blood sample: Blood samples will be collected at 0 h before AM administration (within 1h before AM administration), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 24 h after administration on Day 1 and Day 10; at 0 h before administration (within 1h prior to administration) on day 4, day 6 and Day 8; at 36, 48, 72, and 96 h after the last administration on Day 10. Samples should be obtained within 10% of the nominal time (e.g., within 6 minutes of a 60 minute sample) from dosing.
9. For subjects who prematurely withdraw from the study of Part B, if withdrawing after administration, the test items on Day 14 should be completed.
10. COVID-19 Swab testing is required as per the Investigator's discretion and if required can be done from Day -28 to Day -1 or any other time as required throughout the study.

Schedule of Activities: MAD (Part C)

Evaluation	Screening	Check-in	Dosing period										Safety review	
Study Day(D)	D-28-2	D-1	D1~10										D11~17	
			D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D13[9]	D17/ Follow-up (-1/+2 days)
In	X													
C														
H														
D														
M														
In														
Pl														
B														
U														
12														
C														
P														
S														
R														
A														
S														
Discharge													X	

[redacted]															

Footnotes:

a) The test will not be repeated if performed within 7 days prior to check-in.
b) Will be performed pre-dose (-2-0h), 2h±30min and 6±1h post-dose.
1. Urine drug screening: amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates.
2. Clinical laboratory tests: Hematology, chemistry, coagulation and urinalysis.
3. Pregnancy test: (WOCBP only): Performed on serum (at screening) and urine on Day-1 and Day 13). If a urine pregnancy test is positive or returns an ambiguous result, it must be confirmed by a serum pregnancy test.
4. Serum virology test: hepatitis B surface (HBs Ag) antigen, hepatitis B core antibodies (HBc Ab), anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti-HIV2 Ab). Results obtained within 28 days prior to the first dose may be accepted according to the Investigator's discretion.
5. Randomization will be performed on Day -1 or Day 1 pre-dose.
6. Study drug administration: Subjects will be administered with assigned study drug (IPG1094 or placebo) twice daily while fasted from Day 1 to Day 10 (The Fed or Fasted condition of Cohort M2-bid and Cohort M3-bid will be based on the result of FE study).
7. Vital Signs (In a supine position): Blood pressure, pulse, respiratory rate, and temperature.
8. PK blood sample: Blood samples will be collected at 0 h before AM administration (within 1h before AM 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 of Day 2) after administration on Day 1 and Day 10; at 0 h before administration (within 1h prior to AM administration) on day 3, day 4, day 5 day 6 and Day 8; at 48, 72h after the AM administration on Day 10. Except for the 12 h collection, samples should be obtained within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample) from dosing.
9. For subjects who prematurely withdraw from the study of Part C, if withdrawing after administration, the test items on Day 13 should be completed.
10. 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 the study.

Schedule of Activities: Food Effect Cohort (Part D)

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

[redacted]											
Medications											

Footnotes: In the event assessments are planned for the same scheme time, the order of the assessments should be arranged in such a way that PK blood sampling will be done after the ECG and vital signs recordings have been conducted, with PK blood sampling as close to the planned time as possible. Clinical laboratory blood samples may be taken thereafter.

a) The test will not be repeated if performed within 7 days prior to check-in.
b) Will be performed pre-dose (-2-0h), 2h (±30min) and 6 h (±1h) post-dose. (supine).

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 the study.
2. For subjects who prematurely withdraw from the study, if they withdrew after administration, the test items on Day 4 should be completed. If they withdrew before the first dose, the investigator can determine whether the subjects should undergo examinations for premature withdrawal based on the specific withdrawal reasons.
3. Urine drug screening: amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates.
4. Clinical laboratory tests: Hematology, chemistry, coagulation and urinalysis.
5. Pregnancy test: (WOCBP only): Performed on serum (at screening) and urine (on Day -1 and Day 8). If a urine pregnancy test is positive or returns an ambiguous result, it must be confirmed by a serum pregnancy test.
6. Serum virology test: hepatitis B surface (HbsAg) antigen, hepatitis B core antibodies (HbcAb), anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti-HIV2 Ab). Results obtained within 28 days prior to the first dose may be accepted at the Investigator's discretion.
7. Randomization will be performed on Day -1 or Day 1 pre-dose.
8. Study drug administration: For Cohort FE-1:Subjects will be administered with a single dose of assigned study drug (IPG1094) in fasted state with 240 mL on Day 1 of Period 1, and in fed state with 240 mL on Day 1 of Period 2. For Cohort FE-2:Subjects will be administered with a single dose of assigned study drug (IPG1094) in fed state with 240 mL on Day 1 of Period 1, and in fasted state with 240 mL on Day 1 of Period 2.
9. Fasted Conditions: Following an overnight fast of at least 10 hours, subjects will receive a single dose of IPG1094 with 240 mL water. Water can be ingested as desired except for 1 hour pre-dose until one hour post-dose.
10. 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 minutes after the start of the breakfast. No food or beverage 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.
11. 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).

12. Vital Signs (in a supine position): Blood pressure, pulse, respiratory rate, and temperature. (When multiple procedures are required to be conducted at the same time point, PK blood sample collection will take priority over all other scheduled activities.)
13. PK blood sample: Blood samples will be collected pre-dose (within 1h before administration), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 24, 36, 48, 72 h after administration. Samples should be obtained within 10% of the nominal time (e.g., within 6 minutes of a 60-minute sample). When multiple procedures are required to be conducted at the same time point, PK blood sample collection will take priority over all other scheduled activities.

3.3. Randomization Design and Execution

Block randomization will be utilized for this study. After signing informed consent forms and completing all screening procedures, eligible participants will be randomized to IPG1094 or placebo as specified in each Part below. The randomization code will be generated by an independent statistician who is not directly involved with the study.

Part A/Part B/Part C:

In Part A, Cohort 1 only, two eligible sentinel participants will be randomized in a 1:1 ratio to determine whether they will receive IPG1094 or the placebo. Four subsequent participants in Cohort 1 will be randomized in a 3:1 ratio to determine whether they will receive IPG1094 or the placebo. For all subsequent Part A, Part B and Part C cohorts, eight eligible participants will be randomized in a 3:1 ratio to determine whether they will receive IPG1094 or the placebo, with dosage determined per cohort. Participant randomization numbers will be assigned based on confirmation of eligibility. Randomization numbers will start from 1001. The numbers consist of 4 digits. The first digit indicates the dose cohort (e.g. for Part A, '1' indicates 100mg cohort, '2' indicates 300mg cohort etc.). The second digit indicates substitute participants ('0' means normal, '1' means substitute). The third digit indicates study part (e.g. '0' indicates Part A-SAD, '1' indicates Part B- MAD QD, '2' indicates Part C – MAD BD). The last digit indicates the order of the randomized participants.

Part D:

Randomization numbers will start from F001. The numbers consist of 4 digits. The first digit is 'F', meaning Part D-Food effect study. The second digit indicates substitute participants ('0' means normal, '1' means substitute). The last two digits indicate the order of the randomized participants.

3.4. Blinding Design and Execution

For each dose cohort, the Sponsor, participants and other personnel involved with the conduct of the study will be blinded to the study products.

This blinding will remain in place until the study is completed and the database is locked. The Investigator may breach blinding only in the case of an emergency or in the event of a serious medical condition, where identification of the study product is essential for appropriate clinical management or the welfare of the participant, as determined by the Investigator. In such cases, the Investigator must contact the Sponsor before breaching blinding.

If the blind is breached, the individual responsible must document the date, time and reason for breaching blinding. A written report must be sent to the Sponsor within 1 working day.

4. Sample Size Consideration

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.

5. Analysis Datasets

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.

6. Statistical Methods

6.1. General Statistical Consideration

Unless otherwise specified, SAS 9.4 will be used for statistical analysis. Generally, descriptive statistics will be carried out for measurement data, including number of cases (n), Arithmetic mean, Standard deviation (SD), Median, Minimum (Min), and Maximum (Max). General statistics will be used for counting data (n) and percentage (%).

For continuous variables that are recorded as "< X" or "> X", the value of "X" will be used in the calculation of summary statistics. The original values will be used for the listings.

Decimal points will be presented as follows: N will be presented without decimal, minimum/maximum in same precision as in the database, mean/median in one more decimal than minimum/maximum, and SD in one more decimal than mean/median. And the decimal places of SD should not be greater than 4. Calculated percentage will be reported with one decimal.

Baseline will be defined as the last effective measurement taken before first dose. That is, the measurement or recording of visit 2 will be used, or if the measurement or recording of visit 2 be made after the first treatment dose of study or missing, the measurement or recording of visit 1 would be used. For part D, the baseline for 12-lead ECG and vital sign will be defined as the last effective measurement taken before dose for each period.

Visit definition is listed as below in 12-lead ECG and vital sign for part D:

CRF visit	**Analysis visit**
V3-Part D-FE(D1 Period 1)	D1
V4-Part D-FE(D2 Period 1)	D2
V5-Part D-FE(D3 Period 1)	D3
V6-Part D-FE(D4 Period 1 or Prematurely withdrew)	D4 or Prematurely withdrew
V7-Part D-FE(D5 Period 2)	D1

V8-Part D-FE(D6 Period 2)	D2
V9-Part D-FE(D7 Period 2)	D3
V10-Part D-FE(D8 Period 2 or Prematurely withdrew)	D4 or Prematurely withdrew

Unless otherwise noted, descriptive statistical summary and statistical inferences would be performed based on visits, include the scheduled visit data only. For evaluations involving abnormalities and clinically significant findings, data from both scheduled visits and unscheduled visits should be all included.

6.2. Data Handling

6.2.1. Premature Withdrawal and Missing Data

Other data evaluation will be based on the data collected by CRF without any imputation. If the categorical data is missing, it can be recorded as "missing".

The missing date of AE/CM will be imputed as follows. The imputation of missing date of AE/CM is only used to classify AEs/CMs, and the original missing date record will still be presented when generating the listing of AE/CM related data.

- If the start date of AE/CM was missing
  1) If year and month were known and earlier than that of the first treatment dose, then impute with the last day of the known month
  2) If the year and month were known as same as that of the first treatment dose, then impute the start date with the date of first treatment dosing.
  3) If year and month were known and later than that of the first treatment dosing, then impute with the first day of the known month.
  4) If year only was known and earlier than that of the first treatment dosing, then impute date with December 31.
  5) If year only was known and equal to that of the first treatment dosing, then impute the start date of AE as the first treatment dosing date.
  6) If year only was known and later than that of the first treatment dosing, then impute with January 1.
  7) If year、month and day were all missing, use the first treatment dosing date as the start date of AE.
  8) Other conditions will be regarded as missing.
- If the end data of AE/CM was missing
  1) If year and month were known, then impute with the last day of the known month.
  2) If year only was known, then impute with December 31.
  3) The start date was later than the end date after imputation, then use the start date directly as the end date.
  4) Other condition will be regarded as missing.

6.2.2. Derivation and Transformation on Data

Exposure time = date of last dose - date of first dose + 1

Exposure dose = Cumulative total dose

6.3. Subject Disposition

The number of subjects who screened, screening failure and enrolled will be calculated, distinguishing those screen failure subject and those who had passed screening but were not randomized. Listing will be presented for subjects who were not randomized with reasons.

Based on all subjects receiving randomization, the number and percentage of subjects who completed the study and discontinued, as well as the number and percentage of subjects who discontinued for various reasons, will be calculated and summarized. Listing will be presented for the reasons for discontinuation.

Based on all randomized subjects, listing will be provided for all protocol deviation.

Based on all randomized, the number and percentage of subjects included in the intention-to-treat set and safety set will be calculated and summarized. Listing will be provided for the reason of exclusion from analysis sets.

6.4. Demographics and Baseline Characteristics

The analysis will be based on ITT.

Descriptive statistical summary will be performed on demographic data such as age, sex, race, ethnicity, height and weight, BMI.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A summary table will be presented by system organ class (SOC) and preferred term (PT).

Breath alcohol test (negative, positive, not done), urine drug screening (negative, positive, not done) and serum virology test (normal, abnormal not clinically significant, abnormal clinically significant, not done) will be summarized in descriptive statistics.

Listing will be provided for demographic data and medical history.

6.5. Treatment Compliance and Concomitant Medication

The analysis will be based on SS.

Compliance will be calculated only for part B and part C.

Compliance = Actual Times of Doses/Theoretical Times of Doses * 100%

Theoretical Times of Doses = Theoretical Days of Doses * Times of Doses per Day

For part B, eligible subjects will receive multiple oral doses once daily, over a 10-days period. For part C, eligible subjects will receive multiple oral doses twice daily, Q12±1h, over a 10-days period. Therefore, there will be a total of 10 doses and 20 doses for part B and part C respectively.

The compliance will be summarized in descriptive statistics. A frequency summary of treatment compliance category (80%-120%, <80% and >120%) will also be provided.

All concomitant medications taken within 28 days prior to IMP treatment and during the clinical trial must be recorded in the eCRF. Concomitant medication will be coded using WHODrug GLOBAL (B3) E V2021MAR or above. The number and percentage of subjects used various types of ATC will be calculated.

Concomitant procedure will be coded using MedDRA/E 24.0 or above. All concomitant procedure will be classified and counted according to system organ class (SOC) and preferred term (PT).

Listing will be provided for the concomitant medication and concomitant procedure.

6.6. Safety Analysis

6.6.1. Exposure

Analysis will be performed based on SS.

The number of exposures will be calculated based on part A and part D. The exposure time and exposure dose will be summarized by descriptive statistics for part B and part C.

Listing will be provided for exposure.

6.6.2. Adverse Events

Analysis will be performed based on SS. Adverse events will be coded by MedDRA/E 24.0 or above.

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A serious adverse event (SAE) is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the Investigator, places the participant at immediate risk of death). This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused the death
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal activities)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug

- Is a significant medical event in the Investigator's judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

A significant adverse event is any marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including significant additional concomitant therapy, other than those reported as serious adverse events.

A treatment-emergent adverse event (TEAE) is any adverse event first appears during the treatment, which is absent before or which worsens compared to the pre-treatment status.

Statistical summaries will be performed on general incidence rate of adverse event, including the occurrence rate of all adverse events, TEAEs, drug-related TEAEs, SAEs, significant AEs, drug-related SAEs, TEAEs leading to withdrawal, drug-related TEAEs leading to withdrawal, fatal AEs.

For TEAEs, incidence rate of all TEAEs, drug-related TEAEs, SAE, drug-related SAEs, TEAEs leading to withdrawal, drug-related TEAEs leading to withdrawal, fatal TEAE will be calculated and summarized according to system organ class (SOC) with its preferred terms (PT). If a subject had multiple adverse events of the same SOC and PT, only one event will be counted.

For TEAEs, incidence rate of all adverse events with various severity will be calculated and summarized according to system organ class (SOC) with its preferred terms (PT). If a subject had multiple adverse events of the same PT, only the one event with the highest severity will be counted.

Listing will be provided for all adverse events, TEAEs, drug-related TEAEs, SAEs, significant AEs, drug-related SAEs, TEAEs leading to withdrawal, drug-related TEAEs leading to withdrawal, fatal AEs.

6.6.3. Laboratory Test Results

Analysis will be performed based on SS.

From baseline, the quantitative laboratory tests results of each visit and their changes from baseline will be calculated and summarized in descriptive statistics.

According to the order of abnormal clinical significance > abnormal not clinical significance > normal > not done, the laboratory tests results baseline and the laboratory test results after treatment will be divided into abnormal clinical significance, abnormal not clinical significance, normal and not done, and then the shift table will be generated.

Listing will be provided for all abnormal clinical significance results of laboratory tests.

6.6.4. Vital Signs

Analysis will be performed based on SS.

From baseline, the systolic and diastolic blood pressure, respiratory rate, heart rate and temperature measurements and their changes from baseline will be summarized by descriptive statistics.

Listing will be provided for all results of vital signs.

6.6.5. Physical examination

Analysis will be performed based on SS.

According to the order of abnormal clinical significance > abnormal not clinical significance > normal > not done, the physical examination results baseline and the physical examination results after treatment will be divided into abnormal clinical significance, abnormal not clinical significance, normal and not done, and then the shift table will be generated.

Listing will be provided for all results of physical examination.

6.6.6. 12-lead ECG

Analysis will be performed based on SS.

From baseline, the heart rate, PR, QRS, QT, QTcF results of each visit and their changes from baseline will be summarized by descriptive statistics.

According to the order of abnormal clinical significance > abnormal not clinical significance > normal > not done, the 12-lead ECG results baseline and the 12-lead ECG results after treatment will be divided into abnormal clinical significance, abnormal not clinical significance, normal and not done, and then the shift table will be generated.

Listing will be provided for all results of 12-lead ECG.

6.6.7. Pregnancy Test (Female Only)

Analysis will be performed based on safety set.
Listing will be provided for all the positive results of the pregnancy test.

7. Multiplicity

Not applicable.

8. Interim Analyses

Not applicable.

9. Change from the Analysis Plan in Protocol

Not applicable.

10. Reference

- December 2021, *Planning and Reporting Guidelines of Data Management and Statistical Analysis of Drug Clinical Trails,* China Food and Drug Administration.
- March 2016, *Formulation of Biostatistics Guiding Principles of Drug Clinical Trials,* China Food and Drug Administration

11. TFL Shell and Dataset Specification

11.1. TFL Shell

Referred to attachment *IPG1094-A001_TFL_V1.0_20220830*.

11.2. Dataset Specification

Referred to attachment *IPG1094-A001_SDTM Spec* and *IPG1094-A001_ADaM Spec*.