Clinical Trial Protocol

A randomized, double-blind, placebo parallel-controlled Phase II clinical trial to evaluate the efficacy and safety of TJ0113 capsule in patients with early-stage Parkinson's disease

Protocol No.: **TJJS01-201**

Version No.: **4.0**

Version Date: **February 17, 2025**

Sponsor: **Hangzhou PhecdaMed Co., Ltd.**

Confidentiality Statement

Protocol Signature Page-Sponsor

I agree:

- To strictly follow the protocol, Good Clinical Practice (GCP) and applicable regulations and laws when carrying out the study.
- To keep all materials provided by Hangzhou PhecdaMed Co., Ltd. according to the confidentiality requirements. It must be indicated that these materials are confidential when they are required to be submitted to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

I have read the full text of the protocol and agree to all the contents.

Yasu Zhang		
Responsible Person of the Sponsor	Signature	Date

Protocol Signature Page-Contract Research Organization

I agree:

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Zhipei Wei		
Project Manager	Signature	Date

Protocol Signature Page-Statistical Analysis Institution

I agree:

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Qing Li		
Statistician	Signature	Date

Protocol Signature Page-Study Site

I agree:

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I have read the full text of the protocol and agree to all the contents.

Principal Investigator	Signature	Date

Clinical Study Management Institution or Participating Parties

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Table of Contents

List of Abbreviations and Definitions of Terms

Abbreviations/Terms	Full Name
ADR	Adverse Drug Reactions
AE	Adverse Event
AFP	Alpha-fetoprotein
ALT	Alanine Aminotransferase
ASMI	Appendicular Skeletal Muscle Mass Index
AST	Aspartate Aminotransferase
$AUC_{0\text{-inf}}$	Area Under the Plasma Concentration-Time Curve from Time Zero to Infinity
$AUC_{0\text{-inf,ss}}$	Area Under the Plasma Concentration-Time Curve from Time Zero to Infinity at Steady State
$AUC_{0\text{-last}}$	Area Under the Plasma Concentration-Time Curve from Time Zero to Time of Last Quantifiable Concentration
$AUC_{0\text{-t}}$	Area Under the Plasma Concentration-Time Curve from Time Zero to Time T
$AUC_{0\text{-t,ss}}$	Area Under the Plasma Concentration-Time Curve from Time Zero to Time T at Steady State
$AUC_{0\text{-24h}}$	Area Under the Plasma Concentration-Time Curve from Time 0 to 24 h Post-Dose
BID	Twice Daily
BMI	Body Mass Index
CA125	Carbohydrate Antigen 125
CA153	Carbohydrate Antigen 153
CA199	Carbohydrate Antigen 199
CCCP	Carbonylcyanide-3-Chlorophenylhydrazone
Ccr	Creatinine Clearance
CEA	Carcinoembryonic Antigen
C_{max}	Maximum Concentration
$C_{max,ss}$	Maximum Steady-State Concentration
COX	Cyclo-Oxygenase
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DA	Dopamine
DXA	Dual-energy X-ray Absorptiometry

ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FE	Food Effect
F-PSA	Free Prostate Specific Antigen
GCP	Good Clinical Practice
GFAP	Glial Fibrillary Acidic Protein
GPCR	G-Protein-Coupled Receptor
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IC_{50}	Half-Maximal Inhibitory Concentration
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MAD	Multiple Ascending Dose
Max	Maximum
Mcl-1	Myeloid Cell Leukemia 1
MDS-UPDRS	Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
Median	Median
MI	Myocardial Infarct
Min	Minimum
MMRM	Mixed-Effects Model for Repeated Measures
MPTP	1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine
mRNA	Messenger Ribonucleic Acid

MTD	Maximum Tolerated Dose
mtDNA	Mitochondrial Deoxyribonucleic Acid
NCI	National Cancer Institute
NMPA	National Medical Products Administration
NOAEL	No Observed Adverse Effect Level
NYHA	New York Heart Association
OAT1	Organic Anion Transporter 1
PCR	Polymerase Chain Reaction
PD	Parkinson's Disease
P-gp	P-Glycoprotein
PK	Pharmacokinetics
PPS	Per-Protocol Set
PT	Preferred Term
QA	Quality Assurance
QD	Once Daily
Q1	First Quartile
Q3	Third Quartile
$Rac_{(AUC)}$	Ratio of Accumulation of the Area Under the Plasma Drug Concentration-Time Curve at Steady State
$Rac_{(Cmax)}$	Ratio of Accumulation of Maximum Concentration at Steady State
ROS	Reactive Oxygen Species
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma Antigen
SD	Standard Deviation
SDV	Source Data Verification
SN	Substantia Nigra
SoA	Schedule of Activities
SS	Safety Set
Str	Striatum
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event

T_{max}	Time to Maximum Concentration
TNF	Tumor Necrosis Factor
T-PSA	Total Prostate Specific Antigen
TRAE	Treatment-Related Adverse Events
$t_{1/2}$	Half-Life
$t_{1/2,ss}$	Half-Life at Steady State
ULN	Upper Limit of Normal
URAT1	Urate Transporter 1
V_{ss}	Steady-State Volume of Distribution
WHO DD	World Health Organization Drug Dictionary
6-OHDA	6-Hydroxydopamine

1 Protocol Summary

1.1 Synopsis

Protocol No.	TJJS01-201
Trial Title	A Randomized, Double-blind, Placebo Parallel-Controlled Phase II Clinical Trial to Evaluate the Efficacy and Safety of TJ0113 Capsule in Patients with Early-stage Parkinson's Disease
Version No.	4.0
Version Date	February 17, 2025
Sponsor	Hangzhou PhecdaMed Co., Ltd.
Phase	Phase II
Indication	Parkinson's disease (PD)
Trial Objectives	**Primary Objectives** • To assess the efficacy of TJ0113 capsules in the treatment of patients with early-stage PD. **Secondary Objectives** • To assess the efficacy of TJ0113 capsules in the treatment of patients with early-stage PD; • To assess the safety of TJ0113 capsules in the treatment of patients with early-stage PD. **Exploratory Objectives** • To explore the changes in inflammatory indicators in early-stage PD patients treated with TJ0113 capsules; • To explore the effect of TJ0113 capsules on PD biomarkers in early-stage PD patients; • To explore the effect of TJ0113 capsules on skeletal muscle mass and function in early-stage PD patients; • To explore the association between the efficacy of TJ0113 capsules and the genomic characteristics in early-stage PD patients.
Trial Endpoints	**Primary Endpoints** • Changes from baseline in scores of the Unified Parkinson's Disease

	Rating Scale (MDS-UPDRS) Part III (motor examination) in subjects after 12 weeks of treatment. Evaluation time point: ≥ 12 hours from the most recent dose of anti-PD drug. **Secondary Endpoints** ➢ Efficacy Endpoints • Changes from baseline in scores of MDS-UPDRS Part III (motor examination) in subjects after 1, 4, 8 weeks of treatment. Evaluation time point at each visit: ≥ 12 hours from the most recent dose of anti-PD drug; • Changes from baseline in scores of MDS-UPDRS Part III (motor examination) in subjects after 1, 4, 8, 12 weeks of treatment. Evaluation time point at each visit: 2 ± 1 hours from the most recent dose of anti-PD drug; • Changes from baseline in scores of MDS-UPDRS Part I, II and IV in subjects after 1, 4, 8 and 12 weeks of treatment; • Changes from baseline in the total scores of MDS-UPDRS in subjects after 1, 4, 8, 12 weeks of treatment, including: - Total score 1: II+III; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is ≥ 12 hours from the most recent dose of anti-PD drug; - Total score 2: II+III; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is 2 ± 1 hours from the most recent dose of anti-PD drug; - Total score 3: I+II+III; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is ≥ 12 hours from the most recent dose of anti-PD drug; - Total score 4: I+II+III; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is 2 ± 1 hours from the most recent dose of anti-PD drug; - Total score 5: I+II+III+IV; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is ≥ 12 hours from the most recent dose of anti-PD drug; - Total score 6: I+II+III+IV; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is 2 ± 1 hours from the most recent dose of anti-PD drug.

	➢ Safety Endpoints • Adverse events (AEs); • Laboratory test; • Vital signs; • Physical examination; • 12-lead electrocardiogram (ECG). ➢ Exploratory Endpoint • Changes from baseline in inflammatory indicators after 4, 8, 12 weeks of treatment; • Changes from baseline in α-synuclein and glial fibrillary acidic protein (GFAP) after 12 weeks of treatment; • Changes from baseline in appendicular skeletal muscle mass index (ASMI) measured by dual-energy X-ray absorptiometry (DXA) after 12 weeks of treatment; • Changes from baseline in muscle strength (grip strength) after 12 weeks of treatment; • Changes from baseline in 6-meter walking speed test after 12 weeks of treatment; • The association between the efficacy of TJ0113 capsules and the genomic characteristics in early-stage PD patients.
Trial Design and Methodology	This study is a randomized, double-blind, placebo parallel-controlled phase II clinical trial which is designed to assess the efficacy and safety of TJ0113 capsules in the treatment of patients with early-stage PD. It is planned to include approximately 150 subjects with early-stage PD who will be randomized in a 1:1 ratio into two cohorts (Cohort 1: 200 mg dose group; Cohort 2: 400 mg dose group). Within each cohort, subjects who have been successfully screened will be randomly assigned to TJ0113 capsules group and the placebo group in a ratio of 2:1 within each stratum based on a stratification factor whether they have been receiving levodopa, the background medication for PD (yes vs. no) at a stable dose. Among them, approximately 50 subjects will receive TJ0113 capsules and approximately 25 subjects will receive the placebo. In this study, there will be approximately 50 subjects in each of the TJ0113 capsules 200 mg group, TJ0113 capsules 400 mg group and the placebo group. After randomization, subjects will receive the oral administration of TJ0113 capsules or the placebo for 12 consecutive weeks and continue to receive follow-up visits for 1 week (telephone follow-up) after the end of treatment. For subjects who have been receiving the anti-PD drug at a stable dose for at least 4 weeks prior to study entry, the original regimen of the background medication for PD should be maintained during the study. **Screening period (up to 4 weeks)**

	At screening, the subject will be assigned a "screening number" for ID identification after signing the informed consent form. The day of first dose for subjects screened successfully is taken as Day 1 (D1) of the trial (for other days, by this rule); and subjects are screened within 28 to 2 days before the start of the trial, and the required eligible subjects are screened. The scale scores, demographic data, medical history, medication history, physical examinations, height and weight, vital signs and laboratory tests of the subjects before the trial are recorded. **Treatment period (12 weeks)** Subjects who have been successfully screened will receive oral administration of the drugs as required on D1, once daily for 12 weeks. **Follow-up period (1 week, telephone follow-up)** Follow-up will be continued for 1 week after the end of the treatment period, and AE and concomitant medication information will be collected via telephone follow-up. If an AE/SAE occurs during the study, it will be followed up by the investigator until it has been clinically recovered, stabilized, returns to the screening or baseline level (if baseline level is known), the subject is lost to follow-up (e.g., no more information is available or the subject/caregiver refuses to provide any information), or dead.
Total Number of Subjects	There are about 150 subjects, with approximately 50 subjects in each of the TJ0113 capsules 200 mg group, TJ0113 capsules 400 mg group and the placebo group.
Number of Study Sites	Approximately 7 sites
Study Duration	The duration of this study is expected to be approximately 6 months. Each subject will participate in the study for up to approximately 17 weeks, including a screening period of up to 4 weeks, a treatment period of 12 weeks, and a follow-up period of 1 week.
Subject Selection Criteria	**Inclusion Criteria:** Subjects who meet all of the following criteria will be eligible for this study: 1. Subjects who voluntarily participate in the clinical trial, and have signed the informed consent form (ICF), are able to understand and follow the study protocol, willing to visit the study site on time, fully understand the content, process and potential adverse reactions of the study, and indicate the date of signing the ICF; 2. Males or females aged 30-80 years (both inclusive) at the time of signing the ICF; 3. Subjects who are diagnosed with PD according to the Diagnostic Criteria for Parkinson's Disease in China (2016 edition); 4. The scores of modified Hoehn and Yahr Scale at screening are 1-2.5 (both inclusive);

	5. Subjects who have not previously received anti-PD drugs; or those who have previously used any anti-PD drugs but have not received such drug within 4 weeks before study entry; or those who have received the anti-PD drug at a stable dose for at least 4 weeks before study entry and agree to maintain the original treatment regimen during the study; 6. Subjects with the scores of MDS-UPDRS Part III of ≥ 22 at screening (it should be scored ≥ 12 hours apart from the most recent dose of the anti-PD drug for subjects who have been receiving an anti-PD drug at a stable dose for at least 4 weeks prior to study entry); 7. Subjects of childbearing potential (including spouses of male subjects) who have no childbearing or sperm donation plan from the end of the screening period to within 6 months after the last dose and are willing to use at least one effective method (see Appendix I for details) for contraception. **Exclusion Criteria:** Subjects who meet any of the following criteria will be excluded from this study: 1. Presence of any medical condition that may interfere with full participation in the study, including but not limited to the following: medical history of epilepsy or any complications, medical history of hemolytic anemia, pulmonary embolism, respiratory depression, active psychiatric disease, or malignancy; positive tumor marker detection results at screening and judged by the investigator to be clinically significant; 2. Subjects who have experienced a New York Heart Association (NYHA) Class III or above congestive heart failure, unstable angina pectoris, acute myocardial infarction, hemorrhagic stroke (stroke), and ischemic stroke (including transient ischemic attack) within 6 months before screening; or those who have undergone any percutaneous coronary intervention or coronary artery bypass grafting, heart valve repair/replacement; or those with severe arrhythmia as judged by the investigator at the time of screening; 3. Subjects with prior personal or family history of long-QT syndrome, family history of sudden death of any immediate family members (meaning a parent, child, or sibling) prior to the age of 40 years; and/or personal history of unexplained syncope within 1 year prior to screening; and/or QTcF > 450 ms (male), QTcF > 470 ms (female) measured by ECG at rest during screening; 4. Subjects with unstably controlled hypertension at screening, defined as the

	systolic blood pressure ≥ 160 mmHg and/or the diastolic blood pressure ≥ 100 mmHg (verify before randomization); 5. Subjects with symptomatic orthostatic hypotension at screening, or who experiences a decrease in systolic blood pressure of ≥ 30 mmHg or a decrease in diastolic blood pressure of ≥ 15 mmHg within 3 minutes when changing from the supine to the standing position (verify before randomization); 6. Atypical PD (e.g., Parkinsonism, multiple system atrophy, progressive supranuclear palsy), or secondary PD (e.g., delayed or drug-induced PD); 7. Subjects who have clinically significant hepatic insufficiency which is defined as the total bilirubin (TBIL) > 2 × upper limit of normal (ULN) or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 × ULN; 8. Subjects who have clinically significant renal insufficiency (creatinine clearance [Ccr] < 30 mL/min, see the calculation formula in Appendix II; 9. Any condition (e.g., severe arthritis, severe dyskinesia, traumatic injury with permanent physical disability) that may affect the MDS-UPDRS motor examination; 10. Subjects who have a history of suicidal intention (including actual attempts, interrupted attempts, or failed attempts) and are at risk of committing suicide as judged by the investigator; 11. Subjects who suffer from severe mental abnormalities (anxiety, depression) as judged by the investigator, and the depression or anxiety score as rated by the Part I of the MDS-UPDRS is ≥ 3 at screening; 12. Subjects who have taken any serotonin reuptake inhibitors (such as fluoxetine, paroxetine, trazodone, citalopram, escitalopram, etc.) within 4 weeks prior to screening; 13. Subjects who have dementia or moderate or above cognitive dysfunction and the MDS-UPDRS score for 1.1 cognitive impairment is ≥ 3 at screening; 14. Subjects who have a history of surgical treatment for PD (e.g., deep brain stimulation, pallidotomy, etc.), or those who have undergone any major or medium surgery or have experienced any serious trauma or serious infection within 3 months prior to screening, those who are unsuitable for this study at the discretion of the investigator or plan to undergo any surgical treatment (excluding an outpatient surgery that has no impact on

	subject safety or study results as judged by the investigator) during the study; 15. Subjects who have participated in a clinical trial that involves the administration of an investigational drug (a new chemical entity), device, or surgery within 3 months or 5 half-lives before screening, whichever is longer; 16. Subjects with evidence of alcoholism (≥ 14 units of alcohol per week on average, 1 unit ≈ 360 mL of beer, 45 mL of liquor, or 150 mL of wine) or drug abuse within 6 months prior to screening that may interfere with the subject's understanding of the study or completion of the study as judged by the investigator; 17. Subjects who are known to have hypersensitivity/allergic reaction or intolerance to any component of the investigational product; 18. Subjects with a history of hepatitis B, or positive for any of the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody, and Treponema pallidum antibody (TP-Ab) at screening; 19. Pregnant or breastfeeding women; 20. Subjects who are unable to swallow oral drugs, or have any condition that may significantly affect the absorption, distribution, metabolism and excretion of the drug, or any condition that may pose a hazard to subjects participating in the study, as judged by the investigator; 21. Subjects who have a history of organ transplantation (excluding corneal transplantation); 22. Subjects who have donated or lost blood of ≥400 mL, or received blood transfusions within 3 months prior to screening; 23. Subjects who have any other conditions that may affect study compliance as deemed by the investigator, or those who are unable to participate in the study for their own reasons.
Concomitant Medications/Therapies	**Permitted Concomitant Medications/Therapies** Concomitant medications/therapies allowed to be administered from signing of the ICF to 1 week after the last dose of the investigational product include: • Background medications for PD that have been stably used before study entry, of which the treatment regimen can remain unchanged (for subjects who have used any background medications for PD including levodopa, if any AE such as dyskinesia occur, the dose of

	levodopa is allowed to be reduced at the discretion of the investigator). • Other concomitant medication or therapies that have already been used at the time of screening, of which the original drug/therapy type, dose or treatment frequency and setting should remain unchanged as much as possible. • Drugs required to be used for treating the AEs. **Prohibited Concomitant Medications/Therapies** The following medications/therapies are prohibited during the period from signing the ICF until 1 week after the last dose of the investigational product: • Any procedure/surgery that may affect the progression of PD, including but not limited to brain surgery (such as stereotactic destruction and deep brain stimulation) or traditional Chinese medicine physiotherapy (such as acupuncture), etc.; • Any drugs other than investigational product that may affect the progression of PD (excluding those which have been on a stable dose for PD at the time of study entry); • Serotonin reuptake inhibitors (such as fluoxetine, paroxetine, trazodone, citalopram, escitalopram, etc.); • Any unauthorized drugs (i.e., other investigational drugs that are currently tested in clinical trials and have not been approved for marketing). The investigator will determine and record the use of any emergency medication, drug name, dose, route of administration, purpose of treatment, start and end date of administration. If subjects have used any prohibited drug or non-drug therapy, it will be recorded as a protocol deviation. The investigator will decide whether to continue the follow-up or withdraw the subjects from the study based on the severity of the deviation and the subjects' condition.
Early Withdrawal from the Trial	**Criteria for Early Withdrawal from the Trial:** Subjects may voluntarily request for study withdrawal at any time, or may be withdrawn from the study at any time at the request of the investigator or the sponsor for safety, behavioral or administrative reasons. <u>Withdrawal at the subject's discretion</u> If the subjects are unwilling to continue the clinical trial, they have the right to withdraw their consent and withdraw from the study at any stage. <u>Withdrawal at the investigator's discretion</u> It refers to the condition during the study in which the investigator finds that an

	enrolled subject is no longer suitable for the participation in the study and decides that the subject should be withdrawn from the study. These conditions include, but are not limited to: • Continuing the study may affect the safety of the subject and be unfavorable to the subject at the discretion of the investigator based on the following clinical considerations: - QTcF >500 ms at rest (after resting for at least 5 minutes; the average of two measurements taken within 20 minutes) or an increase of >60 ms from baseline; - Discontinuation of study treatment due to hepatic event or hepatic function abnormal: ✧ ALT or AST>8×ULN; or ✧ ALT or AST>5×ULN for over 2 weeks; or ✧ ALT or AST>3×ULN and (TBIL>2×ULN or International Normalized Ratio [INR]>1.5); or ✧ ALT or AST>3×ULN, with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash, or eosinophilia (> 5%). - Occurrence of other intolerable AEs which requires treatment discontinuation as judged by the investigator; • Any major protocol deviations (such as subjects who fail to meet the inclusion criteria have been mistakenly included in the study) or protocol violations, which may have a significant impact on the evaluation of the efficacy and safety of the drug; • Subjects have poor compliance that affects efficacy and safety assessment; • Female subjects are pregnant; • Subjects are lost to follow-up; • Subjects have participated in other clinical trials (which is defined as having signed the ICF of any other study) during the study; • Subjects have been unblinded due to various reasons; • Other circumstances in which the subject needs to be withdrawn from the trial at the discretion of the investigator. **Handling of Subjects Early Withdrawn** Subjects who have early withdrawn from the study should complete the early withdrawal visit (if it is less than 7 days from the date of the previous visit,

<table>
<tr><td></td><td>repeated tests of the same item can be waived) within 7 days after the investigator's awareness, unless they voluntarily decide to withdraw from the study and refuse to have early withdrawal visit.

For subjects who withdraw from the study due to an AE or SAE, the investigator should take appropriate treatment measures according to the actual situation of the subjects, and closely follow up their condition until the AE or SAE is clinically recovered, stabilized, returns to screening or baseline level (if baseline level is known), the subject is lost to follow-up (e.g., no more information is available or the subject/caregiver refuses to provide any information), or dead, which will be recorded in the original data.

For all the subjects who have early withdrawn from the study, their study medical records should be retained and recorded in the electronic case report form (eCRF), and the EOT page and the reason for failure in completing the study should be filled out.</td></tr>
<tr><td>Investigational Products</td><td>In this study, the investigational products include the investigational drug (TJ0113 capsules) and the placebo.

<table>
<tr><th></th><th>TJ0113 Capsules</th><th>Placebo</th></tr>
<tr><td>Active Ingredient</td><td>TJ0113</td><td>None</td></tr>
<tr><td>Dosage Form</td><td>Capsules</td><td>Capsules</td></tr>
<tr><td>Strength</td><td>100 mg</td><td>100 mg</td></tr>
<tr><td>Package Size</td><td>30 capsules/bottle</td><td>30 capsules/bottle</td></tr>
<tr><td>Description</td><td>Opaque rich yellow hard capsules, and with pale pink solid contents</td><td>Opaque rich yellow hard capsules, and with off-white solid contents</td></tr>
<tr><td>Storage Conditions</td><td>Protected from light, keep in tight container at 2℃ - 8℃</td><td>Protected from light, keep in tight container at 2℃ - 8℃</td></tr>
<tr><td>Provided by</td><td colspan="2">Hangzhou PhecdaMed Co., Ltd.</td></tr>
<tr><td>Method of Administration</td><td colspan="2">Take orally on an empty stomach in the morning, once daily, and fast within half an hour after the administration. It can be taken together with the background medication for PD. It is recommended that subjects should take the drug at the same time ± 1 h each day as much as possible.</td></tr>
</table>
</td></tr>
<tr><td>Statistical Analyses</td><td>Estimation of Sample Size:

The sample size of this study is not determined based on the formal statistical assumptions and it is expected to include approximately 150 subjects with early-stage PD, who will be randomized in a 1:1 ratio into two cohorts (Cohort 1: 200 mg dose group; Cohort 2: 400 mg dose group). Within each cohort, the subjects will be randomized into the TJ0113 capsules group and the placebo group in a ratio of 2:1, with approximately 50 subjects receiving TJ0113 capsules and approximately 25 subjects receiving the placebo. In this study, there will be approximately 50 subjects in each of the TJ0113 capsules 200 mg group, TJ0113 capsules 400 mg group and the placebo group.</td></tr>
</table>

	General Analysis Statistical analyses of efficacy and safety will be performed using the SAS software (V9.4 or later). Unless otherwise specified, descriptive statistics for continuous variables included the number of subjects (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum (Min), and maximum (Max). Categorical variables will be summarized using descriptive statistics including number of subjects (n) and the percentage (%). Unless otherwise specified, it will be summarized by the TJ0113 capsules 200 mg group, TJ0113 capsules 400 mg group, and the placebo group. **Analysis sets** Full analysis set (FAS): including all randomized subjects who have received at least one dose of investigational product. Per-protocol set (PPS): including subjects in the FAS who have not experienced major protocol deviations that affect the primary efficacy endpoint. Safety set (SS): including all subjects who have received at least one dose of the investigational product and have undergone at least one post-dose safety assessment. Demographics and baseline characteristics will be analyzed based on FAS, the efficacy analyses will be performed based on both FAS and PPS, and the safety analyses will be performed based on SS. **Demographics and Baseline** Demographic and baseline characteristics will be summarized using descriptive statistics. Baseline is defined as the last valid measurement or assessment (if applicable) before the first dose of the study drug. **Analysis for Primary Endpoint** The primary objective of this study is to assess the efficacy of TJ0113 capsules in the treatment of patients with early-stage PD. The main concern of interest is the treatment difference in terms of the changes from baseline in the MDS-UPDRS Part III (motor examination) scores after 12 weeks of treatment between the TJ0113 capsules group and the placebo group. Definition of estimand: • Population: patients with early-stage PD • Endpoint: changes from baseline in scores of MDS-UPDRS Part III (motor examination) after 12 weeks of treatment. Evaluation time point: ≥ 12 hours from the most recent dose of anti-PD drug. • Treatment: treatments will be randomly assigned; subject will be randomized in a 1:1 ratio to two cohorts (200 mg dose group and 400 mg dose group); and within each cohort, the subjects will be randomized in a 2:1 ratio to the TJ0113 capsules group and the placebo group. • Concomitant event and management strategy: For any concomitant

	medication (excluding the investigational product and stable anti-PD medications at the time of enrollment) or treatment that could potentially impact the PD disease process, a therapeutic strategy will be employed. • Population-level summary: differences in the least square mean of the changes from baseline in MDS-UPDRS Part III (motor examination) scores after 12 weeks of treatment between the TJ0113 capsules group and the placebo group. The analysis will be performed using a mixed models for repeated measures (MMRM) with the changes from baseline in the MDS-UPDRS Part III scores after 12 weeks of treatment as the dependent variable, whether subjects have been receiving levodopa, the background medication for PD (yes vs. no) at a stable dose at baseline and the baseline MDS-UPDRS Part III score as the covariates, and the treatment group, visit, and the treatment group-by-visit interaction as the fixed effects. **Sensitivity Analysis** The sensitivity analysis of the primary endpoint will be performed using the analysis of covariance. The model will use the changes from baseline in the MDS-UPDRS Part III scores after 12 weeks of treatment as the dependent variable, whether subjects have been receiving levodopa, the background medication for PD (yes vs. no) at a stable dose at baseline, the baseline MDS-UPDRS Part III score, and the treatment group as the covariates. After the primary endpoint is imputed by using different mechanisms for imputing the missing data, the sensitivity analysis will be performed using the same method as that for the primary analysis. The detailed statistical methods will be separately described in the statistical analysis plan (SAP). **Analysis for secondary endpoints** • Efficacy analysis: the secondary efficacy endpoints will be summarized using the same statistical methods described above for primary endpoint. • Safety analysis: includes AEs and other safety-related parameters, which will be summarized by the descriptive statistics. Detailed statistical methods will be described in a separate SAP. **Analysis for Exploratory Endpoint** Exploratory endpoint (inflammatory indicators, α-synuclein, GFAP, ASMI, grip strength, 6-meter walking speed) will be analyzed using the analysis of variance or nonparametric tests, and the correlations between the parameters will be analyzed using the Spearman's or Pearson's correlation coefficients. Detailed statistical methods will be described in a separate SAP.

1.2 Schedule of Activities (SoA)

Study Flow Chart

Study Process	Screening period		Treatment period				Follow-up Period (Telephone)	Early Withdrawal Visit[20]
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**-**
Visit duration (W)	**W-4~-1**	**W-1**	**W1**	**W4**	**W8**	**W12**	**W13**	**-**
Visit duration (D)	**D-28~-2**	**D-1**	**D7**	**D28**	**D56**	**D84**	**D91**	**-**
Window period (days)	**-**	**-**	**±1**	**±2**	**±2**	**±2**	**±3**	**-**
Signing of the ICF	X							
Fasting at visit[1]	X	X	X	X	X	X		X
Review of inclusion and exclusion criteria	X	X						
Randomization		X						
Demographics[2]	X							
History of diagnosis and treatment of PD	X							
Other medical history and treatment history[3]	X							
Other personal history[4]	X							
Vital signs[5]	X	X	X	X	X	X		X
Physical examination[6]	X	X	X	X	X	X		X
12-lead ECG[7]	X	X[a]	X	X	X	X		X
Hematology[8]	X	X[a]	X	X	X	X		X
Blood chemistry[9]	X	X[a]	X	X	X	X		X
Urinalysis[10]	X	X[a]	X	X	X	X		X
Weight measurement and Ccr calculation[11]	X	X[a]	X			X		X
Coagulation function[12]	X	X[a]	X	X	X	X		X
Screening for infectious diseases[13]	X							
B-ultrasound[14]	X							
Tumor marker detection[15]	X							
Serum pregnancy test (only for women of childbearing potential)	X							
Urine pregnancy test (only for women of childbearing potential)		X	X	X	X	X		X

Study Process	**Screening period**		**Treatment period**				**Follow-up Period (Telephone)**	**Early Withdrawal Visit[20]**
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**-**
Visit duration (W)	**W-4~-1**	**W-1**	**W1**	**W4**	**W8**	**W12**	**W13**	**-**
Visit duration (D)	**D-28~-2**	**D-1**	**D7**	**D28**	**D56**	**D84**	**D91**	**-**
Window period (days)	**-**	**-**	**±1**	**±2**	**±2**	**±2**	**±3**	**-**
Test of serum follicle stimulating hormone (only for women with menopause within 24 months or uncertain menopausal status)	X							
Collection of blood samples for exploratory analysis (inflammatory indicators) [16]		X		X	X	X		X
Collection of blood samples for exploratory analysis (α-synuclein and GFAP)[17]		X				X		X
Collection of blood samples for exploratory analysis (genomic resequencing)		X[b]				X		X
Exploratory skeletal muscle mass and function assessment (ASMI, grip strength and 6-meter walking speed test)[18]		X				X		X
Assessment using modified Hoehn and Yahr Scale	X							
MDS-UPDRS score[19]	X	X	X	X	X	X		X
Dispensing of investigational product		X	X	X	X			
Return of investigational product				X	X	X		X
Administration of investigational product			The first dose will be administered on D1 and the last dose on D84. Take orally on an empty stomach in the morning, once daily. Fast for half an hour after oral administration. At site visits, it should be administered together with the background medication for PD. It is recommended that subjects should take the drug at the same time ± 1 h each day as much as possible.					

Study Process	Screening period		Treatment period				Follow-up Period (Telephone)	Early Withdrawal Visit[20]
Visit No.	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**-**
Visit duration (W)	**W-4~-1**	**W-1**	**W1**	**W4**	**W8**	**W12**	**W13**	**-**
Visit duration (D)	**D-28~-2**	**D-1**	**D7**	**D28**	**D56**	**D84**	**D91**	**-**
Window period (days)	**-**	**-**	**±1**	**±2**	**±2**	**±2**	**±3**	**-**
Dispensing of diary cards/instructions for completion		X	X	X	X			
Return of diary cards			X	X	X	X		X
Concomitant Medication	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X

Note:

a. If hematology, blood chemistry, coagulation function test, urinalysis, 12-lead ECG examinations, weight measurement and calculations of creatinine clearance (Ccr) have been performed within 7 days (exclusive) before D-1, these tests are not required to be repeated on D-1; otherwise, they are required to be re-tested on D-1 and the eligibility for the study entry should be confirmed according to the test results.

b. Collection of blood samples for exploratory analysis of genomic resequencing: each subject will be collected once at V2 (if not collected at V2, it is allowed to be supplemented at V6 or early withdrawal visit).

c. If screen failure is caused due to abnormal results during the screening process, and if the investigator judges that there is a clear justification for retesting, and the tests can be repeated within the time window once, but the reason for repeating the test should be recorded. Subjects with screening failure are only allowed for re-screening once during the enrollment stage of this study. Additional medications are not allowed to correct the abnormal values (e.g., hepatoprotective drugs used to address hepatic function abnormal) prior to the re-screening. Parameters that are allowed for retesting include: blood pressure, ECG, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (TBIL).

d. Follow-up period (V7) collects AE and concomitant medication information through telephone follow-up.

1. Subjects must be fasted before each visit (fast for at least 10 hours overnight without depriving of water). It is recommended that fasting blood samples be collected between 7:00 a.m. and 10:00 a.m., and the specific collection time point is subject to the implementation of each study site. The investigational product or background medication for PD should not be administered prior to blood collection. If the subject has not fasted before the visit, an additional fasting collection should be scheduled.

   Parameters to be tested under fasted conditions include: hematology, blood chemistry, B-ultrasound, and exploratory inflammatory indicators. There is no fasting requirement for other parameters.

2. Demographics: date of birth, age, gender, ethnicity, height, weight, body mass index (BIM), etc.;
3. Other medical history and treatment history: including other past and current medical history (excluding PD), treatment history, surgical history and surgical plan, etc.
4. Other personal history: including but not limited to family history, allergy history, alcohol consumption history, substance abuse history, blood transfusion history, and childbearing plan, etc.
5. Vital signs: including respiration, pulse, body temperature, and blood pressure. Among them, blood pressure measurement on the day of V1 and before randomization at V2 should be measured after the subject has rested in a supine position for at least 5 min. After the supine blood pressure measurement is completed, let the patient stand upright and complete the measurement of standing blood pressure within 3 min in a standing resting state; for other vital signs measurements, it can be measured with the subject in a sitting position after having rested for at least 5 min.
6. Physical examination: including skin and mucous membranes, lymph nodes, head, neck, chest, abdomen, spine and limbs, nervous system and mental state.
7. 12-lead ECG: it should be performed with the subject in a supine position after having rested for at least 5 min. Two measurements will be taken within 20 minutes, and the average value is calculated and rounded to the nearest integer. The parameters include: heart rate, PR interval, QRS complex duration, uncorrected QT interval, and Fridericia-corrected QTc (QTcF).
8. Hematology: white blood cell count, absolute neutrophil count, neutrophil percentage, absolute lymphocyte count, lymphocyte percentage, absolute monocyte count, monocyte percentage, absolute eosinophil count, eosinophil percentage, absolute basophil count, basophil percentage, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin content, mean corpuscular hemoglobin concentration, red blood cell distribution width, platelet count, mean platelet volume, platelet hematocrit, and platelet distribution width.
9. Blood chemistry: fasting blood glucose, bile acid, total protein, albumin, globulin, albumin/globulin ratio, total bilirubin (TBIL), direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, creatine kinase, creatine kinase isoenzyme MB, urea/blood urea nitrogen, blood uric acid, creatinine, potassium, sodium, chloride, calcium, magnesium, inorganic phosphorus, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.
10. Urinalysis: urine glucose, urine bilirubin, urine ketone body, urine pH, urine protein, urobilinogen, urine nitrite, urinary occult blood, urine white blood cells, urine red blood cells, urinary sediment microscopic examination (red blood cells, white blood cells) and urine specific gravity.
11. Ccr is calculated based on weight measurement results and creatinine levels in blood chemistry tests, and the calculation formula is shown in Appendix II. If weight has been measured when collecting demographics at V1, it is not necessary to repeat the weight measurement during that visit.
12. Coagulation function test: including prothrombin time, activated partial thromboplastin time,

thrombin time, international normalized ratio and fibrinogen.

13. Screening for infectious diseases: including hepatitis B five-item test (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody, hepatitis B e antigen, hepatitis B e antibody, hepatitis B core antibody), hepatitis C virus (HCV) antibody test, human immunodeficiency virus (HIV) antibody test and treponema pallidum antibody test.
14. B-ultrasound: detection sites include liver, gallbladder, pancreas, spleen, and kidney.
15. Tumor marker detection: including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), carbohydrate antigen 125 (CA125) (only for females), total prostate specific antigen (T-PSA) (only for males), free prostate specific antigen (F-PSA) (only for males), carbohydrate antigen 153 (CA153), squamous cell carcinoma antigen (SCC), ferritin.
16. Inflammatory indicators in the exploratory analysis include interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17A, interferon (IFN)-α, IFN-γ and tumor necrosis factor (TNF)-α; the specific test indicators are subject to the actual implementation of each center.
17. Blood samples for exploratory analysis of α-synuclein and glial fibrillary acidic protein (GFAP) indicators need to be sent to the central laboratory for testing after collection. All other test samples in this trial will be tested in local laboratories.
18. Exploratory skeletal muscle mass and function assessment: including appendicular skeletal muscle mass index (ASMI), muscle strength (grip strength) and 6-meter walking speed test (specific test indicators are subject to the actual operation of each center). Among them, ASMI is detected and calculated by dual-energy X-ray absorptiometry (DXA), and the calculation formula is ASMI = appendicular muscle mass (kg) / height^2 (m^2). If the V2 visit is not assessed, then the V6 and early withdrawal visits should also not be assessed.
19. MDS-UPDRS includes parts I, II, III, and IV. Throughout the study, each subject should have a fixed rater to evaluate his/her score using MDS-UPDRS.
    - For subjects who have received the anti-PD drug at a stable dose for at least 4 weeks prior to study entry, the MDS-UPDRS assessment time points and corresponding assessment parts are as follows:

Visit	MDS-UPDRS assessment part	Assessment time points
V1	Part I	No special requirements
	Part III	Before administration of background medication for PD (≥ 12 hours from the most recent dose of the background medication for PD)
V2, Early Withdrawal Visit (if applicable)	Part III	Before administration of background medication for PD (≥ 12 hours from the most recent dose of the background medication for PD)
		After administration of background medication for PD (to be performed at 2 ± 1 hours after the administration of

		background medication for PD at this visit)
	Parts I, II, and IV	No special requirements
V3~V6	Part III	Before administration of the investigational product and the background medication for PD (≥ 12 hours from the most recent administration of background medication for PD and the investigational product)
		After administration of the investigational product and the background medication for PD (to be performed at 2 ± 1 hours after the administration of the background medication for PD and the investigational product at this visit)
	Parts I, II, and IV	No special requirements

- For subjects who have not received the anti-PD drug at study entry, the MDS-UPDRS assessment time points and corresponding assessment parts are as follows:

Visit	MDS-UPDRS assessment part	Assessment time points
V1	Part I	No special requirements
	Part III	No special requirements
V2	Part III	No special requirements
	Parts I, II, and IV	No special requirements
V3~V6	Part III	Before administration of the investigational product (≥ 12 hours from the most recent administration of the investigational product)
		After administration of the investigational product (to be performed at 2 ± 1 hours after the administration of the investigational product at this visit)
	Parts I, II, and IV	No special requirements
Early Withdrawal Visit (if applicable)	Part III	≥ 12 hours from the most recent administration of the investigational product
	Parts I, II, and IV	No special requirements

20. Subjects who have early withdrawn from the study should complete the early withdrawal visit within 7 days after the investigator's awareness (if it is less than 7 days from the date of the previous visit, repeated tests of the same item can be waived), excluding subjects who have early withdrawn from the study due to withdrawal of consent or are lost to the follow-up.

2 Background Information

2.1 Disease Introduction

Parkinson's disease (PD) is a degenerative neurological disease that occurs in middle-aged and elderly individuals with insidious onset and slow progress. Its characteristic pathological changes are progressive degeneration and decrease of dopaminergic (DA) neurons in substantia nigra and the formation of Lewy bodies, which leads to the decrease of dopamine transmitters in the striatum area, resulting in characteristic clinical symptoms such as bradykinesia, resting tremor, myotonia and postural balance disorder, [1] accompanied by various non-motor symptoms, such as olfactory dysfunction, constipation and sleep disorder [2] and even dementia and depression. The prevalence rate of PD in individuals over 65 years old in China is 1,700/100,000, which is similar to that in western countries.[3] It is estimated that there are nearly 200,000 new cases of PD patients in China every year; and by 2030, the number of PD patients in China will reach 5 million.[4] With the progression of the disease, the motor and non-motor symptoms of PD will gradually aggravate, which will damage the daily activities of patients themselves on the one hand, and on the other hand, it will also bring huge social and medical burdens.

Complete and comprehensive treatments should be taken to address the motor symptoms and non-motor symptoms of PD, including drug therapy, surgical treatment, treatment with botulinum toxin, exercise therapy, psychological intervention, care and nursing, etc. Drug therapy is the first choice and the main treatment approach in the whole treatment process. At present, commonly used PD drugs available at home and abroad include levodopa, dopamine receptor agonists, anticholinergic drugs, amantadine, monoamine oxidase type B inhibitors and catechol-O-methyltransferase inhibitors, but none of these drugs can delay or prevent the development of the disease. In addition, long-term use of these drugs may reduce the efficacy of the drugs and increase the risk of complications.[5] Moreover, it is possible that these drugs cannot achieve the dose of monotherapy required to control the symptoms due to the corresponding treatment-limiting side effects. However, anti-PD drugs especially levodopa and high-dose dopamine receptor agonists should not be discontinued abruptly, so as to avoid the occurrence of malignant withdrawal syndrome.[6] Therefore, discovering new anti-PD treatment drugs will help to break through the current bottleneck in the medical practice and provide more new treatment options for PD patients.

Mitochondrial dysfunction and oxidative stress are the main pathogenesis of PD, and have become the important therapeutic targets for PD in recent years. There are a large number of

enlarged and edematous mitochondria in neurons of animal models of PD, which indicates that the pathogenesis of PD is related to abnormal function and failure in clearance of mitochondria. These abnormally accumulated mitochondria can also cause oxidative stress and increase in toxic burdens, which in turn leads to the death of dopaminergic neurons and ultimately leads to the occurrence of PD.[7, 8] In addition, with the increase in age, iron slowly accumulates in the microglia of brain neurons, and microglia can quickly accumulate and release iron. High iron content in cells may cause oxidative stress, thus changing the mitochondrial autophagy function, and the expression of Parkin protein can reverse this effect. [9] From the perspective of PD patients themselves, the mitochondria in the central nervous system of PD patients undergo morphological changes and functional loss, and the mitochondrial autophagy function of their substantia nigra and amygdala is also defective. [10] Studies have demonstrated that neurons of PD patients with Parkin mutation showed mitochondrial defects and metabolism disorder of mitochondrial deoxyribonucleic acid (mtDNA), and Parkin can also protect midbrain neurons from neuroinflammation and degeneration.[11] Therefore, targeting PINK1/Parkin-mediated mitochondrial autophagy has emerged as a promising therapeutic approach to treat PD.[12]

2.2 Introduction to TJ0113 Capsules

TJ0113 capsules is an innovative mitochondrial autophagy inducer developed by Hangzhou PhecdaMed Co., Ltd., which is enriched onto the mitochondrial outer membraneby interacting with the myeloid cell leukemia 1 (Mcl-1) protein on the mitochondrial outer membrane. Under the circumstance of mitochondrial damage, high concentration of reactive oxygen species (ROS) will accumulate around mitochondria. TJ0113 can bind to the ROS and induces the elevation of Parkin transcriptional level, mediates the enrichment of Parkin to the damaged mitochondria, initiates mitochondrial autophagy, selectively clears damaged mitochondria, and does not affect normal mitochondria, thus restoring cellular homeostasis. The proposed indication of TJ0113 capsules is PD.

2.3 Summary of Non-clinical Studies

Pharmacological, pharmacokinetic (PK) and toxicological studies have been conducted with TJ0113. The selective induction of mitochondrial autophagy by TJ0113 has been demonstrated in a series of pharmacological studies. The therapeutic potential of TJ0113 for PD has been observed in an in vivo model of PD. The non-clinical studies of TJ0113 are sufficient to support the conduct of clinical trials for PD.

This section will summarize the non-clinical studies of TJ0113, and detailed study results are

provided in the Investigator's Brochure.

2.3.1 Non-clinical Pharmacology

The results of the in vitro pharmacology studies conducted with TJ0113 are summarized below:

- In the in vitro surface plasmon resonance assay, TJ0113 could specifically bind to Mcl-1 protein with an affinity constant of 1.12 E-06M, representing the weak binding.
- TJ0113 selectively induced autophagy in damaged mitochondria in HEK293T cells in vitro. TJ0113 at different concentrations (0 μM, 2.5 μM, 5 μM, 10 μM) could selectively induce autophagy in damaged mitochondria with good dose relationship and selectivity.
- In vitro immunoblot assay, TJ01-013 demonstrated strong selectivity for inducing mitochondrial autophagy.
- In the microplate imaging assay, TJ0113 had no impact on mitochondrial membrane potential of HEK293T cells, indicating that TJ0113 did not damage mitochondria or cause changes in proton concentrations inside and outside mitochondria.
- The results of in vitro cell transfection assays showed that TJ0113 alone did not cause Parkin-dependent mitochondrial autophagy in HEK293T cells, but TJ0113 could activate Parkin when mitochondria were damaged by carbonylcyanide-3-chlorophenylhydrazone (CCCP) to induce mitochondrial autophagy and eliminate damaged mitochondria.
- In the in vitro fluorescence quantitative polymerase chain reaction (PCR) assay, TJ0113 could increase the transcriptional level of mitochondrial autophagy genes in the case of mitochondrial damage caused by CCCP, thereby inducing mitochondrial autophagy.

The results of the in vivo pharmacology studies conducted with TJ0113 are summarized below:

- The pharmacodynamic study of TJ0113 (10 mg/kg, 30 mg/kg, 60 mg/kg) on 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) (Day 1-2:10 mg/kg, Day 3-4:15 mg/kg, Day 5-6:20 mg/kg, Day 7-20:25 mg/kg) induced mouse PD model: TJ0113 inhibited MPTP-induced behavioral damage in a dose-dependent manner,

slowed down the dopamine neuronal loss in substantia nigra (SN) brain region, improved nerve ending injury of dopaminergic neurons in striatum (Str) brain region, reduced inflammatory response in the SN and Str brain region, and increased the content of DA neurotransmitters in the Str brain region. In addition, electron microscopy results suggest that TJ0113 could improve the reduction of number and structural abnormalities of mitochondria in SN brain regions.

- The pharmacodynamic study of TJ0113 (5 mg/kg, 15 mg/kg, 30 mg/kg) on 6-Hydroxydopamine (6-OHDA)-induced rat PD model: TJ0113 inhibited behavioral damage induced by 6-OHDA in a dose-dependent manner, slowed down the dopamine neuronal loss in SN brain region, improved nerve ending injury of dopaminergic neurons in Str brain region, reduced inflammatory response in SN and Str brain regions, reduced the content of inflammatory factors in cerebrospinal fluid, and increased the content of DA neurotransmitters in Str brain region.

The results of the secondary pharmacodynamic studies conducted with TJ0113 are summarized below:

- Radioligand binding and enzymatic study: TJ0113 (10 μM) inhibited the activity of cyclooxygenase (COX)-2 at an inhibition rate of 89%. No COX-2-related toxicity manifestations were observed in safety pharmacology studies or toxicology studies.
- The off-target effect of compound TJ0113 on drug-dependent related targets in vitro was evaluated in vitro. The study results showed that the test article TJ0113 had no obvious agonistic or inhibitory effect on the 20 targets of G-protein-coupled receptor (GPCR) and ion channel at 10 μM, and the agonistic or inhibitory rates were all less than 50%.

The results of the safety pharmacology studies conducted with TJ0113 are summarized below:

- The safety of TJ0113 on the central nervous system was evaluated in SD rats. The results showed that following the single oral gavage administration of TJ0113 to SD rats at doses of 50, 100, 200 mg/kg, TJ0113 when dosed at 200 mg/kg had no significant impact on the central nervous system of the animals.
- The safety of TJ0113 on the cardiovascular system and respiratory system was evaluated in Beagle dogs. The results showed that single oral gavage administration of TJ0113 to Beagle dogs at doses of 5, 15, and 30 mg/kg had no significant impact on the cardiovascular system, respiratory system, or body temperature of the animals.

2.3.2 Non-clinical Pharmacokinetics

2.3.2.1 Absorption

In SD rats, following a single oral gavage and intravenous administration of TJ0113, PK profiles including rapid absorption, low apparent volume of distribution, and moderate elimination rate were noted. Following a single oral gavage administration of 10, 30, and 90 mg/kg in SD rats, the plasma exposure of unchanged TJ0113 increased with the increasing dose in a less-than dose proportional manner. Following the oral gavage administration at 30 mg/kg once daily for 7 consecutive days to rats, steady state was reached on Day 4. Compared with the oral gavage administration on Day 1, the maximum concentration (C_{max}), the area under the plasma concentration-time curve from time 0 to 24 h post-dose (AUC_{0-24h}) and the time to maximum concentration (T_{max}) were basically unchanged on Day 7, and the half-life ($t_{1/2}$) showed a decreasing trend, suggesting that there was no obvious accumulation following the oral gavage administration once daily for 7 consecutive days, but there was a trend of rapid elimination. Following a single intravenous dose, the steady-state volume of distribution (V_{ss}) was 184 mL/kg, suggesting a relatively lower tissue distribution of TJ0113. Compared to intravenous injection of TJ0113 at a same dose, the absolute bioavailability of unchanged TJ0113 was 9.55% following a single oral gavage administration of the drug at 10 mg/kg to SD rats.

In Beagle dogs, following the single oral gavage and intravenous administration of TJ0113, the unchanged drug showed a PK profile of rapid absorption, lower apparent volume of distribution, and rapid elimination. Following the single oral gavage administration of 3, 10 and 30 mg/kg in Beagle dogs, the plasma exposure of unchanged TJ0113 increased with increasing dose in an approximately dose-proportional manner. Following the oral gavage administration at 10 mg/kg once daily for 7 consecutive days in dogs, steady state was reached on Day 4. Compared with the oral gavage administration on Day 1, the C_{max}, AUC_{0-24h}, T_{max}, and $t_{1/2}$ remained substantially unchanged on Day 7, suggesting that there was no significant accumulation following the oral gavage administration once daily for 7 consecutive days. Following a single intravenous administration in Beagle dogs, the V_{ss} was 195 mL/kg, suggesting a low degree of tissue distribution of TJ0113. Compared to intravenous injection of TJ0113 at a same dose, the absolute bioavailability of unchanged TJ0113 was 9.47% following a single oral gavage administration of the drug at 3 mg/kg to Beagle dogs.

In the in vitro study with Caco-2 cell model, the apparent permeability coefficient of TJ0113

in the uptake direction of Caco-2 model were <0.116×10^{-6}, 0.00934×10^{-6}, and 0.00951×10^{-6} $cm\cdot s^{-1}$ at the concentrations of 1, 10, and 100 μM, respectively, all of which were lower than the accompanying fluorescein (0.348×10^{-6} $cm\cdot s^{-1}$), suggesting that TJ0113 had very low intestinal permeability. The efflux ratios of TJ0113 were > 2.84, 26.7, and 15.1 at the concentrations of 1, 10, and 100 μM, respectively, all of which were greater than 2. After the addition of P-glycoprotein (P-gp) inhibitor quinidine, the efflux ratio was 8.66. Compared with the results at the absence of the inhibitor, drug efflux could be inhibited to some extent, but the efflux ratio was still significantly greater than 2, suggesting that TJ0113 may be a substrate of other efflux transporters besides being a weak substrate of efflux transporter P-gp.

2.3.2.2 Distribution

In the plasma protein binding study of TJ0113, the plasma protein binding rate of TJ0113 in ICR mice, SD rats, Beagle dogs, cynomolgus monkeys and humans was separately determined to evaluate whether there was a concentration dependence as well as to compare the inter-species differences in plasma protein binding rates. The results showed that, within the concentration range of 0.5-15 μg/mL, the plasma protein binding rate of TJ0113 didn't demonstrate significant concentration dependence in the five species. Based on the different plasma concentrations of all the species, the average binding rates calculated were 99.2 ± 0.110% in mice, 99.9 ± 0.00188% in rats, 98.0 ± 0.0935% in dogs, 99.6 ± 0.0395% in monkeys, and 99.6 ± 0.0223% in humans, respectively.

In the whole blood-to-plasma concentration partition ratio study of TJ0113, the whole blood-to-plasma partition coefficients of TJ0113 in CD-1 mice, SD rats, Beagle dogs, cynomolgus monkeys and healthy humans were determined, and the inter-species differences were compared. The results showed that within the concentration range of 0.4-40 μg/mL, the mean whole blood-to-plasma partition coefficients of all the species at different concentrations were 0.575 (mouse), 0.678 (rat), 0.490 (dog), 0.636 (monkey), and 0.554 (human), respectively, suggesting that within the concentration range of 0.4-40 μg/mL, TJ0113 had a low distribution in the whole blood of mice, rats, dogs, monkeys and humans, and there was no significant concentration dependence or species differences.

According to the tissue distribution study of TJ0113 following the oral gavage administration in rats, following a single oral administration of TJ0113 at 30 mg/kg, the gastric and intestinal concentrations were the highest at 0.167 h post-dose; the Tmax of distribution in the brain, fat, heart, muscle, liver, spleen, kidneys, lungs, uterus and ovary tissues was basically the same as that in the plasma, reaching the peak distribution at 1 h, and that in the testicular tissue lagged

behind the Tmax in the plasma. At 12 h post-dose, the content of TJ0113 in tissues all decreased to less than 1/10 of Cmax. The distribution of TJ0113 in all the other tissues except the gastric tissue was all less than that in the plasma, which was consistent with the low apparent volume of distribution presented in the kinetics studies in the plasma. According to the $AUC_{0\text{-}12h}$ data of TJ0113 in all the tissues, the exposure in the tissues was ranked in the following order: stomach (8.60 times of that in plasma) > plasma > liver, intestine, kidney (30% to 50% of that in plasma) > ovary, lung, uterus, heart (10% to 20% of that in plasma) > testis, spleen, muscle, fat and brain (1% to 10% of that in plasma).

2.3.2.3 Metabolism

In addition to the unchanged TJ0113, 2, 4, 2, 4 and 3 metabolites were identified in the hepatocyte incubation systems of mice, rats, dogs, monkeys and humans, respectively. The metabolic pathways included dehydration, dealkylation, dehydro-oxidation, hydroxylation, sulphating, glutamate binding and the combination of different metabolic pathways. The main metabolites in the hepatocytes of all the species were unchanged TJ0113 and M4 (dealkylation + hydroxylation + dehydro-oxidation).

In mouse, rat, dog, monkey and human liver microsome incubation systems, 3, 3, 2, 2 and 2 metabolites were identified, respectively, in addition to the unchanged drug TJ0113. The major metabolic pathways were mediated by glucuronic acid conjugation, desulfoxidation + glucuronic acid conjugation, and desulfoxidation + monooxidation + glucuronic acid conjugation. The main metabolites in the liver microsomes of humans, monkeys and dogs were M23 (desulfoxidation + glucuronic acid conjugation) and M33 (desulfoxidation+ monooxidation + glucuronic acid conjugation), and none of them responded to the UV except for the unchanged drug; The main metabolites of rat and mouse liver microsomes are M26 (glucuronidation), M23 and M33, and none of them responded to the UV except for the unchanged drug.

After TJ0113 (1 μM) was incubated in hepatocytes of all the species for 180 min, the residual substrate rates were 112% (monkey), 111% (dog), 98.3% (rat), 66.1% (human), and 44.0% (mouse), respectively. TJ0113 had no significant metabolic elimination in the hepatocytes of rats, monkeys and dogs. Metabolic elimination occurred in mouse and human hepatocytes to some extents, with the elimination half-lives of 151 and 252 min, respectively.

Based on the in vitro study of human cytochrome P450 (CYP450) enzyme phenotyping, combined with the results of the study of liver microsome binding to chemical inhibitors and recombinant monomeric enzymes, it showed that TJ0113 was basically not metabolized by

CYP450 enzymes, indicating that human CYP450 enzymes are not the main enzymes involved in the metabolic transformation of TJ0113.

TJ0113 and metabolite M23 (dealkylation + glucuronidation) were the main exposure forms in the circulatory system following the oral gavage administration in rats, and unchanged TJ0113 was the main exposure substance in the circulatory system following the oral gavage administration in dogs. In addition to the unchanged drug, a total of 7 metabolites were detected in the urine of rats following a single oral gavage administration (30 mg/kg). Among them, the unchanged drug and metabolites M12 (dehydroxylation + glucuronic acid conjugation), M15 (dehydroxylation), M26 (glucuronic acid conjugation), and M29 (glucose conjugation) were the main forms of excretion, with the cumulative excretion fractions of 0.552%, 0.500%, 0.752%, 0.638%, and 0.385%, respectively. In addition to the unchanged drug, a total of 12 metabolites were found in rat feces, among which the unchanged TJ0113, M15 (dehydroxylation) and M4 (dealkylation + hydroxylation + dehydro-oxidation) were the main forms of excretion, and the cumulative excretion fractions were 8.82%, 13.3% and 8.61%, respectively. In addition to the unchanged drug, a total of 14 metabolites were found in rat bile, among which the unchanged TJ0113 and M4 (dealkylation + hydroxylation + dehydro-oxidation) were the main forms of excretion, and the cumulative excretion fractions were 2.10% and 1.17%, respectively. The total amount of TJ0113 excreted through urine and feces in the unchanged form and all the metabolite forms was 3.14% and 35.8% of the administered dose, respectively, and the mass balance coefficient was 38.94%. TJ0113 was mainly excreted in the urine through the kidneys in the unchanged form and metabolites M12 (dehydroxylation + glucuronic acid conjugation), M15 (dehydroxylation), M26 (glucuronic acid conjugation), and M29 (glucose conjugation); It was excreted in the feces through the intestines in unchanged form and in the form of metabolites M15 (dehydroxylation) and M4 (dealkylation + hydroxylation + dehydro-oxidation). Based on the current result set and combined with the results of excretion studies, it is suggested that TJ0113 is primarily eliminated in metabolic form, and the main excretion route is the intestinal tract.

In the metabolite profiling study of the first and last plasma samples collected following the repeated oral gavage administration of TJ0113 in SD rats and Beagle dogs, the first dose plasma exposure profile analysis showed that after repeated oral gavage administration of 200 mg/kg TJ0113 to SD rats, in addition to the unchanged drug, 17 metabolites were identified in the plasma on D1. The unchanged drug (female 35.5%/male 38.7%), metabolite M6 (dehydrogenation: female 12.1%/male 16.8%) and metabolite M15 (deoxygenation: female

23.0%/male 11.5%) were the main exposure forms, and the remaining metabolites accounted for 0.0245% to 9.21% of the total related substances. Following repeated oral gavage administration of 100 mg/kg TJ0113 to Beagle dogs, in addition to the unchanged drug, a total of 16 metabolites were identified in the plasma on D1. The unchanged drug (female 35.0%/male 31.6%), metabolite M6 (dehydrogenation: female 19.4%/male 17.6%), metabolite M5 (desulfoxidation + sulphation: female 10.1%/male 12.9%) and metabolite M37 (deoxidation + decarbonization: female 10.7%/male 12.6%) were the major exposure forms in plasma of Beagle dogs. The remaining metabolites accounted for 0.222% to 7.66% of total related substances. According to analysis results of plasma exposure profile after the last dose: In addition to the unchanged drug, 21 metabolites were identified in plasma on D91 following repeated intragastric administration of 200 mg/kg TJ0113 to SD rats. The unchanged drug (female 21.7%/male 24.9%), metabolite M6 (dehydrogenation: female 7.71%/male 10.9%), metabolite M39 (S-dealkylation + oxidation: female 13.2%/male 11.8%) and metabolite M15 (deoxygenation: female 22.5%/male 19.6%) were the main exposure forms, and the remaining metabolites accounted for 0.0197% to 7.71% of the total related substances. Following the repeated oral gavage administration of 100 mg/kg TJ0113 to Beagle dogs, in addition to the unchanged drug, a total of 20 metabolites were identified in the plasma on D91. The unchanged drug (female 28.4%/male 31.1%), metabolite M6 (dehydrogenation: female 15.8%/male 17.2%), metabolite M5 (desulfoxidation + sulphation: female 12.3%/male 11.0%) and metabolite M37 (deoxidation + decarbonization: female 11.6%/male 11.0%) were the major exposure forms in plasma of Beagle dogs. The remaining metabolites accounted for 0.0467% to 6.62% of total related substances.

2.3.2.4 Excretion

Following a single oral gavage dose of TJ0113 30 mg/kg in SD rats, the proportions of TJ0113 excreted as unchanged in feces (8.85%) > bile (2.11%) > urine (0.552%), and the total fraction of TJ0113 excreted as unchanged in urine and feces was 9.40%, suggesting that TJ0113 was eliminated in vivo mainly in the form of metabolism.

2.3.2.5 Drug Interactions

TJ0113 may cause CYP induction in vitro and, therefore, may reduce exposure levels to drugs metabolized by CYP enzymes. The in vitro induction of human CYP450 enzymes by TJ0113 showed that within the concentration range of 0.2-10 μM, TJ0113 did not significantly induce the expression of CYP1A2, CYP2B6, and CYP3A4 messenger ribonucleic acid (mRNA) in human hepatocytes from the two donors of HUB and BEI; TJ0113 showed a concentration-

dependent induction effect on the expression of CYP1A2, CYP2B6, and CYP3A4 mRNA in human hepatocytes from Lhuf15906 donors within the concentration range of 1-10 μM.

The in vitro inhibitory effect study of TJ0113 on human CYP450 enzymes showed that following the administration of TJ0113, the half inhibitory concentrations (IC_{50}) for CYP1A2, CYP2D6 and CYP3A4 (midazolam and testosterone as substrates) were greater than 50 μM, and the IC_{50} for CYP2B6, CYP2C8, CYP2C9 and CYP2C19 were 23.1 μM, 24.7 μM, 10.8 μM and 38.3 μM, respectively, and there was no significant inhibitory effect on all the CYP enzyme isoforms.

TJ0113 had very low intestinal permeability and may be a substrate for other efflux transporters in addition to being a weak substrate for the efflux transporter P-gp. In addition, MDCK-OAT1 and HEK293-URAT1 cell lines were used to study the inhibitory effect of TJ0113 on organic anion transporter 1 (OAT1) and urate transporter 1 (URAT1), and the transport effect of transporters OAT1 and URAT1 on TJ0113. The study results showed that TJ0113 inhibited transporter OAT1 significantly, with an IC_{50} of 4.32 μM; there was no significant inhibitory effect on transporter URAT1, with an IC_{50} greater than 30 μM. TJ0113 was not a substrate of transporter OAT1, and it might be a substrate of transporter URAT1.

2.3.3 Toxicology

2.3.3.1 Single-dose Toxicity Studies

In SD rats, following the single oral administration of 500, 1,000, and 1,500 mg/kg of TJ0113, no abnormalities were found in the cage-side observation in each group on the day of administration (D0). During the observation period, animal No. 28 (F) developed piloerection symptoms from D1-D2 of the observation period, and recovered on D3. No abnormality was found in the cage-side observations of other animals. During the study period, the body weight gain of animals in each dose group was normal. At the end of the observation period, all surviving animals were subjected to gross dissection, and there were no abnormalities in the volume, color and texture of heart, liver, kidney, spleen, lung, gastrointestinal tract and other organs.

Following the single oral administration of 500, 1,000, and 1,500 mg/kg TJ0113 to Beagle dogs, all the animals in the dose groups survived to the end of the study. During the study, no significant abnormality was observed in the animals of the vehicle control group. Following the administration on D0, except the female animals in the 500 mg/kg dose group, all other animals showed vomiting symptoms, and individual animals had loose stools. From D1 to before dissection, loose stools and vomiting were occasionally observed in male animals in

the 1,000 mg/kg and 1,500 mg/kg dose groups, while no obvious abnormalities were observed in other animals. During the study, there was no obvious abnormality in the body weight or body temperature of all animals in the dose group. On Day 14 after administration, there were no obvious abnormalities in the ECG parameters such as heart rate, PR interval, QRS interval and QT interval in all animals in the dose groups. At the end of the observation period, there were no obvious abnormalities in hematology, serum chemistry, and coagulation parameters of all animals in the dose groups. At the end of the observation period, all animals were subjected to gross dissection, and no obvious abnormalities were found in the heart, liver, kidney, spleen, lung, gastrointestinal tract or the administration site.

The maximum tolerated dose of TJ0113 was greater than 1,500 mg/kg following the single oral gavage administration to SD rats and greater than 1,500 mg/kg following the single oral administration to Beagle dogs, and TJ0113 was generally well tolerated.

2.3.3.2 Repeat-dose Toxicity Studies

TJ0113 was given to SD rats via intragastric route for 4 consecutive weeks at doses of 30, 100, and 300 mg/kg/day, respectively. The results showed that there were changes in hematology and serum chemistry parameters in each dose group of TJ0113, but these changes were not considered toxicologically significant, and completely reversible at the end of the recovery period. The renal coefficient of female rats in the 300 mg/kg/day dose group was higher than that in the vehicle control group, and it was reversible at the end of the recovery period. Histopathological results showed that test article-related pathological changes were seen in the kidneys of male rats, mainly manifested as basophilic lesions of renal tubules, which were not completely reversible at the end of the recovery period. No obvious test article-related pathological changes were observed in the kidneys of female rats in each dose group. Following the repeated oral gavage administration of TJ0113, exposure in SD rats increased with increasing dose. After the last dose, the exposure in female and male SD rats in the 30 and 100 mg/kg/day dose groups was significantly lower than that at the first dose. There was no gender difference in the exposure of each dose group in SD rats. The NOAEL following the oral gavage administration of TJ0113 to SD rats for 4 consecutive weeks was 100 mg/kg. At this dose, the last C_{max} was 11,906 ng/mL (male) and 11,144 ng/mL (female), respectively and the area under the plasma concentration-time curve from time zero to time t (AUC_{0-t}) was 66,728 h*ng/mL (male) and 43,818 h*ng/mL (female), respectively.

Following the repeated oral administration of TJ0113 to Beagle dogs at doses of 10, 30, and 100 mg/kg/day (at a dose volume of 5 mL/kg) once daily for 28 consecutive days followed by

a 28-day recovery period. There were no test article-related toxicity changes in general physiological parameter, clinical pathology, and histopathological examinations. The NOAEL following the 4-week repeat doses of TJ0113 to Beagle dogs was 100 mg/kg. On Day 28, the AUC_{0-t} was 42,847 ± 17,551 h*ng/mL for males and 51,542 ± 14,505 h*ng/mL for females, respectively.

No test article-related abnormal changes in each parameter were observed following intragastric administration of TJ0113 at 30, 80, and 200 mg/kg/day to SD rats for 13 consecutive weeks. TJ0113 was given to SD rats via intragastric route for 13 consecutive weeks. The NOAEL in SD rats was 200 mg/kg. At this dose, the C_{max} in SD rats was 17.8 ± 4.86 μg/mL (female) and 11.2 ± 1.99 μg/mL (male), and the AUC_{0-24h} was 92.7 ± 34.1 h·μg/mL (female) and 63.3 ± 10.9 h·μg/mL (male), respectively.

Beagle dogs were given 10, 30, 100 mg/kg TJ0113 by intragastric route for 13 consecutive weeks. The main test article-related symptoms were as follows: (1) Soft stools, loose stools and vomiting were observed in the animals of each dose group, and gastrointestinal reactions, such as watery stools and red liquid in stools, were observed occasionally, which recovered significantly after drug withdrawal. (2) Individual male animals in the ≥ 30 mg/kg dose groups showed decreased activity, and one male animal in the 100 mg/kg dose group developed slight mental depression. No obvious abnormal changes were observed in body weight, food consumption, clinical laboratory tests, organ weight and coefficient, and histopathology. The NOAEL of TJ0113 following the oral gavage administration for 13 consecutive weeks to beagle dogs was 100 mg/kg. At this dose, C_{max} in female and male dogs after the last dose was 6.50 ± 1.59 and 6.02 ± 0.933 μg/mL, respectively, and AUC_{0-24h} was 25.3 ± 8.19 and 23.0 ± 2.58 h·μg/mL, respectively. There was no significant sex difference or remarkable accumulation in vivo after continuous administration.

2.3.3.3 Genotoxicity

The results of genotoxicity study showed that TJ0113 exhibited no mutagenic effect on strains TA97a, TA98, TA100, TA102 and TA1535 within the dose range of 128-5,000 μg/dish under activated and non-activated conditions. Under non-activated or S9 activated conditions, TJ0113 did not increase the chromosome aberration of CHL cells within the concentration range of 3-12 μg/mL. Following the oral gavage administration of TJ0113 at 500, 1,000, and 2,000 mg/kg to the ICR mice, no effect of inducing an increase in micronucleus rate of bone marrow polychromatic erythrocytes was observed. TJ0113 had no mutagenic effect.

2.3.3.4 Reproductive Toxicity

TJ0113 at doses of 30, 80 and 200 mg/kg had no significant systemic toxicity to both male and female parental rats, and no significant toxicity to fertility and early embryonic development of rats. The NOAEL of TJ0113 for both male and female parental rats and early embryonic development was 200 mg/kg.

After intragastric administration of TJ0113 at doses of 30, 100 and 300 mg/kg to pregnant rats from GD6 to GD17, 30 and 100 mg/kg TJ0113 had no obvious systemic toxicity to pregnant rats; weight gain of parental pregnant rats in the 300 mg/kg dose group decreased. The NOAEL of TJ0113 for parental female rats was 100 mg/kg. At this dose, C_{max} of the unchanged drug in maternal rats was 14.1±1.47 μg/mL and $AUC_{0\text{-}24h}$ was 107±32.0 h·μg/mL. TJ0113 at the dose of 30 mg/kg had no significant effect on fetal growth and skeletal development, while TJ0113 at 100 and 300 mg/kg had an impact on fetal growth and skeletal development. The NOAEL for embryo-fetal development was 30 mg/kg. At this dose, C_{max} of the unchanged drug in maternal rats was 6.44 ± 0.87 μg/mL and $AUC_{0\text{-}24h}$ was 36.2 ± 18.5 h·μg/mL.

After intragastric administration of TJ0113 at doses of 10, 30 and 100 mg/kg to New Zealand rabbits from GD6 to GD19, TJ0113 at the doses of 10 and 30 mg/kg had no obvious systemic toxicity to parental female rabbits. TJ0113 when dosed at 100 mg/kg had an impact on fertility of parental rabbits. The NOAEL of TJ0113 for parental rabbits was 30 mg/kg. At this dose, C_{max} of the unchanged drug in maternal rabbits was 0.427±0.103 μg/mL and $AUC_{0\text{-}24h}$ was 0.842±0.116 h·μg/mL. TJ0113 when dosed at 10, 30 and 100 mg/kg had no obvious toxicity to fetal growth and skeletal development. The NOAEL for embryo-fetal development was 100 mg/kg. At this dose, C_{max} of the unchanged drug in maternal rabbits was 0.899 ± 0.584 μg/mL, and $AUC_{0\text{-}24h}$ was 2.28 ± 1.00 h·μg/mL.

2.4 Summary of Clinical Trials of TJ0113 Capsules

2.4.1 Trial Design

A phase I clinical trial to evaluate the safety, tolerability and pharmacokinetics of single dose, multiple doses of TJ0113 capsules and oral dose of TJ0113 capsules under fed conditions in healthy subjects (registration number: CTR20232426) has been completed. This study consisted of a single ascending dose (SAD) study, a multiple ascending dose (MAD) study, and a high-fat diet food effect (FE) study.

A total of 6 dose groups (A1 to A6) were set up in the SAD study, namely 80 mg, 160 mg, 260 mg, 400 mg, 540 mg and 720 mg dose groups, respectively. A total of 72 healthy adult

subjects (12 subjects/group), including men and women, were enrolled at this stage. Subjects in each dose group were randomized in a 5:1 ratio to receive either investigational drug TJ0113 capsules or placebo (10 of whom received study drug and 2 received placebo). Two subjects in the 80 mg dose group were assigned as the sentinel group and were randomly assigned to receive TJ0113 capsules or placebo in a 1:1 ratio. The remaining 10 subjects in the 80 mg dose group were randomly assigned to receive either TJ0113 capsules or placebo in a 9:1 ratio after completion of the 24-h post-dose safety observation in the sentinel group.

A total of three dose groups (B1 to B3) were set up in the MAD study, namely, 200 mg once daily (QD), 400 mg QD, and 300 mg twice daily (BID) dose groups. A total of 36 healthy adult subjects (12/group), including men and women, were enrolled. Subjects in each dose group were randomized in a 5:1 ratio to receive either investigational drug TJ0113 capsules or placebo (10 of whom received study drug and 2 received placebo). The drugs were orally administered with warm water for 7 consecutive days (only once in the morning on Day 7).

The FE study adopted a single-center, single-dose (200 mg), randomized, open-label, 2-sequence, 2-period, crossover design, in which a total of 20 healthy adult subjects were randomly assigned in a 1:1 ratio to 2 dosing sequences (C1: fasting-after a meal; C2: after a meal-fasting) with 10 subjects in each group (all of them were orally administered with study drug TJ0113 capsules). Each dosing sequence consisted of 2 periods, and the drugs were administered once in each period. In Group C1, the drugs were administered under a fasted state in Period I and after a meal in Period II; and in Group C2, the drugs were administered after a meal in Period I and under a fasted state in Period II. There was an interval of 7 days (the washout period between two doses) between the two periods.

2.4.2 Trial Results

A total of 562 subjects were screened in the phase I study, and 130 (23.1%) subjects were eligible at the screening and were randomized. Among them, 74, 36 and 20 subjects were enrolled in the SAD, MAD and FE studies, respectively, and completed the studies (2 subjects in the SAD study were withdrawn early at the investigator's discretion and did not use the investigational drug). The population enrolled in this study was homogeneous, and the main demographic characteristics were relatively balanced between the investigational drug group and the placebo group.

The results of the PK analysis are summarized below:

- After a single dose within the range of 80 mg to 720 mg, the C_{max} (range: 967.30-3,100.00 ng/mL) increased non-linearly along with the increasing dose in a less-than

dose proportional manner. The average $t_{1/2}$ decreased first and then increased along with the increasing dose, mainly within the range of 3.20 to 2.24 h. The median T_{max} increased along with the increasing dose (except for 720 mg dose group), mainly within the range of 1.50 to 2.00 h. The exposure ($AUC_{0\text{-last}}$ [range: 3,008.21-15,927.76 h * ng/mL] and $AUC_{0\text{-inf}}$ [range: 3,027.12-16,338.11 h * ng/mL]) showed a nonlinear increase in the 80-720 mg range in a less-than dose proportional manner, but a linear increase in the 80-400 mg range.

- After multiple dose within the range of 200 mg QD to 300 mg BID for 7 days, $C_{max,ss}$ (1,972.00 ng/mL vs 2,115.00 ng/mL), $AUC_{0\text{-t,ss}}$ (7,235.06 h*ng/mL vs 9,675.24 h*ng/mL), and $AUC_{0\text{-inf,ss}}$ (7,399.83 h*ng/mL vs 9,907.55 h*ng/mL) in the 200 mg QD and 400 mg QD dose groups increased along with the increasing dose. The average $t_{1/2,ss}$ (2.37 ± 0.338 h vs. 2.26 ± 0.378 h) and the median T_{max} (2.00 vs. 1.98 h) were close for the two dose groups. The $Rac_{(Cmax)}$ and $Rac_{(AUC)}$ in the 200 mg QD dose group were 1.21 ± 0.281 and 1.10 ± 0.184, respectively, suggesting that TJ0113 almost had no accumulation in vivo after 200 mg QD administration. The $Rac_{(Cmax)}$ and $Rac_{(AUC)}$ in the 400 mg QD dose group were 1.46 ± 0.422 and 1.40 ± 0.661, respectively, suggesting that TJ0113 had a slight accumulation in vivo after 400 mg QD administration. The $C_{max,ss}$ (2,323.00 ng/mL), $AUC_{0\text{-t,ss}}$ (11,056.15 h*ng/mL) and $AUC_{0\text{-inf,ss}}$ (11,412.01 h*ng/mL) in the 300 mg BID dose group were higher than those in the other two groups. The average $t_{1/2,ss}$ was 2.56 ± 0.791 h, the median T_{max} was 1.50 h, and $Rac_{(Cmax)}$ and $Rac_{(AUC)}$ were 0.90 ± 0.173 and 0.86 ± 0.222, respectively, indicating that TJ0113 almost had no accumulation in vivo after 300 mg BID administration.
- A high-fat diet reduced the absorption of TJ0113 in humans and delayed the absorption of the drug in humans.
- There was no significant correlation between the level of mtDNA and the dose in healthy people.

Safety results were summarized as follows:

- In the SAD study, a total of 33 subjects experienced adverse events (AEs) (28 in the treatment group and 5 in the placebo group) and all AEs were treatment-emergent adverse events (TEAEs). By the preferred term (PT), the top three common TEAEs in terms of incidence (with an incidence of > 5%) were white blood cell count decreased (9.7%), hyperuricaemia (9.7%) and neutrophil count decreased (8.3%).

The incidences of TEAEs by each PT were similar between the treatment group and the placebo group. A total of 31 subjects experienced adverse drug reactions (ADRs) (26 in the treatment group and 5 in the placebo group). There were no serious adverse events (SAEs) or AEs leading to death, and there were no grade ≥ 3 AEs, ADRs, or TEAEs. The incidence of grade 2 TEAEs related to the investigational drug in each treatment group (80 mg, 160 mg, 260 mg, 400 mg, 540 mg, and 720 mg) was 0%, 0%, 10.0%, 10.0%, 10.0%, and 0%, respectively. No dose group met the dose termination criteria, suggesting that a single dose of TJ0113 within the dose range of 80-720 mg was well tolerated.

- In the MAD study, a total of 17 subjects experienced AEs (13 in the treatment group and 4 in the placebo group), all of which were TEAEs. By the PT, the top three common TEAEs in terms of incidence were white blood cell count decreased (8.3%), neutrophil count decreased (8.3%) and hyperuricaemia (8.3%). The incidences of TEAEs by each PT were similar between the treatment group and the placebo group. A total of 15 subjects experienced ADRs (11 in the treatment group and 4 in the placebo group); only one subject experienced a grade 3 TEAE (200 mg QD dose group), and none of the remaining subjects experienced any grade ≥ 3 AEs, ADRs, and TEAEs. There were no SAEs or AEs leading to death. The incidence of grade 2 TEAEs related to the investigational drug in each treatment group (200 mg QD, 400 mg QD, and 300 mg BID) was 0%, 10.0%, and 10.0%, respectively. None of the dose groups met the dose termination criteria, suggesting that multiple doses of TJ0113 within the dose range of 200 mg QD to 300 mg BID were well tolerated.
- In the FE study, a total of 6 subjects receiving administration under fasted conditions had AEs, all of which were TEAEs. There were 4 subjects with ADRs. One AE in a subject who received administration under fed conditions was an TEAE and considered to be an ADR. The incidence of TEAEs was numerically higher with administration under a fasted state than that with the administration after a meal, and the incidence of all TEAEs (lymphocyte count decreased, white blood cells urine positive, neutrophil count decreased, oropharyngeal pain, dermatitis allergic, and abdominal pain) in the FE study was 5.0% by PT. There were no SAEs or AEs leading to death and no grade 3 and above AEs or ADRs in the FE study. The incidence of grade 2 TEAEs related to the investigational drug occurred in the treatment groups (fasted group and fed group) was 0% and 20.0%, respectively.

In summary, the safety profile of TJ0113 capsules at the current dose-finding level was good, the incidence of AEs was similar between the treatment group and the placebo group, and no unexpected or serious safety signals have been identified.

2.5 Benefit/Potential Risk Assessment

2.5.1 Risk Assessment

Based on the results of the toxicological studies and the guidance of drug clinical trial approval letter (No. 2023LP01405), TJ0113 capsules were generally well tolerated. The main toxicities were gastrointestinal toxicity (vomiting, loose stools), renal toxicity (basophilic lesions in renal tubules), hepatotoxicity (total bilirubin [TBIL] increased, liver coefficient increased), potential impact on QT interval, and embryo-fetal reproductive toxicity, etc. Based on the completed phase I clinical trial in healthy subjects (registration No.: CTR20232426), the safety profile of TJ0113 capsules following the single dose administration within the dose range of 80-720 mg, and that following the multiple dose administration at 200 mg QD, 400 mg QD, and 300 mg BID was good; the incidences of AEs were similar between the treatment group and the placebo group, and no unexpected or serious safety signals have been identified.

In the phase II study, in order to minimize the overall risk of subjects and ensure the safety of subjects, the following measures were taken: enrollment of appropriate subject population based on the inclusion/exclusion criteria, conducting the screening examinations/tests (medical history and treatment history, vital signs, physical examination, laboratory tests, serum virology test, 12-lead electrocardiogram [ECG], etc.), and safety evaluation and follow-up. This study will also strictly require the subjects to take highly effective contraceptive measures and conduct regular pregnancy tests for women of childbearing potential. In addition, all subjects will be closely monitored for clinical safety assessments such as vital signs, laboratory tests, 12-lead ECG, etc. according to schedule of activities (SoA). Therefore, it can be considered that the expected risks of TJ0113 capsules in the phase II study is controllable.

2.5.2 Benefit Assessment

TJ0113 capsules is a new oral selective mitochondrial autophagy inducer developed by Hangzhou PhecdaMed Co., Ltd., and the proposed indication under development is PD.

Based on the fact that the marketed anti-PD treatment drugs in China cannot meet the treatment needs in large PD patient population, there is an urgent need for developing new anti-PD treatment drugs with good efficacy and safety to provide patients with more options and clinical benefits. Targeting PINK1/Parkin-mediated mitochondrial autophagy has

emerged as a promising approach for the treatment of PD. TJ0113 has demonstrated its mitochondrial autophagy effect in a series of pharmacological studies. In MPTP-induced PD mouse model and 6-OHDA-induced PD rat model, TJ0113 was observed to improve neuronal damage and reduce inflammation after administration, which has the potential to treat PD. In addition, TJ0113 not only has a good effect of ROS scavenging, but also can scavenge damaged mitochondria from the source, thus fundamentally inhibit the generation of ROS.

To sum up, TJ0113 is expected to improve the motor function of PD patients by improving neuronal damage, repairing mitochondrial damage, reducing inflammation, and inhibiting oxidative stress. TJ0113 capsules are expected to confer significant benefits to PD subjects in the phase II study.

2.5.3 Benefit/Risk Assessment

Based on the safety and PK/PD profiles of TJ0113 capsules demonstrated in non-clinical and clinical studies, TJ0113 capsules are safe and well tolerated, and it is expected to effectively improve motor function of PD patients.

In the phase II study, the following measures will be taken to ensure the safety of subjects: enrollment of appropriate subject population based on the inclusion/exclusion criteria, conducting the screening examinations/tests (medical history and treatment history, vital signs, physical examination, laboratory tests, serum virology test, 12-lead ECG, etc.), and safety evaluation and follow-up. This study will also strictly require the subjects to take highly effective contraceptive measures and conduct regular pregnancy tests for women of childbearing potential, which are expected to further effectively control the risk of subjects.

To sum up, it can be considered that the benefits of subjects in the phase II study in the PD population outweigh the risks, and the risks are manageable.

3 Trial Objectives and Endpoints

3.1 Trial Objectives

Primary Objectives

- To assess the efficacy of TJ0113 capsules in the treatment of patients with early-stage PD.

Secondary Objectives

- To assess the efficacy of TJ0113 capsules in the treatment of patients with early-stage PD;
- To assess the safety of TJ0113 capsules in the treatment of patients with early-stage PD.

Exploratory Objectives

- To explore the changes in inflammatory indicators in early-stage PD patients treated with TJ0113 capsules;
- To explore the effect of TJ0113 capsules on PD biomarkers in early-stage PD patients;
- To explore the effect of TJ0113 capsules on skeletal muscle mass and function in early-stage PD patients;
- To explore the association between the efficacy of TJ0113 capsules and the genomic characteristics in early-stage PD patients.

3.2 Trial Endpoints

Primary Endpoints

- Changes from baseline in scores of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (motor examination) in subjects after 12 weeks of treatment. Evaluation time point: ≥ 12 hours from the most recent dose of anti-PD drug.

Secondary Endpoints

➢ Efficacy Endpoints

- Changes from baseline in scores of MDS-UPDRS Part III (motor examination) in subjects after 1, 4, 8 weeks of treatment. Evaluation time point at each visit: ≥ 12 hours from the most recent dose of anti-PD drug;
- Changes from baseline in scores of MDS-UPDRS Part III (motor examination) in

subjects after 1, 4, 8, 12 weeks of treatment. Evaluation time point at each visit: 2 ± 1 hours from the most recent dose of anti-PD drug;

- Changes from baseline in scores of MDS-UPDRS Part I, II and IV in subjects after 1, 4, 8 and 12 weeks of treatment;
- Changes from baseline in the total scores of MDS-UPDRS in subjects after 1, 4, 8, 12 weeks of treatment, including:
  - Total score 1: II+III; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is ≥ 12 hours from the most recent dose of anti-PD drug;
  - Total score 2: II+III; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is 2 ± 1 hours from the most recent dose of anti-PD drug;
  - Total score 3: I+II+III; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is ≥ 12 hours from the most recent dose of anti-PD drug;
  - Total score 4: I+II+III; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is 2 ± 1 hours from the most recent dose of anti-PD drug;
  - Total score 5: I+II+III+IV; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is ≥ 12 hours from the most recent dose of anti-PD drug;
  - Total score 6: I+II+III+IV; wherein, the evaluation time point for MDS-UPDRS Part III (motor examination) is 2 ± 1 hours from the most recent dose of anti-PD drug.

- Safety Endpoints
- AE;
- Laboratory test;
- Vital signs
- Physical examination;
- 12-lead ECG.

➢ Exploratory Endpoint

- Changes from baseline in inflammatory indicators after 4, 8, 12 weeks of treatment;
- Changes from baseline in α-synuclein and glial fibrillary acidic protein (GFAP) after

12 weeks of treatment;

- Changes from baseline in appendicular skeletal muscle mass index (ASMI) measured by dual-energy X-ray absorptiometry (DXA) after 12 weeks of treatment;
- Changes from baseline in muscle strength (grip strength) after 12 weeks of treatment;
- Changes from baseline in 6-meter walking speed test after 12 weeks of treatment.
- The association between the efficacy of TJ0113 capsules and the genomic characteristics in early-stage PD patients.

4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible for this study:

1. Subjects who voluntarily participate in the clinical trial, and have signed the informed consent form (ICF), are able to understand and follow the study protocol, willing to visit the study site on time, fully understand the content, process and potential adverse reactions of the study, and indicate the date of signing the ICF;
2. Males or females aged 30-80 years (both inclusive) at the time of signing the ICF;
3. Subjects who are diagnosed with PD according to the Diagnostic Criteria for Parkinson's Disease in China (2016 edition);
4. The scores of modified Hoehn and Yahr Scale at screening are 1-2.5 (both inclusive);
5. Subjects who have not previously received anti-PD drugs; or those who have previously used any anti-PD drugs but have not received such drug within 4 weeks before study entry; or those who have received the anti-PD drug at a stable dose for at least 4 weeks before study entry and agree to maintain the original treatment regimen during the study;
6. Subjects with the scores of MDS-UPDRS Part III of ≥ 22 at screening (it should be scored ≥ 12 hours apart from the most recent dose of the anti-PD drug for subjects who have been receiving an anti-PD drug at a stable dose for at least 4 weeks prior to study entry);
7. Subjects of childbearing potential (including spouses of male subjects) who have no childbearing or sperm donation plan from the end of the screening period to within 6 months after the last dose and are willing to use at least one effective method (see Appendix I for details) for contraception.

4.2 Exclusion Criteria

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

1. Presence of any medical condition that may interfere with full participation in the study, including but not limited to the following: medical history of epilepsy or any complications, medical history of hemolytic anemia, pulmonary embolism, respiratory depression, active psychiatric disease, or malignancy; positive tumor marker detection results at screening and judged by the investigator to be clinically significant;
2. Subjects who have experienced a New York Heart Association (NYHA) Class III or above congestive heart failure, unstable angina pectoris, acute myocardial infarction,

hemorrhagic stroke (stroke), and ischemic stroke (including transient ischemic attack) within 6 months before screening; or those who have undergone any percutaneous coronary intervention or coronary artery bypass grafting, heart valve repair/replacement; or those with severe arrhythmia as judged by the investigator at the time of screening;

3. Subjects with prior personal or family history of long-QT syndrome, family history of sudden death of any immediate family members (meaning a parent, child, or sibling) prior to the age of 40 years; and/or personal history of unexplained syncope within 1 year prior to screening; and/or QTcF > 450 ms (male), QTcF > 470 ms (female) measured by ECG at rest during screening;
4. Subjects with unstably controlled hypertension at screening, defined as the systolic blood pressure ≥ 160 mmHg and/or the diastolic blood pressure ≥ 100 mmHg (verify before randomization);
5. Subjects with symptomatic orthostatic hypotension at screening, or who experiences a decrease in systolic blood pressure of ≥ 30 mmHg or a decrease in diastolic blood pressure of ≥ 15 mmHg within 3 minutes when changing from the supine to the standing position (verify before randomization);
6. Atypical PD (e.g., Parkinsonism, multiple system atrophy, progressive supranuclear palsy), or secondary PD (e.g., delayed or drug-induced PD);
7. Subjects who have clinically significant hepatic insufficiency which is defined as the total bilirubin (TBIL) > 2 × upper limit of normal (ULN) or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 × ULN;
8. Subjects who have clinically significant renal insufficiency (creatinine clearance [Ccr] < 30 mL/min, see the calculation formula inAppendix II);
9. Any condition (e.g., severe arthritis, severe dyskinesia, traumatic injury with permanent physical disability) that may affect the MDS-UPDRS motor examination;
10. Subjects who have a history of suicidal intention (including actual attempts, interrupted attempts, or failed attempts) and are at risk of committing suicide as judged by the investigator;
11. Subjects who suffer from severe mental abnormalities (anxiety, depression) as judged by the investigator, and the depression or anxiety score as rated by the Part I of the MDS-UPDRS is ≥ 3 at screening;
12. Subjects who have taken any serotonin reuptake inhibitors (such as fluoxetine, paroxetine,

trazodone, citalopram, escitalopram, etc.) within 4 weeks prior to screening;

13. Subjects who have dementia or moderate or above cognitive dysfunction and the MDS-UPDRS score for 1.1 cognitive impairment is ≥ 3 at screening;
14. Subjects who have a history of surgical treatment for PD (e.g., deep brain stimulation, pallidotomy, etc.), or those who have undergone any major or medium surgery or have experienced any serious trauma or serious infection within 3 months prior to screening, those who are unsuitable for this study at the discretion of the investigator or plan to undergo any surgical treatment (excluding an outpatient surgery that has no impact on subject safety or study results as judged by the investigator) during the study;
15. Subjects who have participated in a clinical trial that involves the administration of an investigational drug (a new chemical entity), device, or surgery within 3 months or 5 half-lives before screening, whichever is longer;
16. Subjects with evidence of alcoholism (≥ 14 units of alcohol per week on average, 1 unit ≈ 360 mL of beer, 45 mL of liquor, or 150 mL of wine) or drug abuse within 6 months prior to screening that may interfere with the subject's understanding of the study or completion of the study as judged by the investigator;
17. Subjects who are known to have hypersensitivity/allergic reaction or intolerance to any component of the investigational product;
18. Subjects with a history of hepatitis B, or positive for any of the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody, and Treponema pallidum antibody (TP-Ab) at screening;
19. Pregnant or breastfeeding women;
20. Subjects who are unable to swallow oral drugs, or have any condition that may significantly affect the absorption, distribution, metabolism and excretion of the drug, or any condition that may pose a hazard to subjects participating in the study, as judged by the investigator;
21. Subjects who have a history of organ transplantation (excluding corneal transplantation);
22. Subjects who have donated or lost blood of ≥400 mL, or received blood transfusions within 3 months prior to screening;
23. Subjects who have any other conditions that may affect study compliance as deemed by the investigator, or those who are unable to participate in the study for their own reasons.

4.3 Definition and Handling of Screen Failures

If a subject does not meet the eligibility for this study, it will be considered a screen failure, and the reasons should be documented in detail in the original medical record.

If screen failure is caused due to abnormal results during the screening process, and if the investigator judges that there is a clear justification for retesting, and the tests can be repeated within the time window once, but the reason for repeating the test should be recorded. Subjects with screening failure are only allowed for re-screening once during the enrollment stage of this study. Additional medications are not allowed to correct the abnormal values (e.g. hepatoprotective drugs used to address hepatic function abnormal) prior to the re-measurement or re-screening. Parameters that are allowed for retesting include: blood pressure, ECG, creatinine, AST, ALT, and TBIL.

In the event of re-screening, the subject must sign a new ICF, a new subject screening number will be assigned, and all sample collection and assessment will be performed again.

4.4 Criteria for Early Withdrawal from the Trial

Subjects may voluntarily request for study withdrawal at any time, or may be withdrawn from the study at any time at the request of the investigator or the sponsor for safety, behavioral or administrative reasons.

Withdrawal at the subject's discretion

If the subjects are unwilling to continue the clinical trial, they have the right to withdraw their consent and withdraw from the study at any stage.

Withdrawal at the investigator's discretion

It refers to the condition during the study in which the investigator finds that an enrolled subject is no longer suitable for the participation in the study and decides that the subject should be withdrawn from the study. These conditions include, but are not limited to:

- Continuing the study may affect the safety of the subject and be unfavorable to the subject at the discretion of the investigator based on the following clinical considerations:
  - QTcF >500 ms at rest (after resting for at least 5 minutes; the average of two measurements taken within 20 minutes) or an increase of >60 ms from baseline;
  - Discontinuation of study treatment due to hepatic event or hepatic function abnormal:
    - ✧ ALT or AST>8×ULN; or

- ✧ ALT or AST>5×ULN for over 2 weeks; or
- ✧ ALT or AST>3×ULN and (TBIL>2×ULN or International Normalized Ratio [INR]>1.5); or
- ✧ ALT or AST>3×ULN, with fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash, or eosinophilia (> 5%).

- Occurrence of other intolerable AEs which requires treatment discontinuation as judged by the investigator;

- Any major protocol deviations (such as subjects who fail to meet the inclusion criteria have been mistakenly included in the study) or protocol violations, which may have a significant impact on the evaluation of the efficacy and safety of the drug;
- Subjects have poor compliance that affects efficacy and safety assessment;
- Female subjects are pregnant;
- Subjects are lost to follow-up;
- Subjects have participated in other clinical trials (which is defined as having signed the ICF of any other study) during the study;
- Subjects have been unblinded due to various reasons;
- Other circumstances in which the subject needs to be withdrawn from the trial at the discretion of the investigator.

Handling of Subjects Early Withdrawn

Subjects who have early withdrawn from the study should complete the early withdrawal visit (if it is less than 7 days from the date of the previous visit, repeated tests of the same item can be waived) within 7 days after the investigator's awareness, unless they voluntarily decide to withdraw from the study and refuse to have early withdrawal visit.

For subjects who withdraw from the study due to an AE or SAE, the investigator should take appropriate treatment measures according to the actual situation of the subjects, and closely follow up their condition until the AE or SAE is clinically recovered, stabilized, returns to screening or baseline level (if baseline level is known), the subject is lost to follow-up (e.g., no more information is available or the subject/caregiver refuses to provide any information), or dead, which will be recorded in the original data.

For all the subjects who have early withdrawn from the study, their study medical records should be retained and recorded in the electronic case report form (eCRF), and the EOT page and the reason for failure in completing the study should be filled out.

4.5 Criteria for Study Termination/Site Closure

The sponsor has the right to terminate the study at any time, and the sponsor and the investigator have the right to close the study site at any time. However, such a procedure can be implemented only after mutual agreement. When the study is terminated, it must be reported to the Independent Ethics Committee (IEC) and Institutional Review Board (IRB). Upon early termination of study or early closure of study site, all study materials (except those documents that must be retained at the site) must be returned to the sponsor. The investigator must retain other documents until notified by the sponsor of their destruction. Reasons for the early termination of the study or the closure of the study site include but are not limited to:

- The study is required to be terminated due to significant AEs occurred in the study for safety reasons;
- An event that seriously violates the clinical study protocol, Good Clinical Practice (GCP) or relevant regulatory requirements occurs during the study, requiring termination of the study;
- The sponsor requests termination under the premise of fully protecting the rights and interests, and safety of subjects (e.g., funding reasons, management reasons, efficacy reasons, etc.);
- National Medical Products Administration (NMPA) or the Ethics Committee orders the termination of the trial for some reason.

5 Overall Trial Design

5.1 Trial Design

5.1.1 Overall Design

This study is a randomized, double-blind, placebo parallel-controlled phase II clinical trial which is designed to assess the efficacy and safety of TJ0113 capsules in the treatment of patients with early-stage PD. It is planned to include approximately 150 subjects with early-stage PD who will be randomized in a 1:1 ratio into two cohorts (Cohort 1: 200 mg dose group; Cohort 2: 400 mg dose group). Within each cohort, subjects who have been successfully screened will be randomly assigned to TJ0113 capsules group and the placebo group in a ratio of 2:1 within each stratum based on a stratification factor whether they have been receiving levodopa, the background medication for PD (yes vs. no) at a stable dose. Among them, approximately 50 subjects will receive TJ0113 capsules and approximately 25 subjects will receive the placebo. In this study, there will be approximately 50 subjects in each of the TJ0113 capsules 200 mg group, TJ0113 capsules 400 mg group and the placebo group.

After randomization, subjects will receive the oral administration of TJ0113 capsules or the placebo for 12 consecutive weeks and continue to receive follow-up visits for 1 week (telephone follow-up) after the end of treatment. For subjects who have been receiving the anti-PD drug at a stable dose for at least 4 weeks prior to study entry, the original regimen of the background medication for PD should be maintained during the study.

5.1.2 Trial Period

This trial consists of a screening period, a treatment period and a follow-up period.

Screening period (up to 4 weeks)

At screening, the subject will be assigned a “screening number” for ID identification after signing the informed consent form. The day of first dose for subjects screened successfully is taken as Day 1 (D1) of the trial (for other days, by this rule); and subjects are screened within 28 to 2 days before the start of the trial, and the required eligible subjects are screened. The scale scores, demographic data, medical history, medication history, physical examinations, height and weight, vital signs and laboratory tests of the subjects before the trial are recorded.

Treatment period (12 weeks)

Subjects who have been successfully screened will receive oral administration of the drugs as required on D1, once daily for 12 weeks.

Follow-up period (1 week, telephone follow-up)

Follow-up will be continued for 1 week after the end of the treatment period, and AE and concomitant medication information will be collected via telephone follow-up. If an AE/SAE occurs during the study, it will be followed up by the investigator until it has been clinically recovered, stabilized, returns to the screening or baseline level (if baseline level is known), the subject is lost to follow-up (e.g., no more information is available or the subject/caregiver refuses to provide any information), or dead.

5.2 Justification for Design (Population, Dose, etc.)

5.2.1 Justification for Overall Study Design

This is a randomized, double-blind, placebo parallel-controlled phase II clinical trial, which is planned to enroll 150 PD subjects. Subjects who are successfully screened will be randomized, and the efficacy will be evaluated after oral administration for 12 consecutive weeks and subjects will continue to be followed up for 1 week after the end of treatment. Male or female subjects aged between 30 and 80 years (both inclusive) will be included in this study, including elderly subjects. Based on the PK model, the PK profile of TJ0113 following the oral administration at doses of 80 mg, 160 mg, and 400 mg in the elderly population (65, 70, and 80 years) is speculated to be similar to that of adult subjects.

5.2.2 Justification for Dose

The proposed doses of TJ0113 capsules for this study are 200 mg QD and 400 mg QD. The dose design is primarily based on the results of non-clinical pharmacology studies of TJ0113 and the currently completed phase I study.

The PD studies of compound TJ0113 in the MPTP-induced mouse PD model and the study of the mitochondrial repair effect of compound TJ0113 in the MPTP-induced mouse PD model indicated that TJ0113 has different degrees of therapeutic effect on PD model within the dose range of 10, 30, and 60 mg/kg once daily. Based on this data, the human equivalent dose (HED) calculated by the body surface area normalization method was 0.9, 2.7, and 5.4 mg/kg, respectively and 54, 162, and 324 mg based on an adult body weight of 60 kg.

The PD study of TJ0113 in the 6-OHDA-induced rat PD model suggested that TJ0113 had different degrees of therapeutic effect on the PD model at doses of 5, 15, and 30 mg/kg once daily. Based on this data, the HED calculated by the body surface area normalization method was 0.8, 2.5, and 4.9 mg/kg, respectively, and 48, 150, and 294 mg based on an adult weight of 60 kg.

In the kinetics study in the plasma of rats (TJ22039PKAB18), the results of the mean plasma PK parameters of the unchanged drug after single oral gavage administration to SD rats

showed that the $AUC_{0\text{-}24h}$ was 10.7 ± 4.44 h·μg/mL in the 10 mg/kg dose group and 22.1 ± 6.66 h·μg/mL in the 30 mg/kg dose group. The results of phase I clinical trial of TJ0113 were as follows: the $AUC_{0\text{-}last}$ of the SAD study was 8,570.86 ± 2,413.178 h·ng/mL in the 260 mg dose group and 12,785.99 ± 4,491.670 h·ng/mL in the 400 mg dose group. Combined with the PD study of the 6-OHDA-induced rat PD model, both the 200 mg and 400 mg dose levels are expected to be within the clinically effective dose range.

In addition, data from the phase I study of TJ0113 showed that following the single dose administration within the dose range of 80-720 mg, and the multiple dose administration at 200 mg QD, 400 mg QD, and 300 mg BID, the safety profiles of TJ0113 capsules were favorable and the incidence of AEs were similar between the treatment group and the placebo group. Within the dose range of 80-400 mg, the exposures ($AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) increased in a linear fashion. After 200 mg QD administration, TJ0113 basically did not accumulate in vivo; after 400 mg QD administration, there was a slight accumulation of TJ0113 in vivo.

In summary, combined with the current strength (100 mg) and clinical compliance of TJ0113 capsules, the proposed doses for this study are 200 mg QD and 400 mg QD.

5.3 Randomization and Blinding

5.3.1 Randomization

After subjects enter the screening period, the screening numbers will be assigned strictly according to the sequence of study entry. The screening numbers will be expressed by five Arabic numerals, the first two digits are the site number, and the last three digits are the screening sequence number. For example, the screening number for the first subject in Site 01 is 01001. Once the subject is assigned with a number, the number cannot be reused.

Subject randomization numbers and drug randomization numbers are compiled by project-independent randomization statisticians from the Statistics Department. The randomization statistician generates a subject randomization list and a drug randomization list using the SAS 9.4 or later PLAN process. It is planned to include approximately 150 subjects who will be randomized in a 1:1 ratio into two cohorts (Cohort 1: 200 mg dose group; Cohort 2: 400 mg dose group). Within each cohort, subjects who have been successfully screened will be randomly assigned to TJ0113 capsules group and the placebo group in a ratio of 2:1 within each stratum based on a stratification factor whether they have been receiving levodopa, the background medication for PD (yes vs. no) at a stable dose. Among them, approximately 50 subjects will receive TJ0113 capsules and approximately 25 subjects will receive the placebo. The subject randomization list and drug randomization list will be imported into the

Interactive Web Response System (IWRS) by the system director. For subjects who have been successfully screened, the randomization number of the subjects will be obtained by the investigator through the IWRS, and the subjects will enter the corresponding group according to the randomization number. Subjects who withdraw from the study midway will not be allowed to re-enter the study. The specific randomization procedure will be described in the randomization protocol.

5.3.2 Blinding

The blinding of this study is completed under the guidance of a randomized statistician independent of the statistical analysis of this project, and the electronic blind code will be kept by the randomized statistician in a folder with permission control.

During the treatment period, in order to maintain the double-blind status of the study, the packages for investigational drug and placebo will be identical in physical appearance. The sponsor, investigators and other personnel involved in the assessment of subjects and implementation of the trial will not be aware of the distribution of therapeutic drugs.

Throughout the study, all personnel involved in blinding should remain blinded until the database is locked.

5.3.2.1 Blinding Implementation

The placebo has the same dosage form, appearance, strength, color, weight, smell and taste as the investigational drug, and does not contain any active ingredients. The packages for investigational drug and placebo will be identical in physical appearance to ensure the implementation of the blinding method. The sponsor or its designee will assign a blind code to the investigational drug and placebo.

Subjects who meet all inclusion criteria and none of the exclusion criteria will be randomized. For subjects who require to be randomized and dispensed with drug, the information of randomization number, randomization time, drug number and drug dispensing time are all provided by the Clinflash drug dispensing system. The investigator or his/her designee will log in to the Clinflash IRT system, obtain the information of the randomization number and the corresponding drug number, and distribute the corresponding investigational product according to the drug number.

5.3.2.2 Unblinding Provisions

The database will be locked when all eCRF data are entered and signed as well as reviewed in a blinded manner, the analysis population is determined, and the statistical analysis plan (SAP)

is signed. After the database is locked, unblinding is carried out to determine the subject group, and the unblinding record is kept. The unblinding must be signed and confirmed by the sponsor and the statistician.

5.3.2.3 Emergency Unblinding

Emergency unblinding refers to obtaining the treatment grouping information of individual or some subjects in emergency through pre-established standard operating procedures based on the safety considerations of subjects and other special reasons in accordance with the clinical trial protocol. It should only be performed if the investigator must know the treatment grouping information of the subject who experiences an emergency (e.g., when the subject experiences an SAE or is in urgent need of rescue treatment). There is no need for emergency unblinding, if it is known that the treatment grouping information is not necessary for management of the emergency.

In the event of emergency unblinding, it is necessary to timely record the time, reason and operator of emergency unblinding, notify the CRA as soon as possible, and submit the safety event report to the Ethics Committee. Upon emergency unblinding, the subject must terminate the treatment. The investigator should record the reason for termination of treatment in the case report form.

In addition, if an unexpected serious adverse event occurs, the Pharmacovigilance Department should also unblind the individual subjects according to the corresponding procedures.

5.4 Definition of End-of-Study (EOS)

The end of the study (EOS) is when the last subject has his/her last study visit, unless the EOS is caused by a condition described in Section 4.5 (Criteria for Study Termination/Site Closure).

The EOS for an individual subject is defined as when the subject completes V7 or is early withdrawn from the study (see Section 4.4 for criteria for early withdrawal). For subjects who early withdraw from the study, the date on which the last visit is completed or the last contact is made is the date of EOS (whichever occurs later).

5.5 Definition and Handling of Loss to Follow-up

If the investigator fails to contact the subject through multiple attempts of various methods (at least 3 telephone calls and 1 SMS/WeChat, and each attempt is not on the same day), the subject can be judged as lost to follow-up, and the corresponding contact records (contact person, contact information and specific time) should be maintained, and the date of the last contact should be considered as the date of the subject's early withdrawal.

6 Study Treatment

6.1 Investigational Products

In this study, the investigational products include the investigational drug (TJ0113 capsules) and the placebo.

	TJ0113 Capsules	Placebo
Active Ingredient	TJ0113	None
Dosage Form	Capsules	Capsules
Strength	100 mg	100 mg
Package Size	30 capsules/bottle	30 capsules/bottle
Description	Opaque rich yellow hard capsules, and with pale pink solid contents	Opaque rich yellow hard capsules, and with off-white solid contents
Storage Conditions	Protected from light, keep in tight container at 2℃ - 8℃	Protected from light, keep in tight container at 2℃ - 8℃
Provided by	Hangzhou PhecdaMed Co., Ltd.	
Method of Administration	Take orally on an empty stomach in the morning, once daily, and fast within half an hour after the administration. It can be taken together with the background medication for PD. It is recommended that subjects should take the drug at the same time ± 1 h each day as much as possible.	

6.2 Drug Storage

Both the investigational drug and the placebo will be provided free of charge by Hangzhou PhecdaMed Co., Ltd. and distributed to the study site as scheduled. The investigational drug should be kept and distributed by specially-assigned person in the clinical trial institution, and stored in a refrigerator at 2-8℃ as required. Returned drugs (used, partially used or unused drugs, including empty packaging materials) must be kept separately from the drugs that are not dispensed.

6.3 Drug Dispensing

All investigational products will be randomized by the IWRS, and each subject will be assigned multiple drug numbers by visit during the study. The system will automatically record the drug allocation information of each subject, including the date of drug dispensing and drug number. The drug manager should dispense the drugs according to the drug number

assigned by the system at each visit.

6.4 Drug Receipt, Record and Accountability

The drugs will be administered at each site by the principal investigator or his or her authorized representative (e.g., pharmacist), i.e., the drug manager. The third-party transportation company designated by the sponsor will transport the drugs to each study site according to the transportation requirements of the drug. The drug manager will receive the drug after confirming that the packaging of the drug is intact and there is no temperature excursion, and ensure that all investigational drugs are safely stored according to relevant regulations and drug storage requirements. The quantity of received drugs, the date of receipt, the quantity used, the date of use, and the storage amounts will be recorded and counted accordingly, and the CRA should check and conduct accountability at each visit.

6.5 Drug Return and Destruction

All drugs will be returned by the investigator after the EOS or returned to the third-party drug destruction company designated by the sponsor in batches according to the actual situation of the site during the study. The company will carry out uniform destruction according to the corresponding regulations and requirements.

7 Treatment for Study Participants

7.1 Study Treatment

Subjects enrolled in this study will be randomized in a 1:1 ratio into two cohorts (Cohort 1: 200 mg dose group; Cohort 2: 400 mg dose group) based on a stratification factor whether they have been receiving levodopa, the background medication for PD (yes vs. no) at a stable dose. Within each cohort, the subjects will be randomized into the TJ0113 capsules group and the placebo group in a ratio of 2:1.

7.2 Concomitant Medication

All concomitant medications used during the study must be documented with indication and dose information (including dose, route of administration and dosing frequency), and start and stop dates of administration. Medications used prior to signing the ICF will be recorded as prior medications, and those used after signing the ICF will be recorded as concomitant medications. All concomitant medications should be documented in the subject's original medical record and the eCRF.

7.2.1 Permitted Concomitant Medications/Therapies

Concomitant medications/therapies allowed to be administered from signing of the ICF to 1 week after the last dose of the investigational product include:

- Background medications for PD that have been stably used for at least 4 weeks before study entry, of which the treatment regimen can remain unchanged (for subjects who have used any background medications for PD including levodopa, if any AE such as dyskinesia occur, the dose of levodopa is allowed to be reduced at the discretion of the investigator);
- Other concomitant medication or therapies that have already been used at the time of screening, of which the original drug/therapy type, dose or treatment frequency and setting should remain unchanged as much as possible;
- Drugs required to be used for treating the AEs.

7.2.2 Prohibited Concomitant Medications/Therapies

The following medications/therapies are prohibited during the period from signing the ICF until 1 week after the last dose of the investigational product:

- Any procedure/surgery that may affect the progression of PD, including but not

limited to brain surgery (such as stereotactic destruction and deep brain stimulation) or traditional Chinese medicine physiotherapy (such as acupuncture), etc.;

- Any drugs other than investigational product that may affect the progression of PD (excluding those which have been on a stable dose for PD at the time of study entry).
- Serotonin reuptake inhibitors (such as fluoxetine, paroxetine, trazodone, citalopram, escitalopram, etc.);
- Any unauthorized drugs (i.e., other investigational drugs that are currently tested in clinical trials and have not been approved for marketing).

The investigator will determine and record the use of any emergency medication, drug name, dose, route of administration, purpose of treatment, start and end date of administration.

If subjects have used any prohibited drug or non-drug therapy, it will be recorded as a protocol deviation. The investigator decides on whether the subjects will continue the follow-up or be withdrawn from the study based on the severity of the deviation and the subjects' condition

7.3 Compliance of Study Subjects

During the study, the administration of both the investigational product and the background medication for PD will be recorded in the eCRF. Subjects' medication compliance will be calculated according to the quantity of investigational product dispensed and returned and combined with the diary card.

Calculation method for medication compliance: medication compliance = actual dose/planned dose * 100%.

If the subject's compliance is between 80% and 120%, it means that the compliance is good; if the subject's compliance is < 80% or > 120%, it indicates poor compliance.

8 Endpoint-Related Assessment

8.1 Efficacy Assessment

8.1.1 MDS-UPDRS

The MDS-UPDRS consists of four parts: Part I (Nonmotor Experiences of Daily Living), Part II (Motor Experiences of Daily Living), Part III (Motor Examination), and Part IV (Motor Complications). Throughout the study, each subject should have a fixed rater to evaluate his/her score using MDS-UPDRS.

- For subjects who have received the anti-PD drug at a stable dose for at least 4 weeks prior to study entry, the MDS-UPDRS assessment time points and corresponding assessment parts are as follows:

Visit	MDS-UPDRS assessment part	Assessment time points
V1	Part I	No special requirements
	Part III	Before administration of background medication for PD (≥ 12 hours from the most recent dose of the background medication for PD)
V2, Early Withdrawal Visit (if applicable)	Part III	Before administration of background medication for PD (≥ 12 hours from the most recent dose of the background medication for PD)
		After administration of background medication for PD (to be performed at 2 ± 1 hours after the administration of background medication for PD at this visit)
	Parts I, II, and IV	No special requirements
V3~V6	Part III	Before administration of the investigational product and the background medication for PD (≥ 12 hours from the most recent administration of background medication for PD and the investigational product)
		After administration of the investigational product and the background medication for PD (to be performed at 2 ± 1 hours after the administration of the background medication for PD and the investigational product at this visit)
	Parts I, II, and IV	No special requirements

- For subjects who have not received the anti-PD drug at study entry, the MDS-UPDRS assessment time points and corresponding assessment parts are as follows:

Visit	MDS-UPDRS assessment part	Assessment time points
V1	Part I	No special requirements
	Part III	No special requirements
V2	Part III	No special requirements
	Parts I, II, and IV	No special requirements
V3～V6	Part III	Before administration of the investigational product (≥ 12 hours from the most recent administration of the investigational product)
		After administration of the investigational product (to be performed at 2 ± 1 hours after the administration of the investigational product at this visit)
	Parts I, II, and IV	No special requirements
Early Withdrawal Visit (if applicable)	Part III	≥ 12 hours from the most recent administration of the investigational product
	Parts I, II, and IV	No special requirements

8.2 Safety Assessment

8.2.1 Vital Signs

They include respiration, pulse, body temperature, and blood pressure. Among them, blood pressure measurement on the day of V1 and before randomization at V2 should be measured after the subject has rested in a supine position for at least 5 min. After the supine blood pressure measurement is completed, let the patient stand upright and complete the measurement of standing blood pressure within 3 min in a standing resting state; for other vital signs measurements, it can be measured with the subject in a sitting position after having rested for at least 5 min.

Vital signs will be measured at all site visits in this study.

8.2.2 Physical Examination

It includes skin and mucous membranes, lymph nodes, head, neck, chest, abdomen, spine and limbs, nervous system and mental state.

Physical examination will be performed at all site visits in this study.

8.2.3 12-lead ECG

It should be performed with the subject in a supine position after having rested for at least 5 min. Two measurements will be taken within 20 minutes, and the average value is calculated

and rounded to the nearest integer.

The parameters include: heart rate, PR interval, QRS complex duration, uncorrected QT interval, and Fridericia-corrected QTc (QTcF).

12-lead ECG will be performed at all site visits in this study. If a 12-lead ECG has been performed within 7 days (exclusive) prior to V2, it is not necessary to repeat this examination at V2; otherwise, it should be re-examined at V2 and confirm the eligibility for study entry based on the examination results.

8.2.4 Laboratory Tests

They include hematology, blood chemistry, urinalysis, coagulation function, serum pregnancy test, urine pregnancy test, etc. Each test item includes:

- Hematology: white blood cell count, absolute neutrophil count, neutrophil percentage, absolute lymphocyte count, lymphocyte percentage, absolute monocyte count, monocyte percentage, absolute eosinophil count, eosinophil percentage, absolute basophil count, basophil percentage, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin content, mean corpuscular hemoglobin concentration, red blood cell distribution width, platelet count, mean platelet volume, platelet hematocrit, and platelet distribution width;
- Blood chemistry: fasting blood glucose, bile acid, total protein, albumin, globulin, albumin/globulin ratio, TBIL, direct bilirubin, indirect bilirubin, ALT, AST, gamma-glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, creatine kinase, creatine kinase isoenzyme MB, urea/blood urea nitrogen, blood uric acid, creatinine, potassium, sodium, chloride, calcium, magnesium, inorganic phosphorus, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol;
- Urinalysis: urine glucose, urine bilirubin, urine ketone body, urine pH, urine protein, urobilinogen, urine nitrite, urinary occult blood, urine white blood cells, urine red blood cells, urinary sediment microscopic examination (red blood cells, white blood cells) and urine specific;
- Coagulation function test: including prothrombin time, activated partial thromboplastin time, thrombin time, international normalized ratio and fibrinogen;
- Serum pregnancy test: female subjects of childbearing potential will receive serum

pregnancy test at screening;

- Urine pregnancy test: female subjects of childbearing potential will receive urine pregnancy test from V2 to V6 and other visits specified in the protocol. If the urine pregnancy test result is positive, serum pregnancy test must be performed for confirmation.

Hematology, blood chemistry, urinalysis, and coagulation tests are performed at all on-site visits in this study; creatinine clearance (Ccr) is calculated at visits V1, V2, V3, V6, and the early termination visit (if applicable) based on body weight measurements and serum creatinine levels from the blood chemistry tests, with the calculation formula provided in Appendix II. (If body weight was measured during demographic data collection at V1, remeasurement is not required during that visit.) If hematology, blood chemistry, coagulation function test, urinalysis body weight measurement and Ccr calculation have been performed within 7 days (exclusive) before V2, these tests are not required to be repeated on V2; otherwise, they are required to be re-tested at V2 and the eligibility for the study enrollment should be confirmed according to the test results.

Although the screening for infectious diseases also requires laboratory tests, it is not a relevant parameter for the evaluation of the endpoint of this study. It should only be tested during the screening period; therefore, it is not listed in this section. Screening for infectious diseases is detailed in Section 8.4.

Laboratory tests that require subjects to be fasted are provided in Section 8.5.

If certain items are not included in routine tests at some study sites, they can be tested separately.

Information on sample collection, processing, preservation and destruction should comply with the regulations of the laboratory of the study site.

8.3 Evaluation of Exploratory Indicators

8.3.1 Exploratory Inflammatory Indicators

The exploratory inflammatory indicators of this study include interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17A, interferon (IFN)-α, IFN-γ, and tumor necrosis factor (TNF)-α; the specific indicators to be tested are subject to the actual implementation at

each center.

The design of blood sampling points for exploratory inflammatory indicators is as follows:

- V2, V4, V5, V6;
- Early withdrawal visit (if applicable).

8.3.2 Exploratory PD Biomarkers

The exploratory PD indicators of this study include α-synuclein and GFAP. Blood samples will be collected at V2, V6, and Early Discontinuation/Early Withdrawal Visit (if applicable), with a total of 5 mL of blood collected per visit, and sent to the central laboratory for testing. All other test samples in this trial will be tested in local laboratories.

8.3.3 Exploratory Skeletal Muscle Mass and Function Assessment

The exploratory skeletal muscle mass and function assessment indicators of this study include ASMI, muscle strength (grip strength) and 6-meter walking speed test (the specific indicators to be tested are subject to the actual operation at each center), all of which will be assessed at V2, V6, and early withdrawal visit (if applicable). Among them, ASMI is detected and calculated by dual-energy X-ray absorptiometry (DXA), and the calculation formula is ASMI = appendicular muscle mass (kg) / height^2 (m^2). If the V2 visit is not assessed, then the V6 and early withdrawal visits should also not be assessed.

8.3.4 Exploratory Genomic Resequencing

To explore the association between the efficacy of TJ0113 capsules and the genomic characteristics in patients with early-stage PD, this study will collect blood samples from subjects for genomic resequencing. Each subject will be collected once at V2 (if not collected at V2, it is allowed to be supplemented at V6 or early withdrawal visit).

8.4 Tests/Assessments Required for V1 during Screening Period Only

Tests/assessments required for V1 only include:

- Screening for infectious diseases: including hepatitis B five-item panel (HBsAg, hepatitis B virus surface antibody, hepatitis B virus e antigen, hepatitis B virus e antibody, hepatitis B virus core antibody), HCV antibody, HIV antibody, and Treponema pallidum antibody detection. If certain items are not included in routine tests at some study sites, they can be tested separately.

- B-ultrasound: detection sites include liver, gallbladder, pancreas, spleen, and kidney.
- Tumor marker detection: including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), carbohydrate antigen 125 (CA125) (only for females), total prostate specific antigen (T-PSA) (only for males), free prostate specific antigen (F-PSA) (only for males), carbohydrate antigen 153 (CA153), squamous cell carcinoma antigen (SCC), ferritin.
- Test of serum follicle stimulating hormone: this test is performed at screening only in women whose menopause occurred within the last 24 months or who are uncertain about their menopausal status.
- Assessment using modified Hoehn and Yahr Scale.

8.5 Parameters to be Tested Under a Fasted State

Subjects must be fasted before each visit (fast for at least 10 hours overnight without depriving of water). It is recommended that fasting blood samples be collected between 7:00 a.m. and 10:00 a.m., and the specific collection time point is subject to the implementation of each study site. The investigational product or background medication for PD should not be administered prior to blood collection. If the subject has not fasted before the visit, an additional fasting collection should be scheduled.

Parameters to be tested under a fasted state at site visit include: hematology, blood chemistry, B-ultrasound, and exploratory inflammatory indicators; there is no fasting requirement for other parameters at site visit.

8.6 Sample Submission Plan

Blood samples (total 5 mL) for exploratory analysis of α-synuclein and GFAP indicators need to be sent to the central laboratory for testing after collection. Blood samples (total 5 mL) for exploratory analysis of genomic resequencing need to be sent to the central laboratory for testing after collection. All other test samples in this trial will be tested in local laboratories.

8.7 Trial Procedure

The study consists of a screening period, a treatment period and a follow-up period. After subjects sign the written ICF, they will receive all the tests and trial procedures according to the study requirements.

Before V1, the investigator should inform the subject in advance that the last dose of the background medication for PD on the day before V1 should be at least 12 hours apart from the agreed visit time of V1, and the subject should bring background medication for PD (at least a single dose) that has been stably taken to the hospital on the day of V1, and take the first dose of such medication on the day of V1 under the guidance of the investigator.

Collection of blood samples for exploratory analysis of genomic resequencing: each subject will be collected once at V2 (if not collected at V2, it is allowed to be supplemented at V6 or early withdrawal visit).

8.7.1 Screening Period

8.7.1.1 V1 (D-28-D-2, W-4-W-1)

At V1, the following procedures will be performed:

- Sign an ICF;
- Subjects must be fasted before each visit (fast for at least 10 hours overnight without depriving of water).
- Collect demographics: including date of birth, age, gender, ethnicity, height, weight, and BIM, etc.;
- Collect the history of diagnosis and treatment of PD;
- Collect other medical history and treatment history: including other past and current medical history (excluding PD), treatment history, surgical history and surgical plan, etc.;
- Collect other personal history: including but not limited to family history, allergy history, alcohol consumption history, substance abuse history, blood transfusion history, and childbearing plan, etc.;
- Vital signs: blood pressure measurement should be performed after the subject has rested in a supine position for at least 5 min; after supine blood pressure measurement is completed, have the patient stand upright and measure standing blood pressure within 3 min while resting in an upright position; other vital signs can be measured with the subject in a sitting position after having rested for at least

5 min;

- Physical examination;
- 12-lead ECG;
- Laboratory tests: including hematology, blood chemistry, urinalysis, coagulation function, screening for infectious diseases, serum pregnancy test (only for women of childbearing potential), serum follicle stimulating hormone test (only for women whose menopause occurred within the last 24 months or who are uncertain about their menopausal status);
- Weight measurement and Ccr calculation (If weight has been measured when collecting demographics at V1, it is not necessary to repeat the weight measurement during that visit);
- B-ultrasound: detection sites include liver, gallbladder, pancreas, spleen, and kidney;
- Tumor marker detections: including AFP, CEA, CA199, CA125 (only for females), T-PSA (only for males), F-PSA (only for males), CA153, SCC, ferritin;
- Assessment using modified Hoehn and Yahr Scale;
- MDS-UPDRS Part I and III scores (if the subject has received stable medication for PD within at least 4 weeks prior to study entry, Part III score must be ≥ 12 hours from the most recent dose of background medication for PD);
- Use background medication for PD (if applicable);
- Record concomitant medications/therapies;
- Record AEs;
- Assess against inclusion/exclusion criteria;
- Note:
  - At V2, subjects who are eligible after screening should return to the study site in the morning (recommended from 7:00 am to 10:00 am) for a site visit;
  - If the subject has received stable medication for PD within at least 4 weeks prior to study entry, the last dose of the background medication for PD on the day before V2 should be at least 12 hours apart from the agreed visit time of V2, and the subject should bring background medication for PD (at least a single

dose) that has been stably taken to the hospital on the day of V2, and take the first dose of such medication on the day of V2 under the guidance of the investigator.

If screen failure is caused due to abnormal results during the screening process, and if the investigator judges that there is a clear justification for retesting, and the tests can be repeated within the time window once, but the reason for repeating the test should be recorded. Subjects with screening failure are only allowed for re-screening once during the enrollment stage of this study. Additional medications are not allowed to correct the abnormal values (e.g. hepatoprotective drugs used to address hepatic function abnormal) prior to the re-measurement or re-screening. Parameters that are allowed for retesting include: blood pressure, ECG, creatinine, AST, ALT, and TBIL.

8.7.1.2 V2 (D-1, W-1)

At V2, the following procedures will be performed:

- Subjects must be fasted before each visit (fast for at least 10 hours overnight without depriving of water);
- Vital signs: blood pressure measurement should be performed after the subject has rested in a supine position for at least 5 min; after supine blood pressure measurement is completed, have the patient stand upright and measure standing blood pressure within 3 min while resting in an upright position; other vital signs can be measured with the subject in a sitting position after having rested for at least 5 min;
- Physical examination;
- 12-lead ECG;
- Laboratory tests: including hematology, blood chemistry, urinalysis, coagulation function test, and urine pregnancy test (only for women of childbearing potential);
- Weight measurement and Ccr calculation;
- Assess against inclusion/exclusion criteria;
- Randomization;
- Collect blood samples for exploratory analysis (one blood sample each for inflammatory indicators and PD biomarkers; among these, 5 mL of blood is

collected for PD biomarker testing and sent to the central laboratory for testing);

- Exploratory skeletal muscle mass and function assessment: including ASMI, muscle strength (grip strength) and 6-meter walking speed test (specific test indicators are subject to the actual operation of each center). Among them, ASMI is detected and calculated by DXA, and the calculation formula is ASMI = appendicular muscle mass (kg) / height^2 (m^2);
- MDS-UPDRS Part III score before the administration of background medication for PD (only applicable to subject who has received stable medication for PD within at least 4 weeks prior to study entry, and this score should be ≥ 12 hours from the most recent dose of background medication for PD);
- Dispense the drug using the Clinflash IRT system;
- Take background medication for PD (only applicable to subject who has received stable medication for PD within at least 4 weeks prior to study entry);
- MDS-UPDRS score: Parts I, II, III, IV (if the subject has received stable medication for PD within at least 4 weeks prior to study entry, Part III score must be assessed at 2 ± 1 hours after the administration of background medication for PD at this visit);
- Record concomitant medications/therapies;
- Record AEs;
- Dispense and instruct subjects to complete diary cards;
- Note:
  - At V3, subjects should return to the study site for a visit in the morning (recommended from 7:00 a.m. to 10:00 a.m.) with their diary cards and on an empty stomach (fast for at least 10 hours overnight without depriving of water);
  - If the subject has received stable medication for PD within at least 4 weeks prior to study entry, the administration of investigational product and last dose of the background medication for PD on the day before V3 should be at least 12 hours apart from the agreed visit time of V3, and the subject should bring background medication for PD (at least a single dose) that has been stably taken to the hospital on the day of V3, and take the first dose of such medication on the day of V3 under the guidance of the investigator.

If hematology, blood chemistry, coagulation function test, urinalysis, 12-lead ECG examinations, weight measurement and Ccr calculation have been performed within 7 days (exclusive) before V2, these tests are not required to be repeated on V2; otherwise, they are required to be re-tested at V2 and the eligibility for the study enrollment should be confirmed according to the test results.

8.7.2 Treatment Period

8.7.2.1 V3 (D7, W1)

At V3, the following procedures will be performed:

- Subjects must be fasted before each visit (fast for at least 10 hours overnight without depriving of water);
- Vital signs;
- Physical examination;
- 12-lead ECG;
- Laboratory tests: including hematology, blood chemistry, urinalysis, coagulation function test, and urine pregnancy test (only for women of childbearing potential);
- Weight measurement and Ccr calculation;
- Return diary card;
- MDS-UPDRS Part III score before administration of the investigational product and the background medication for PD (if applicable) (≥ 12 hours from the most recent administration of background medication for PD (if applicable) and the investigational product);
- Dispense the drug using the Clinflash IRT system;
- Take investigational product and background medication for PD (if applicable) concomitantly;
- MDS-UPDRS Part III score after administration of the investigational product and the background medication for PD (if applicable) (to be performed at 2 ± 1 hours after the administration);
- MDS-UPDRS Parts I, II, and IV scores;
- Record concomitant medications/therapies;

- Record AEs;
- Dispense a new diary card;
- Note:
  - At V4, subjects should return to the study site for a visit in the morning (recommended from 7:00 a.m. to 10:00 a.m.) with their diary cards and on an empty stomach (fast for at least 10 hours overnight without depriving of water);
  - If the subject has received stable medication for PD within at least 4 weeks prior to study entry, the administration of investigational product and last dose of the background medication for PD on the day before V4 should be at least 12 hours apart from the agreed visit time of V4, and the subject should bring background medication for PD (at least a single dose) that has been stably taken to the hospital on the day of V4, and take the first dose of such medication on the day of V4 under the guidance of the investigator.

8.7.2.2 V4 (D28, W4), V5 (D56, W8)

At V4 and V5, the following procedures will be performed:

- Subjects must be fasted before each visit (fast for at least 10 hours overnight without depriving of water);
- Vital signs;
- Physical examination;
- 12-lead ECG;
- Laboratory tests: including hematology, blood chemistry, urinalysis, coagulation function test, and urine pregnancy test (only for women of childbearing potential);
- Collect blood samples for exploratory analysis (inflammatory indicators);
- Return investigational product;
- Return diary card;
- MDS-UPDRS Part III score before administration of the investigational product and the background medication for PD (if applicable) (≥ 12 hours from the most recent administration of background medication for PD (if applicable) and the investigational product);
- Dispense the drug using the Clinflash IRT system;

- Take investigational product and background medication for PD (if applicable) concomitantly;
- MDS-UPDRS Part III score after administration of the investigational product and the background medication for PD (if applicable) (to be performed at 2 ± 1 hours after the administration);
- MDS-UPDRS Parts I, II, and IV scores;
- Record concomitant medications/therapies;
- Record AEs;
- Dispense a new diary card;
- Note:
  - At V5 and V6, subjects should return to the study site for a visit in the morning (recommended from 7:00 a.m. to 10:00 a.m.) with their diary cards and on an empty stomach (fast for at least 10 hours overnight without depriving of water);
  - The administration of investigational product and last dose of the background medication for PD (if applicable) on the day before V5 and V6 should be at least 12 hours apart from the agreed visit time of V5 and V6, and the subject should bring background medication for PD (if applicable, at least a single dose) that has been stably taken to the hospital on the day of V5 and V6, and take the first dose of such medication on the day of V5 and V6 under the guidance of the investigator.

8.7.2.3 V6 (D84, W12)

At V6, the following procedures will be performed:

- Subjects must be fasted before each visit (fast for at least 10 hours overnight without depriving of water);
- Vital signs;
- Physical examination;
- 12-lead ECG;
- Laboratory tests: including hematology, blood chemistry, urinalysis, coagulation function test, and urine pregnancy test (only for women of childbearing potential);
- Weight measurement and Ccr calculation;

- Collect blood samples for exploratory analysis (one blood sample each for inflammatory indicators and PD biomarkers; among these, 5 mL of blood is collected for PD biomarker testing and sent to the central laboratory for testing);
- Exploratory skeletal muscle mass and function assessment: including ASMI, muscle strength (grip strength) and 6-meter walking speed test (specific test indicators are subject to the actual operation of each center). Among them, ASMI is detected and calculated by DXA, and the calculation formula is ASMI = appendicular muscle mass (kg) / height^2 (m^2);
  - Return investigational product;
- Return diary card;
- MDS-UPDRS Part III score before administration of the investigational product and the background medication for PD (if applicable) (≥ 12 hours from the most recent administration of background medication for PD (if applicable) and the investigational product);
- Take investigational product and background medication for PD (if applicable) concomitantly;
- MDS-UPDRS Part III score after administration of the investigational product and the background medication for PD (if applicable) (to be performed at 2 ± 1 hours after the administration);
  - MDS-UPDRS Parts I, II, and IV scores;
- Record concomitant medications/therapies;
- Record AEs;

8.7.3 Follow-up Period (Telephone Follow-up; V7, D91, W13)

At V7, AEs and concomitant medication information will be collected via telephone follow-up.

8.7.4 Early Withdrawal Visit

Subjects who have early withdrawn from the study should complete the early withdrawal visit within 7 days after the investigator's awareness (if it is less than 7 days from the date of the

previous visit, repeated tests of the same item can be waived), excluding subjects who have early withdrawn from the study due to withdrawal of consent or are lost to the follow-up.

At the early withdrawal visit, the following procedures will be performed:

- Subjects must be fasted before each visit (fast for at least 10 hours overnight without depriving of water);
- Vital signs;
- Physical examination;
- 12-lead ECG;
- Laboratory tests: including hematology, blood chemistry, urinalysis, coagulation function test, and urine pregnancy test (only for women of childbearing potential);
- Weight measurement and Ccr calculation;
- Collect blood samples for exploratory analysis (one blood sample each for inflammatory indicators and PD biomarkers; among these, 5 mL of blood is collected for PD biomarker testing and sent to the central laboratory for testing);
- Exploratory skeletal muscle mass and function assessment: including ASMI, muscle strength (grip strength) and 6-meter walking speed test (specific test indicators are subject to the actual operation of each center). Among them, ASMI is detected and calculated by DXA, and the calculation formula is ASMI = appendicular muscle mass (kg) / height^2 (m^2);
- Return diary card;
- Return investigational product;
- MDS-UPDRS Part III score before the administration of background medication for PD (only applicable to subject who has received stable medication for PD within at least 4 weeks prior to study entry, and this score should be ≥ 12 hours from the most recent dose of background medication for PD);
- Take background medication for PD (only applicable to subject who has received stable medication for PD within at least 4 weeks prior to study entry);
- MDS-UPDRS score: Parts I, II, III, IV (if the subject has received stable medication for PD within at least 4 weeks prior to study entry, Part III score must be assessed at

2 ± 1 hours after the administration of background medication for PD at this visit);

- Record concomitant medications/therapies;
- Record AEs;

8.7.5 Unscheduled Visit

If a subject participates an unscheduled visit at the study site, it should be documented accordingly.

9 AE-related Assessment

9.1 Definition of AEs

9.1.1 AEs

An AE is any untoward medical occurrence in a patient administered an investigational product (TJ0113 capsules or placebo) and which does not necessarily have to have a causal relationship with this treatment. It can manifest as symptoms, signs, diseases or laboratory test abnormalities. Therefore, the AE can be any unfavorable or unexpected, or clinically significant symptoms, signs or diseases, including ADRs, important laboratory abnormal findings, new diseases during the study, and exacerbation of pre-existing conditions or symptoms (excluding the conditions to be treated with the investigational product; daily fluctuation in underlying disease is not considered as an AE).

9.1.2 Treatment-Emergent Adverse Events (TEAEs)

A TEAE refers to any AE that emerges during treatment (absent pre-treatment) or worsens relative to the pre-treatment state after the first dose of the investigational product.

9.1.3 Treatment-Related Adverse Events (TRAEs)

A TRAE refers to any TEAE related to the investigational product at the investigator's discretion.

9.1.4 Serious Adverse Events (SAEs)

An SAE refers to any adverse medical event that results in death[a], is life-threatening event[b], requires hospitalization or prolongation of existing hospitalization for the subject[c], results in persistent or significant disability/incapacity[d], or is congenital abnormaly or birth defect[e], or is other important medical event[f] after the subject uses an investigational product.

Further explanations for the above criteria are as follows:

a. An AE that results in subject's death;
b. An AE in which the subjects was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (e.g., drug-induced hepatitis without liver failure);
c. Any AEs resulting in hospitalization or prolongation of existing hospitalization (hospitalization: refers to that a subject has been admitted at the inpatient department

or emergency ward for observation or treatment over 24 h; prolongation of existing hospitalization: the AEs occur during hospitalization period and prolong the existing hospitalization), excluding elective surgery or admission for examination, etc., decided prior to study participation and for which the treatment is not changed.

d. The consequences of the AE may cause serious inconvenience or interference with the subject's normal life and activities, cause impairment, damage or destruction of the subject's physical function and/or physiological structure, physical activities or quality of life;

e. It is suspected that exposure of a parent to the study drug may cause malformation or congenital functional defect, etc., in the subject's offspring;

f. Medical and scientific judgment must be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may be considered serious if medical intervention is necessary to prevent one of the above situations. For example, important treatment in emergency room or allergic bronchospasm at home, cachexia or convulsion requiring no hospitalization, development of drug dependence or addiction etc.

9.1.5 Adverse Drug Reactions (ADRs)

All noxious and unintended responses to a medicinal product related to any dose should be considered Adverse Drug Reactions (ADRs). There is at least a reasonable possibility of the causal relationship between the investigational product and an AE, i.e., the relationship cannot be ruled out.

For a new medicinal product or new usage, all harmful or unexpected reactions at any dose causally related to administration of the drug in clinical use before approval, particularly in the period when therapeutic dose has not been determined should be considered ADRs.

9.1.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs refer to suspected unexpected serious adverse reactions whose clinical manifestations are beyond the Investigator’s Brochure for the investigational drug, package inserts for marketed medicinal products, summary of product characteristics and other existing information in terms of their nature and severity.

Assessment of expectedness: It should be assessed based on the relevant sections of the Investigator's Brochure for the investigational product that is effective at the date of the event, which serves as the safety reference information. Unexpected, for the investigational product, means that the event is not listed on the Investigator's Brochure of the investigational product, or the nature or severity of the event exceeds that described in the Investigator's Brochure of the investigational product.

9.2 Causal Relationship

The investigator should conduct a comprehensive analysis according to the specific circumstances of AEs of the subjects and their past medical history, concomitant diseases and concomitant medications, to determine the correlation between AEs and the investigational product. The investigator should perform causality analyses for treatment-emergent symptoms in order to identify potential correlations between the AE and the investigational product.

The specific criteria for adjudicating the causal relationship between the AE and the investigational product are shown in Table 9-1. The causal relationship between the AE/SAE and investigational product is judged as definitely related, probably related, possibly related, unlikely related and not related. Among them, "definitely related, probably related, and possibly related" are classified as related to the investigational product, and this type of AEs are regarded as ADRs. "Unlikely related and not related" are classified as unrelated to the investigational product, and this type of AEs will not be included in ADR analysis.

Table 9-1 Classification and Rationale for Correlation Determination Results of AEs in Drug Clinical Studies

5-category method	Rationale for determination	2-category method
Definitely related	• Whether there is reasonable temporal relationship • Whether it conforms to the known mechanism of action, properties of the drug or known adverse reactions • Positive de-challenge test • Positive re-challenge test	Related

5-category method	Rationale for determination	2-category method
	• Whether it is not justified by other reasons	
Probably related	• Whether there is reasonable temporal relationship • Whether it conforms to the known mechanism of action, properties of the drug or known adverse reactions • Positive de-challenge test • Lack of evidence for a positive re-challenge • Whether it is not justified by other reasons	
Possibly related	• There is a reasonable temporal relationship; • Lack of evidence for a positive re-challenge; • It is manifested as any of the following conditions: a) The AE is consistent with the known mechanism of action, characteristics or known adverse reactions of the drug, de-challenge test is positive, but the AE can also be reasonably explained by other factors; b) The AE is consistent with the known mechanism of action, characteristics or known adverse reactions of the drug, there is a lack of evidence for a positive de-challenge, and the AE cannot be reasonably explained by other factors; c) The AE is not consistent with the known mechanism of action, characteristics or known adverse reactions of the drug, de-challenge test is positive, and the AE cannot be reasonably explained by other factors; d) The AE is not consistent with the known mechanism of action, characteristics or known adverse reactions, there is a lack of evidence for a	

5-category method	Rationale for determination	2-category method
	positive de-challenge, and the AE cannot also be reasonably explained by other factors;	
Unlikely related	• Temporal relationship cannot be ruled out • Lack of evidence for a positive de-challenge • Lack of evidence for a positive re-challenge • It is manifested as any of the following conditions: a) Although the AE is consistent with the known mechanism of action, characteristics or known adverse reactions, it can be more reasonably explained by other factors; b) The AE is not consistent with the known mechanism of action, characteristics or known adverse reactions, and can be reasonably explained by other factors;	Unrelated
Not related	• There is no reasonable temporal relationship • It does not conform to the known mechanism of action, properties of the drug or known adverse reactions • Lack of evidence for a positive de-challenge • Lack of evidence for a positive re-challenge • It can be justified by other reasonable reasons	

9.3 Determination of the Severity

The severity of AEs will be recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For AEs not listed in NCI-CTCAE, its severity can be graded as follows:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting

age-appropriate instrumental activities of daily living (instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.);

- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);
- **Grade 4:** Life-threatening, urgent intervention indicated;
- **Grade 5:** Adverse event-related death.

9.4 Collection, Recording and Reporting of AEs

9.4.1 Collection and Recording of AEs and SAEs

9.4.1.1 Collection Time of AEs

AEs are collected in this trial from the time the subject receives the investigational product (i.e., TJ0113 capsules or placebo) until the end of the follow-up period. Supplementary description is as follows:

- Untoward medical occurrences (including abnormalities at baseline) that newly occur or worsen relative to pre-signing state from subject's signing ICF to the first dose of the investigational product, if assessed by the investigator as related to the subject's participation in this trial (such as a protocol-specified procedure or invasive test), should be recorded and reported as AEs, otherwise should be recorded as medical history;
- The investigator needs to collect all AEs (regardless of whether it is causally related to the investigational product or related to clinical procedure) from the first dose of the investigational product to the end of the follow-up period;
- AEs that occur after the follow-up period must also be collected and recorded if the investigator considers that it is related to the investigational product (including SAEs) after awareness.

9.4.1.2 Recording of AEs

The investigator or other designee will be responsible for monitoring, recording and reporting events that meet the definition of AEs/SAEs.

At each visit during the entire study period, the investigator or his/her designee should ask the

subject non-directive questions to learn about the occurrence of AEs/SAEs, and may also find AEs/SAEs through the subject's spontaneous reports, physical examinations, laboratory tests or other assessments during the visit or non-visit period. The subject or his/her caregiver may also report AEs occurring during the trial.

For any unexplainable or unexpected laboratory abnormalities of clinical significance throughout the study period, retest should be performed as soon as possible and the abnormality should be followed up until returning to the normal range and/or adequate explanation can be given for the abnormality. The investigator should clearly mark the laboratory results out of normal range and indicate whether they are of clinical significance or not.

All AEs must be followed up until they have clinically recovered, stabilized, return to the screening or baseline level (if baseline level is known), the subject is lost to follow-up (e.g., no more information is available or the subject/caregiver refuses to provide any information), or dead. This means that further follow-up observations may be required even after the last protocol-specified visit, and the monitoring team may require the investigator to perform additional follow-up.

All AEs occurring within the collection time limit specified in this protocol must be completely recorded (after the end of the trial, the collection of follow-up data for subjects with ongoing AEs does not affect the on-time database lock after the end of the trial).

For the recording of AEs/SAEs, a single diagnosis or syndrome should be used to describe their term as far as possible. The documentation should be supported by original documents and each event should be described in detail, including:

- Term of AEs (use the term for a sign, symptom, diagnosis, or syndrome);
- Onset date, ongoing or not, end date;
- Severity;
- Investigator's judgment of the causality between the event and investigational product or study procedure, including details of the suspected procedure;
- The actions taken with investigational product may include dose not changed, temporarily discontinued, dose reduced, drug withdrawn, not applicable, and

unknown;

- Event outcomes: ① recovered/resolved; ② recovering/resolving; ③ not recovered/not resolved/ongoing; ④ recovered/resolved with sequelae; ⑤ fatal; and ⑥ unknown;
- Seriousness: Whether it is an SAE or not;
- Drug therapies and other interventions given to correct the AE.
  - None;
  - Drug therapy;
  - Non-drug intervention;
  - Drug therapies and non-drug interventions.

In addition, the investigator should collect other information required by the sponsor.

9.4.1.3 Precautions for Recording of AEs/SAEs

Diagnosis versus signs and symptoms

The diagnosis that is available should be recorded rather than single symptom or sign. However, if the symptoms and signs cannot be categorized as a single diagnosis during reporting period, each single event should be recorded as AE or SAE. If the diagnosis is confirmed later, the AE previously reported based on signs and symptoms should be canceled and be replaced with an AE report based on a single diagnosis, noting that the start date should be the start date of the first symptom used for the final diagnosis.

AEs secondary to other events

In general, for events secondary to other AEs (such as cascading events or clinical sequelae), they should not be recorded as separate AEs, except for severe or serious secondary events. If the secondary event is medically significant and the two events occurred independently of each other, the secondary event should be recorded as a separate AE in the eCRF. For example:

- If vomiting has caused severe dehydration, two AEs should be separately reported on the eCRF.
- If severe gastrointestinal bleeding has caused renal failure, two AEs should be separately reported on the eCRF.
- If dizziness caused a fall followed by a fracture, three AEs should be separately

reported on the eCRF.

- If neutropenia caused infection, two AEs should be separately reported on the eCRF.
- If it is not clear whether the events are interrelated, all AEs should be recorded separately in the AE Record of the eCRF.

Persistent or recurrent AEs

Persistent AEs are AEs that persist without any remission between the two evaluation time points of the subject. If the event meets the seriousness criteria, it is an SAE. The investigator should report it to the sponsor and the Contract Research Organization (CRO) designated by the sponsor within 24 hours of awareness. In such case, the AE should be updated to change the AE from "non-serious" to "serious", the date when the AE developed into SAE should be recorded, and all the information fields related to SAE should be filled in.

Recurrent AEs refer to AEs that have resolved or resolved with sequelae, but then reoccur. AEs that reoccur should be recorded separately.

Abnormal laboratory values and vital signs

Not all abnormal laboratory values or vital signs are reportable as AEs. An AE must be reported if the laboratory test or vital sign meets any of the following criteria:

- Accompanied by clinical symptoms;
- Resulting in changes in the study treatment (e.g. dose adjustment, treatment interruption or discontinuation);
- Requiring medical intervention (e.g., potassium supplementation to treatment hypokalemia) or resulting in changes in concomitant therapies;
- Clinically significant results at the investigator's discretion.

The investigators are responsible for reviewing all the abnormal laboratory findings and vital signs, and determine whether to record them as AEs.

If clinically significant abnormal laboratory tests or abnormal vital signs are manifestations of certain disease or syndrome (e.g., alkaline phosphatase and bilirubin increase more than 5 times the upper limit of normal, which are caused by cholecystitis), only the diagnosis is recorded (i.e., cholecystitis). Conversely, abnormal laboratory tests or abnormal vital signs should be recorded. Moreover, it should be indicated whether the test value is higher or lower

than the normal range (for example, it should be recorded as "blood potassium increased" instead of "abnormal blood potassium"). If there is a standard clinical term corresponding to abnormal laboratory tests or abnormal vital signs, the clinical term should be recorded. For instance, serum potassium increasing to 7.0 mEg/L should be recorded as "hyperkalemia".

9.4.2 Reporting of SAEs

For all SAEs that occur within the collection time limit specified in this protocol, the investigator must fill in, sign and date the SAE Report Form within 24 hours of awareness, immediately report it to the sponsor (or the CRO appointed by the sponsor).

In case of reports involving death events, the investigator should provide the sponsor and Ethics Committee with other necessary information, such as autopsy report and final medical report.

The investigator should provide detailed written follow-up reports in a timely manner. For follow-up information of SAEs, the reporting method and time limit are the same as those for the initial report.

Time for collecting SAEs:

- Only SAEs related to protocol-specified procedure or invasive test, etc. will be reported from subject's signing ICF to the first dose of the investigational product.
- The investigator needs to collect and report all SAEs (regardless of whether it is causally related to the investigational product or related to clinical procedure) from the first dose of the investigational product to the end of the follow-up period;
- SAEs that occur after the end of the clinical trial or the end of the follow-up until the conclusion of the review and approval is obtained, if assessed by the investigator that the relevance to the investigational product cannot be ruled out, should be informed to the sponsor (or the CRO appointed by the sponsor) within 24 hours of awareness.

9.4.3 Reporting of SUSARs

The sponsor (CRO appointed by the sponsor) should comprehensively analyze, evaluate and judge the safety information received of any sources in a timely manner, including severity, correlation with the investigational product and whether it is an expected event, as well as

report in an expedited manner depending on the nature (category) of the event within the time limit set out by the regulatory authorities. The sponsor (CRO appointed by the sponsor) should expeditely report SUSARs to all investigators and clinical trial institutions participating in the study, Ethics Committee, drug regulatory authorities and health authorities within specified time limit.

The processing and expedited reporting of SUSAR reports will be completed in accordance with Good Vigilance Practice and FAQs for Expedited Reporting of Safety Data during Drug Clinical Trials (V2.0).

SUSARs occurring after the end of the clinical trial and before obtaining the approval conclusion will be reported in the same manner as for expedited reporting before the end of trial.

For the SUSAR report and clinical trial-related safety information provided by the sponsor, the investigator should sign and read it in time, and report to the clinical trial institution and the Ethics Committee.

9.5 Reporting of Special Conditions

9.5.1 Death

Regardless of relevance to the investigational product, all deaths during the trial must be recorded as SAE (including death due to the disease proposed to be treated with the investigational product) and reported to the sponsor (or a CRO appointed by the sponsor) within 24 hours of awareness.

Death should be regarded as the outcome rather than a separate event. Death is not reported as SAE term, but the cause of death must be reported as the SAE term. Information of events leading to death can also be further improved in follow-up reports. The term "sudden death" is used only to describe where a subject with or without pre-existing heart disease died suddenly and accidentally within 1 hour of onset of the acute symptoms, and the cause of death is presumed to be the heart disease; or the subject died without any witness within 24 hours after the subject is last seen (when the subject's vital signs are stable). If the cause of death cannot be determined at the time of reporting, the SAE term may be recorded and reported as “death

unexplained". If the cause of death is subsequently established (e.g., after an autopsy), the SAE term should be replaced with the established cause of death.

9.5.2 Pregnancy

If the female subject of childbearing potential or the female partner of a male subject becomes pregnant from the first dose of investigational product to within 6 months after the last dose of the investigational product, the investigator should be immediately informed. The investigator should complete the Clinical Trial Pregnancy Report Form within 24 hours of awareness, sign and date, and report it to the sponsor (or the CRO appointed by the sponsor) by email. All pregnancy events should be followed up until the pregnancy outcome or lost to follow-up.

In the case of live birth, the case must be followed up until 30 days after the birth of the baby. Spontaneous abortion or termination of pregnancy for medical reasons (except for uncomplicated elective abortion for non-medical reasons) should be considered as an SAE, that is, the SAE should also be reported at the same time as the completion and reporting of the pregnancy report form. Any birth defects/congenital abnormalities of newborns, stillbirth, death, and serious complications during pregnancy of female subjects or female partners of male subjects and of newborns, etc., if meeting the SAE criteria, are also considered as SAEs, that is, SAEs should also be reported at the same time as the completion and reporting of the pregnancy report form.

Pregnant female subjects must immediately discontinue the investigational product and withdraw from the trial. The male subject whose partner becomes pregnant does not have to withdraw from this study. The investigator should provide recommendations for the male subject and his female partner, discussing risk of continued pregnancy and potential effect on the fetus.

9.5.3 AEs Related to Overdose or Medication Error

Medication error is defined as an unexpected deviation in the administration of the investigational product, such as an omission, incorrect medication dose (e.g., overdose), wrong time of administration, wrong route of administration, wrong medication, and use of expired/contaminated/deteriorated study drug, among which, overdose is defined as the actual

dose of the investigational product administered being greater than the planned dose. Overdose or medication error of investigational product itself is not an AE, but it may lead to an AE. All AEs related to overdose or medication error of the investigational drug should be recorded on the AE Record of the eCRF. If the relevant AE meets the seriousness criteria for SAE, it should be reported to the sponsor immediately (i.e., within 24 hours of awareness).

10 Data Management

10.1 Completion and Transfer of Source Data and Case Report Form

Data in eCRF are all from source data and documents. They are filled in by the investigator or the person designated by the investigator. Information completeness and accuracy must be ensured. If there is any error that needs to be corrected, the modification should be carried out according to the eCRF completing instructions, and the name of data modifier and modification date should be recorded. After filling in the eCRF, it should be submitted timely to Electronic Data Capture (EDC) system via the Internet. After the data in the EDC system are confirmed correct after source data verification (SDV), review and query by data manager, the investigator is required to provide electronic signature for confirmation before data locking.

10.2 Design and Establishment of Database

The database is established by the data department of the CRO assigned by the sponsor. The database should manage the system login, data entry, modification, deletion and other data traces.

10.3 Data Entry and Modification

In this trial, data are collected using EDC, and online data management is completed through the functions of electronic data entry, data verification and data inspection of EDC system.

Data in eCRF should be filled in by the investigator or the person designated by the investigator. Information completeness and accuracy must be ensured. If there is any error that needs to be corrected, the modification should be carried out according to the instructions for filling out the eCRF, and the EDC system would automatically record the name of data modifier and modification date.

The eCRF, once completed, will be timely submitted through the network to EDC system. After data in the EDC system are verified against the source data, reviewed by DM, and the queries are well resolved, the investigator will confirm it by providing an electronic signature before data lock.

10.4 Data Review

After data entry and verification are completed, the data manager, the principal investigators, the sponsor, and statistical analysis personnel will jointly review the data, and complete the final definition and judgment of the analyzed population.

10.5 Data Coding

The data manager is responsible for medical coding. Coding contents include medical history, concomitant medications and AEs.

The medical history and AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). The concomitant medications are coded using World Health Organization Drug Dictionary (WHO DD). All dictionaries used are the latest version confirmed by the sponsor.

During the coding process, the data manager will ask the investigator, in the form of data queries, to verify and confirm any data problems such as failure to code due to improper, inaccurate, and vague medical terms provided.

Prior to database lock, the data manager will send medical coding report to the sponsor, which will be reviewed by the sponsor.

10.6 Data Lock

Database can be locked when the following conditions are met:

1) All data have been entered into database;

2) All questions have been resolved;

3) The analysis population has been defined and evaluated.

At the end of the study, once the accuracy of the established database is confirmed through a data verification meeting, the principal investigator, the sponsor, and the statistical analysts jointly lock the database. In principle, any changes to the locked database are not allowed. After database locking, if any data errors are identified, the project team (sponsor, statistical analyst, clinical team, data manager, etc.) will discuss and decide whether the database needs to be unlocked. If the sponsor confirms that the data are of vital importance to statistical

analysis and must be corrected, the DM should complete the database unlocking application form and send it to the sponsor for approval, and then unlock the database. If it is confirmed after evaluation that unlocking is not necessary, the application and approval form for hard code implementation should be completed and sent to the statistical analyst. The statistical analysts perform statistical analysis for database according to the SAP.

11 Statistical Analyses

11.1 Sample Size

The sample size of this study is not determined based on the formal statistical assumptions and it is expected to include approximately 150 subjects with early-stage PD, who will be randomized in a 1:1 ratio into two cohorts (Cohort 1: 200 mg dose group; Cohort 2: 400 mg dose group). Within each cohort, the subjects will be randomized into the TJ0113 capsules group and the placebo group in a ratio of 2:1, with approximately 50 subjects receiving TJ0113 capsules and approximately 25 subjects receiving the placebo. In this study, there will be approximately 50 subjects in each of the TJ0113 capsules 200 mg group, TJ0113 capsules 400 mg group and the placebo group.

11.2 Statistical Analysis Population

Full analysis set (FAS): including all randomized subjects who have received at least one dose of investigational product.

Per-protocol set (PPS): including subjects in the FAS who have not experienced major protocol deviations that affect the primary efficacy endpoint.

Safety set (SS): including all subjects who have received at least one dose of the investigational product and have undergone at least one post-dose safety assessment.

Demographics and baseline characteristics will be analyzed based on FAS, the efficacy analyses will be performed based on both FAS and PPS, and the safety analyses will be performed based on SS.

11.3 General Analysis

Statistical analyses of efficacy and safety will be performed using the SAS software (V9.4 or later).

Unless otherwise specified, descriptive statistics for continuous variables included the number of subjects (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum (Min), and maximum (Max). Categorical variables will be summarized using descriptive statistics including number of subjects (n) and the percentage (%).

Unless otherwise specified, it will be summarized by the TJ0113 capsules 200 mg group,

TJ0113 capsules 400 mg group, and the placebo group.

11.4 Statistical Analysis Methods

11.4.1 Demographics and Baseline

Demographic and baseline characteristics will be summarized using descriptive statistics. Baseline is defined as the last valid measurement or assessment (if applicable) before the first dose of the study drug.

11.4.2 Analysis for Primary Endpoint

The primary objective of this study is to assess the efficacy of TJ0113 capsules in the treatment of patients with early-stage PD. The main concern of interest is the treatment difference in terms of the changes from baseline in the MDS-UPDRS Part III (motor examination) scores after 12 weeks of treatment between the TJ0113 capsules group and the placebo group.

Definition of estimand:

- Population: patients with early-stage PD
- Endpoint: changes from baseline in scores of MDS-UPDRS Part III (motor examination) after 12 weeks of treatment. Evaluation time point: ≥ 12 hours from the most recent dose of anti-PD drug.
- Treatment: treatments will be randomly assigned; subject will be randomized in a 1:1 ratio to two cohorts (200 mg dose group and 400 mg dose group); and within each cohort, the subjects will be randomized in a 2:1 ratio to the TJ0113 capsules group and the placebo group.
- Concomitant event and management strategy: For any concomitant medication (excluding the investigational product and stable anti-PD medications at the time of enrollment) or treatment that could potentially impact the PD disease process, a therapeutic strategy will be employed.
- Population-level summary: differences in the least square mean of the changes from baseline in MDS-UPDRS Part III (motor examination) scores after 12 weeks of treatment between the TJ0113 capsules group and the placebo group.

The analysis will be performed using a mixed models for repeated measures (MMRM) with the changes from baseline in the MDS-UPDRS Part III scores after 12 weeks of treatment as

the dependent variable, whether subjects have been receiving levodopa, the background medication for PD (yes vs. no) at a stable dose at baseline and the baseline MDS-UPDRS Part III score as the covariates, and the treatment group, visit, and the treatment group-by-visit interaction as the fixed effects.

11.4.3 Sensitivity Analysis

The sensitivity analysis of the primary endpoint will be performed using the analysis of covariance. The model will use the changes from baseline in the MDS-UPDRS Part III scores after 12 weeks of treatment as the dependent variable, whether subjects have been receiving levodopa, the background medication for PD (yes vs. no) at a stable dose at baseline, the baseline MDS-UPDRS Part III score, and the treatment group as the covariates.

After the primary endpoint is imputed by using different mechanisms for imputing the missing data, the sensitivity analysis will be performed using the same method as that for the primary analysis. Detailed statistical methods will be described in a separate SAP.

11.4.4 Analysis for Secondary Endpoints

11.4.4.1 Analysis of Efficacy

The secondary efficacy endpoints will be summarized using the same statistical methods described above for primary endpoint.

11.4.4.2 Safety Analysis

It includes AEs and other safety-related parameters, which will be summarized by the descriptive statistics.

Detailed statistical methods will be described in a separate SAP.

11.4.5 Analysis for exploratory endpoint

Exploratory endpoint (inflammatory indicators, α-synuclein, GFAP, ASMI, grip strength, 6-meter walking speed) will be analyzed using the analysis of variance or nonparametric tests, and the correlations between the parameters will be analyzed using the Spearman's or Pearson's correlation coefficients. Detailed statistical methods will be described in a separate SAP.

11.4.6 Sub-group Analysis

Sub-group analyses will be performed for the primary endpoint, where data are available, and specific sub-group information will be described in a separate SAP.

12 Trial Management

12.1 Statement

This clinical study will be conducted according to the standard operating procedures of the sponsor and CRO. The procedures are established aiming at guaranteeing that this study can be conducted in accordance with the requirements of Declaration of Helsinki, E6 Guidelines for Good Clinical Practice issued by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), GCP issued by NMPA and all applicable regulations.

If the investigators sign the protocol, it means that they will agree to conduct this study in strict accordance with the protocol, clinical trial principles and relevant laws and regulations. All materials and information provided by the sponsor are kept according to the confidentiality requirements.

12.2 Ethical Considerations

This study is designed and prepared on the basis of Declaration of Helsinki of World Medical Association after the consideration of rights and welfare of patients. The principal investigator or investigator of the clinical trial will explain objective and all potential possibilities of the trial to patients. Those patients who voluntarily agree to participate in the clinical trial and sign the ICF will become subjects.

The investigators and personnel participating in this study should appropriately understand and be familiar with study plan, and prepare in advance, such as for treatment measures in case of unexpected AEs, required reports and sufficient training. The clinical investigators must conduct clinical trials in strict accordance with Declaration of Helsinki, E6 Guidelines for Good Clinical Practice issued by ICH, Good Clinical Practice (GCP) issued by NMPA and applicable laws and regulations.

The investigators and personnel participating in this study should conduct this study according to the contents of study protocol by scientifically using the currently recognized technical level.

According to the national policies and regulations, the investigator should provide trial-related

documents for the Ethics Committee.

The approval of the Ethics Committee and drug regulatory authorities must be obtained before the initiation of clinical study.

Modifications to the study protocol should be submitted to the Ethics Committee for approval and sent to Health Authorities (HA) for record keeping according to the local requirements.

During the clinical study period, should any SAEs or unexpected AEs which are associated with clinical study safety and may affect the safety of subjects and study implementation occur, the investigators should report to the Ethics Committee according to the regulatory requirements.

After the study is completed, the Ethics Committee (EC) should be informed.

12.3 Source Data Verification

The Investigator must properly handle all data obtained during the clinical study to guarantee the rights and privacy of subjects. The investigators must allow the CRAs/auditors/inspectors to review and check the required clinical study documents so as to verify the accuracy of the source data and learn about the study progress. If the source data cannot be verified, the investigator should agree to assist the CRAs/auditors/inspectors in the further confirmation of data quality control.

12.4 Quality Assurance/Audit

The quality of all drugs and supplies used in the clinical study must be controlled. The sponsor and its authorized personnel or relevant medical management institutions have the right to review the clinical study, which aims at ensuring that the data recorded in clinical study are accurate and the study is conducted in accordance with the clinical study protocol.

This study will be organized, performed and reported according to the study protocol as well as the standard operating procedures (SOPs) of the sponsor and CRO. In ICH E6, the definition of quality assurance (QA) is “all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).” The QA work of the sponsor will be carried out in accordance

with the study auditing plan. According to the requirement of ICH E6 section 5.19.3 (b), the sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s). The QA work can be outsourced to a CRO or an independent consulting agency. It is required that the investigator should support audit, attend audit activities according to the requirements of auditors, allow auditors to directly access to original data/document, including all medical records, documents and letters related to the study and ICFs of the clinical trial, etc. The clinical trial subjects will be informed of such clinical study inspecting or auditing process, but the privacy and data materials of subjects will be strictly protected.

12.5 Informed Consent

The investigators are responsible for explaining the purposes, methods, benefits and potential risks of this clinical trial, other optional treatment methods, rights and obligations to each subject meeting the requirements of the Declaration of Helsinki. The subjects should be informed that they have rights to withdraw from this trial at any time. Signed ICF must be obtained from the subject before any study-specific procedures.

Verbal explanation must be provided when obtaining written informed consent from the subject. The informed consent form must be dated and signed by each subject or impartial witness. One of the signed ICF (including information page) will be kept by the subject and the other will be kept by the study site as study archives.

Before any study related procedure, the ICF must be agreed on and signed by the subject or impartial witness. Before obtaining informed consent, the investigator or designated personnel should provide the subject with sufficient time and opportunity to ask about details of the trial and decide whether to participate in this trial or not. The process of the informed consent should be documented in the progress note at the day of screening visit or medical records.

The investigator should be responsible for the process of informed consent. If any information related to the subject's willingness to continue participating in the trial is available during the trial, the written ICF must be updated and provided to the subject to confirm if the subject is

willing to continue. Ethical approval has to be obtained for the revised ICF before providing to subjects.

After signing the ICF, the subjects must also agree that the sponsor, drug approval regulatory authorities, auditors and/or the sponsor-authorized clinical trial CRAs check the available source data related to clinical study. Moreover, the reviewer must follow confidentiality statement.

12.6 Trial Protocol Revision Rules

After this protocol has been approved by the Ethics Committee, in case any amendment has been made to the protocol during the conduct of the study, the amendment can be implemented only after being submitted to the Ethics Committee and the approval is obtained. Any changes to the protocol are required to be made in a written form, regardless of major or non-major protocol amendments. Substantive protocol modifications which may definitely affect the safety of subjects, study scope or scientific quality of this study should be approved by the Ethics Committee of all study sites. In order to protect the safety of all subjects in this study, the investigators or sponsor should not be prevented to take any emergency measures by the limitation of the above requirements. If the investigators consider that protocol modifications must be immediately made for the consideration of safety, they must immediately notify the institutions designated by the sponsor and inform the Ethics Committee of study sites according to the policies stipulated by EC who approves this study, local regulations and policies. Any changes which affect study administration only do not require substantive protocol modifications or EC approval, however, these changes must be reported to EC. Under these conditions, the sponsor will send an authentication letter to EC to carefully specify these changes.

12.7 Protocol Deviations

The investigator has to conduct this clinical trial according to the clinical study protocol approved by the EC and GCP regulations. The protocol is established to make the investigator follow regulations in ICH E6 Section 4. During the trial, the investigator should avoid protocol deviations, except emergency actions taken to avoid direct harm to subjects. In case

of other unexpected situation requiring deviation from protocol-specified procedures, the investigator should discuss with the medical personnel (and the Ethics Committee when necessary) to determine appropriate measures.

All protocol deviations should be recorded by the study site, including but not limited to time of protocol deviation, time of awareness, description of event and action taken. In case of a significant protocol deviation, the medical personnel, CRA, and EC should be notified in a timely manner.

If a subject withdraws from the trial early due to withdrawal of consent or loss to follow-up, and fails to complete the early withdrawal visit and post-treatment follow-up as specified in the protocol, it will not be recorded as a protocol deviation, but the investigator must make corresponding records in the medical records.

12.8 Case Report Form

The database programmer of CRO will establish eCRF in the Clinflash system. Different subjects are identified on the eCRF only by appropriate identification codes (e.g., site No. and subject number). The eCRFs are used for the documentation of clinical study data of subjects, and are a component of this study and relevant study reports. Entry must be therefore accurate and complete. The eCRFs are entered into Clinflash system by the investigator or personnel authorized by the investigators (indicated in the study authorization table). It must be ensured that all data entry is completed and stored. The investigator must state that all information in eCRF is true by electronic signature.

In clinical study, eCRF should be completed as soon as possible after each visit to record the condition of subjects.

The medical records and other records related to disease progression of subjects during the study period will be stored by the investigators. These records should contain the following contents: original or copy of laboratory data and other medical test results (e.g., 12-lead ECG, etc.). These materials must be stored at the site with subjects' medical records.

12.9 Monitoring

Monitoring will be conducted by the sponsor or its commissioned CRO.

Before certain study site is selected to participate in this study, one site selection visit will be performed to confirm that such site, equipment and site personnel meet protocol requirements and GCP.

During the study period, the monitors should routinely perform on-site monitoring. At each monitoring, visit date will be documented at site visit records of the study sites. The sponsor shall determine whether to perform site monitoring based on the quality of the study.

CRA's study monitoring activities include:

- Perform study initiation visit to the study site, collect and distribute necessary documents before study; provide guidance and description of the protocol, study procedure and expectation to investigators and site staff; obtain investigators' guarantee of conducting the trial in compliance with study requirements and the GCP and introduce study materials to investigators and corresponding study staff.
- Monitoring visit: According to the requirements of GCP, CRAs taking part in the current study should completely understand affairs of confidentiality and compare the data in the eCRF with those in the hospital or clinical record (source documents). Before the initiation of the study, the CRA should discuss the specific items required as source documents with the investigator and confirm the nature and storage place of all source documents, so as to guarantee that the sponsor or the investigator could know the origin of source data for eCRF completion, and the CRA authorized by the sponsor has the right to check and verify the data. All observations and findings during the monitoring process must be verified. If the electronic records are stored at study institutions, the verification methods must be discussed with the study personnel.

Source documents must be available for confirming:

- The identity of subject, whether the subjects are qualified and participate the study or not;
- Appropriate informed consent procedure;
- Visit date;
- Records of safety and efficacy parameters;
- Sufficient reports and visits of AEs;
- Treatment with concomitant medications;

- Records of receipt/dispensing/return of drugs;
- Administration information of investigational product;
- Subjects' completion of treatment, termination of treatment or withdrawal from the study and appropriate reasons;
- The data are authentic, accurate and complete;
- Subjects' safety and rights are protected;
- Investigator's implementation complies with the currently approved protocol, GCP and all relevant regulatory requirements.

Objectives that the monitoring should realize include:

- Check and assess the trial progress;
- Review the collected trial data;
- Carry out verification of source documents;
- Identify any problems and develop solutions.

During the study period, CRAs are required to directly review all related documents with the consent of the investigator. The investigators should ensure that they and relevant study personnel should regularly meet with CRAs to discuss findings during monitoring visits and related issues.

12.10 Intellectual Property

All study materials on study drug, such as patent application, dosage form, manufacturing process, basic research, etc., are considered confidential as long as they are not published. All information obtained from the trial sponsor and the trial belongs to the intellectual property rights of the trial sponsor. Therefore, all relevant personnel of the clinical trial must strictly keep it confidential, and should not disclose it to any third party without the prior consent of the sponsor. It should not be used for other purposes other than the study.

12.11 Subject's Privacy

Study personnel must ensure to protect privacy of subjects in the clinical trial. In all eCRFs, documents and files submitted to sponsor, the clinical trial subjects can only be identified by clinical trial screening number. Full name of a subject is never indicated. The investigator must store the private information, e.g., name and address, of the subjects in the clinical trial

in a strictly confidential manner, and may not submit it to the sponsor.

13 Paper Publications

The study data and manuscript obtained in this study will also be considered confidential. Hangzhou PhecdaMed Co., Ltd., as the sponsor, has the exclusive right to this trial and has the right to decide to disclose it to other clinical study staffs and national regulatory agencies. Authors and the manuscript will reflect coordination between investigators and study sites and staff of the Sponsor. Authors will be identified before drafting of the manuscript. Many study sites are participating in this study, unless prior consent has been obtained from the Sponsor, individual shall not publish any data related to the clinical study before the final report of the multi-center study has been completed. The sponsor has the right of final decision about the manuscript and publication.

14 Clinical Data Archiving

14.1 Source Data and Source Documents

In this trial, source data includes records on the clinical findings, observations, and other activities required to reconstruct and evaluate the clinical trial. The original data is contained in the source files.

The source files involved in the clinical study are original records, documents and data (such as hospital medical records, medical images, laboratory records, memos, subject diaries or assessment forms, drug distribution records, data automatically recorded by instruments, subject files, clinical trial-related documents and records kept by pharmacies, laboratories, and medical technology departments, including certified copies, etc.). Source documents must be retained to support the information provided in eCRFs.

14.2 Data Archiving of Study Site

14.2.1 Materials related to the Ethics Committee

Personnel responsible for data storage at the study site must keep records and synopsis of EC meetings till 5 years after termination or completion of the study. If the sponsor wishes to retain for a longer period, the two parties will discuss and decide the retention duration and methods. If the study site makes any changes in document retention, personnel or investigator responsible for document retention should contact the sponsor.

14.2.2 Materials related to Trial Conduct

The personnel in charge of materials preservation in the study site must keep the following files until 5 years after the investigational drug is approved for marketing. If the sponsor wishes to retain for a longer period, the two parties will discuss and decide the retention duration and methods. If the study site makes any changes in document retention, personnel or investigator responsible for document retention should contact the Sponsor.

- Original materials;
- Trial contract, original copy or copies of the ICF, other GCP-related materials provided by the site staff;
- Study protocol, GCP-related materials obtained from the EC, or other GCP-related materials obtained;

- Records of management of the investigational product and other records related to trial conduct.

14.3 Data Archiving of Sponsor

The sponsor will store the following materials (including documents and data) until 5 years after the investigational drug is approved to be marketed. A longer retention period may be required according to relevant regulations. It is the responsibility of sponsor to inform the investigator/study site as to when such data is no longer required to be retained:

- Study protocol, trial agreement, the original or duplicate copies of the study reports, or GCP-related materials provided by the sponsor;
- Case report form, GCP-related notifications, or GCP-related materials obtained from the investigators;
- Monitoring and audit records, or other relevant operation records;
- Data obtained in the trial;
- Relevant records specified in GCP.

15 Protocol Amendments

After this protocol has been approved by the Ethics Committee, if any modifications should be made, the protocol amendment statement should be drafted and signed by the principal investigator. Protocol amendment is allowed after the approval of the sponsor. Protocol amendment can be implemented after being reviewed or archived by the EC.

Protocol/Amendment	Version	Formulation Date	Revised Content
TJJS01-201	V1.0	August 19, 2024	Initial version
TJJS01-201	V2.0	September 24, 2024	See corresponding amendment record
TJJS01-201	V3.0	December 20, 2024	See corresponding
TJJS01-201	V4.0	February 17, 2025	See corresponding

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17 Appendices

17.1 Appendix I: Definition of Women of Childbearing Potential and Contraceptive Requirements for Subjects

Definition of women of childbearing potential

Woman of childbearing potential (WOCBP) is defined as any female who have not undergone sterilization and are able to become pregnant anatomically and physiologically after menarche and before menopause.

Women without childbearing potential are defined as postmenopausal women or premenopausal women who have undergone sterilization procedure.

Postmenopause is defined as menopause for ≥12 months without alternative medical treatment.

Sterilization procedures include bilateral tubal ligation or bilateral oophorectomy or hysterectomy.

Requirements for contraception

In the whole study period and up to 6 months after the last dose of the investigational product, subjects and their partners must agree to one of the following operations:

- Complete abstinence of subjects and their partners. Periodic abstinence (e.g., calendar, ovulation, symptothermal or post-ovulation methods) is not allowed; or
- Correct use of one of the contraceptive methods with a failure rate of < 1%:
  - Intrauterine device or intrauterine hormone-releasing system with an annual failure rate of < 1% for subjects or their partners;
  - Vasoligation for subjects or their partners;
  - Subjects use double barrier method: Condoms and/or occlusion caps (diaphragm or cervical cap/dome cap), spermicide (foam/gel/film/cream/suppository) barrier method should be used as supplementary measures.

17.2 Appendix II: Calculation of Ccr

Ccr as calculated using the Cockcroft-Gault formula:

Ccr (mL/min) = (140-age (year)) × weight (kg)/72 × serum creatinine (mg/dL) (× 0.85, for female)

Ccr (mL/min) = (140-age (year)) × weight (kg)/0.814 × serum creatinine (μmol/L) (× 0.85, for female)