Phase: **Phase II**

Protocol No.: **WD-1603-2001**

Version No.: **V1.2**

Version Date: **2021-06-22**

A Phase II Randomized, Parallel, Double-blind, Placebo-controlled, Multi-Center Study of the Efficacy and Safety of WD-1603 Carbidopa-Levodopa Extended-Release Tablets in Subjects with Parkinson's Disease

Principle Investigator

Sponsor: Shanghai WD Pharmaceutical Co., Ltd.

Shanghai, China

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SIGNATURE PAGE

PROTOCOL WD-1603-2001

STUDY TITLE: A phase II randomized, parallel, double-blind, placebo-controlled, multi-center study of the efficacy and safety of WD-1603 carbidopa-levodopa extended-release tablets in subjects with Parkinson's disease.

Sponsor's Approval:

Signature Date

Chief Medical Officer
Shanghai WD Pharmaceutical Co., Ltd.
Mobile:
Email:

INVESTIGATOR'S SIGNATURE PAGE

Protocol Title： A phase II randomized, parallel, double-blind, placebo-controlled, multi-center study of the efficacy and safety of WD-1603 carbidopa-levodopa extended-release tablets in subjects with Parkinson's disease.

Protocol Number： WD-1603-2001

Investigational Product： WD-1603 (Carbidopa-Levodopa Extended-Release Tablets)

I have read this protocol, protocol number: WD-1603-2001, version number: 1.2 (version date 2021-06-22), and agree to conduct this study in full accordance with the Chinese Rules and Regulation, the " Standards of Quality Management for Clinical Trials in Drug Development" (2020 by NMPA) and the "Declaration of Helsinki" (2013 Revision in October), and ICH GCP. This study can only be implemented after obtaining the approval of the Ethics Committee.

In the conduct of this study, I will strictly follow the design and specific provisions of this protoco. If the protocol needs to be revised, it can only be implemented after it is approved by the sponsorand by the Ethics Committee unless the measures must be taken to protect the safety, rights and well-beings of the subjects.

I will keep this protocol and related information confidential.

Investigator	Signature	Date

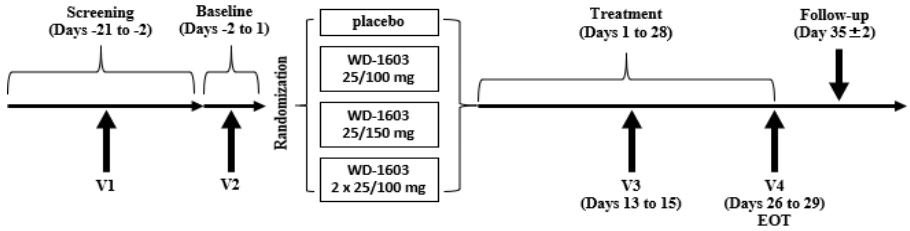
Protocol Revision List

Protocol/Revision No.	Version	Version Date	Revised Content
WD-1603-2001	1.0	February 27, 2021	
WD-1603-2001	1.1	May 18, 2021	*Describeed the objectives of study and clinical endpoints separately.* *Added time windows for UPDRS and PK blood sample collections.* *Clarified that MDS-UPDRS-II will be evaluated only once during each visit.* *The inclusion criteria were modified as the total score of the second and third parts of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-II+ MDS-UPDRS-III) ≥ 18* *The 2015 version of MDS Parkinson's Disease Diagnostic Criteria was specified as diagnostic staddards.* *The use of dopamine receptor agonists within 30 days before screening was added to the exclusion criteria*
	1.2	June 22, 2021	*The primary objective of the study was revised to: " To investigate the concept verification of the effectiveness of WD-1603 Carbidopa-Levodopa Extended-Release Tablets in subjects with Parkinson's disease". See pages 5 and 27 of the protocol.* *Section 9.8 Measures for prevention and risk managementwas added: see page 47 of the protocol.* *The 2015 version of MDS Parkinson's disease diagnostic criteria was added to the appendix, and "Subjects not treated with anti-Parkinson drugs" was added to the inclusion criteria.*

PROTOCOL SYNOPSIS

Sponsor： Shanghai WD Pharmaceutical Co., Ltd.	**Phase：** Phase II
Investigational Product: WD-1603 (Carbidopa-Levodopa Extended-Release Tablets) **Active Ingredients：** Carbidopa/Levodopa	**Protocol No.：** WD-1603-2001 **Version：** 1.2 **Version Date：** 2021-06-22
Protocol Title： A phase II randomized, parallel, double-blind, placebo-controlled, multi-center clinical trial of the efficacy and safety of WD-1603 carbidopa-levodopa extended-release tablets in subjects with Parkinson's disease.	
Principlal Investigator：	
Study Center of the Principlal Investigator：	
Study Duration： It is estimated that each subject will participate in the study for 8 weeks, including: screening period of 3 weeks, baseline determination (D-1), treatment period of 4 weeks, and follow-up period of 1 week. Planned time for clinical trial: October 2021 to March 2022	
Study Objectives： **Primary objective:** To investigate the effectiveness and safety of WD-1603 carbidopa-levodopa extended-release tablets in subjects with Parkinson's disease. **Secondary objective:** To measure pharmacokinetic parameters and plasma fluctuation of levodopa in subjects with Parkinson’s disease. **Primary Endpoint：** Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 27th day. **Secondary Endpoints：** (1) Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 14th day. (2) Changes in MDS-UPDRS-II scores from the baseline to the 14th and 27th days. (3) Changes in the MDS-UPDRS-III scores from the baseline to the 14th and 27th days. (4) To evaluate the pharmacokinetics and fluctuation index of levodopa on the 28th day. (5) To evaluate the safety of WD-1603 in subjects with Parkinson's disease.	
Study Design： This is a phase II randomized, double-blind, parallel, fixed-dose, placebo-controlled study in subjects with early Parkinson’s disease for 4 weeks of treatment, which aims to evaluate the efficacy and safety of WD-1603 carbidopa-levodopa extended-release tablets in subjects with Parkinson's disease. Eligible subjects will be randomly divided into four treatment groups at a ratio of 1:1:1:1: (1) WD-1603 25/100 mg, (2) 25/150 mg, (3) 2x25/100 mg or (4) placebo group. The subjects will take study drugs orally three times a day, in the morning before meals, and the second and third medications will be taken after meals, once every 5 hours (±30 minutes). Eligible subjects are between 30 and 75 years old, diagnosed with early idiopathic Parkinson's disease and have not received levodopa-containing drugs for at least 30 days. **Study Treatment and Procedures** Screening period: After signing the Informed Consent Form (ICF), subjects will enter the screening period. Subjects who complete the screening specified in the protocol and meet the inclusion/exclusion criteria will enter the baseline evaluation period (Day -2 to 1) and qualified subjects will be randomly assigned to each study group. The study design schematic is shown below:	

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Baseline Evaluation: The subject will be admitted to the Clinics on Day -2, and the MDS-UPDRS-II and MDS-UPDRS-III assessments will be performed on Day -1. There will be 6 time points for the MDS-UPDRS-III assessments. Eligible subjects will be randomly assigned to each group. On Day 1, the subjects will be discharged from the hospital with study medications. During double-blinded Treatment Period, subjects will be randomly assigned into four treatment groups at 1:1:1:1 ratio, namely 25/100mg, 25/150mg, 2 x 25/100mg and placebo tablets, taking medication orally 3 times a day, before the morning meal for the first time medication, after meals for the second and third time medications, 3 tablets each time. During Days 13-15 and Days 26-29 subjects will return to the clinics for on-site assessments.

After the treatment period is completed, subjects will receive a safety follow-up on the 7th day after the last medication. For the subjects who have not completed 4 weeks of treatment, the early termination visit must be completed.

Subjects can continue to use anticholinergic drugs or amantadine, MAO-B inhibitors for the treatment of Parkinson's disease during the course of the study.

Rater Requirements: Clinicians who evaluate MDS-UPDRS-II and MDS-UPDRS-III should remain blind to the treatments.

Visit 1: Screening Period (Days -21 to -2):

The screening visit will be conducted up to 21 days before the start of treatment. Subjects are required to sign ICF before conducting any study procedures. Subjects who provide informed consent will receive medical screening. Subjects must meet all of the inclusion criteria and must not meet any of the exclusion criteria to be eligible to participate in the study.

Visit 2: Baseline Assessment (Days -2 to 1):

Eligible subjects will be admitted to the Clinics in the afternoon/evening of Day -2, and stay in the Clinics for 2 nights and 3 days. On Day -1, MDS-UPDRS-II and MDS-UPDRS-III evaluations will be performed. The time points for MDS-UPDRS-III assessments for the subjects who take non-levodopa drugs are (1) before the first dose (morning dose) (2) 2.5 hours (±15 minutes) after the first dose, (3) 5 hours (±15 minutes) after the first dose or before the second dose, (4) 2.5 hours (±15 minutes) after the second dose , (7.5 hours after the first dose), (5) 10 hours (±15 minutes) after the first dose or before the third dose , (6) 2.5 hours ± 15 minutes after the third dose (12.5 hours after the first dose). Subjects without medications before the trial will follow the same time points as the treatment period (Visit 3) to evaluate MDS-UPDRS-III. Eligible subjects after the baseline assessment will be randomly divided into one of the four treatment groups. On Day 1, subjects will take the first study drugs orally and discharge after completing blood pressure monitoring. The subjects will continue to take the medications 3 times a day, before meals the morning dose, and the second and third medications will be given after meals, 3 tablets (100 mg, 150 mg, 200 mg or placebo) each time with a total of 28 days. The baseline assessment includes the Beck Depression Inventory-II (BDI-II) assessment and orthostatic hypotension monitoring.

Visit 3 Interim Evaluation (Days 13 to 15):

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The subjects will be admitted to the clinics in the afternoon/evening on Day 13 and stay in the clinics for 2 nights and 3 days. On Day 14, MDS-UPDRS-II and MDS-UPDRS-III evaluations will be performed. The time points for MDS-UPDRS-III evaluations will be before and 2.5 hours (±15 minutes) after the morning dose administration, before and 2.5 hours (± 15 minutes) after the second dose administration, before and 2.5 hours ± (15 minutes) after the third dose administration, and then discharge on Day 15.

Visit 4 Endpoint Evaluation (Days 26 to 29)：

Subjects will be admitted to the clinics in the afternoon/evening on Day 26, and stay in the clinics for 3 nights and 4 days. On day 27, MDS-UPDRS-II and MDS-UPDRS-III evaluations will be performed. Time points for MDS-UPDRS-III evaluations will be before and 2.5 hours (± 15 minutes) after the first morning dose, before and 2.5 hours (± 15 minutes) after the second dose administration, before and 2.5 hours (± 15 minutes) after the third dose administration. On Day 28, PK blood samples will be collected from the subjects after the second dose administration for PK evaluation: blood samples will be collected -15 to 0 minutes before the second dose administration, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, and 9.0 hours after the second dose administration (time window for each blood sample collection: ≤1-hour time window is ±2 minutes, >1-hour time window is ±5 minutes). Medications will only be given twice on Day 28, in the morning and noon, and subjects will discharge on Day 29. The Day 28 evaluations include the subject's Baker Depression Self-Rating Scale evaluation and orthostatic hypotension monitoring.

Visit 5 Follow-up (Day 35±2) or Early Termination：

Outpatient safety follow-up: Approximately 7 days (±2) after the last dose, the subject will return to the clinics for safety follow-up.

PK Blood Sample Collection	On Day 28, blood samples will be collected for plasma drug concentration measurements from all subjects. Time points for blood sample collection include before the second dose (-15 to 0 minutes) and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, and 9.0 hours after the second dose (time window for each blood sample collection: ± 2 minutes for ≤1 hour and ± 5 minutes for ≥ 1 hour) of the second administration.
Sample Size：	The sample size estimated in this study is 10 subjects per group, for a total of 40 subjects. The sample size is estimated based on the experience of similar clinical trials, not based on statistically significance.

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Investigational Product

The study drugs include two strengths of WD-1603 tablets and two matching placebo tablets. The general information and methods of administration are shown in the table below:

	WD-1603 (Carbidopa-Levodopa Extended Release Tablets)	**Placebo**
Manufacturer	[redacted]	[redacted]
Strength	25/100mg, 25/150 mg carbidopa/levodopa tablets	matched tablets of WD-1603
Regimen	(1) 25mg/100mg tablet+ Placebo-1 tablet + Placebo-2 tablet (2) 25mg/150mg tablet + Placebo 1 tablet + Placebo 2 tablet (3) 2 x 25mg /100mg tablets + Placebo-2 tablet	3 placebo tablets (2 x Placebo-1 tablets + Placebo-2 tablet
Route of Administration	Oral, TID, the first dose will be taken before breastfirst, the second and third doses will be taken after meals, for 4 consecutive weeks	Oral, TID, the first dose will be taken before meals, the second and third doses will be taken after meals, for 4 consecutive weeks

Inclusion Criteria:

Subjects meeting all of the following inclusion criteria are eligible for this study:

1. Male/female subjects with early Parkinson's disease who are over 30 years old and under 75 years old, inclusive.
2. Able to understand and willing to sign an informed consent form (ICF) voluntarily.
3. The diagnosis of Parkinson's disease complies with idiopathic Parkinson's disease (2015 version of MDS Parkinson's disease diagnostic criteria).
4. Modified Hoehn and Yahr Scale≥1, ≤2.5 points.
5. The total scores of the second and third parts of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-II + MDS-UPDRS-III) ≥18.
6. Subjects must have not received levodopa drugs or Catechol-O-methyltransferase inhibitors or have not been treated with any anti-Parkinson drugs within 4 weeks before baseline.
7. If subjects are currently receiving anticholinergic therapy, amantadine or monoamine oxidase B (MAO-B) inhibitors, they should maintain a stable treatment regimen at least 4 weeks before baseline, and agree to maintain the same doses throughout the study.

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	8. Agree to use medically acceptable contraceptive methods throughout the study and within 1 month after completing the study. 9. Female subjects of non-childbearing potential must be postmenopausal (postmenopausal referring to amenorrhea without other reasons for at least 1 year, and follicle stimulating hormone level ≥26IU/L) or surgical infertility (hysterectomy, bilateral oophorectomy) or bilateral tubal ligation).
Exclusion Criteria：	Subjects who meet any of the following exclusion criteria are not eligible for this study: 1. Have a history of severe allergic reactions or allergies to levodopa or carbidopa. 2. Pregnancy or breastfeeding. 3. Diagnosed as atypical Parkinson's disease or any known secondary Parkinson's syndrome. 4. Use dopamine receptor agonists within 30 days before screening. 5. The patient has been treated with one of the following drugs within 28 days before screening: non-selective MAO inhibitors, dopamine releasing agents (for example, amphetamine), reserpine, dopamine antagonists (for example, metoclopramide), antipsychotics or other drugs that may interact with dopamine function. 6. The investigator believes that the placebo treatment cannot be tolerated. 7. Acute psychosis or hallucinations, using any antipsychotic to treat psychosis or clinically obvious depression. 8. History of epilepsy or epilepsy. 9. A history of digestive system disease or digestive system surgery that interferes with the absorption of levodopa. 10. The history of narrow-angle glaucoma. 11. Subjects with a history of malignant melanoma. 12. Human immunodeficiency virus antibody (HIV)-1/2Ab, hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV-Ab) are positive. 13. Have received the clinical trial study drug within 30 days before the administration of the test drug, or the treated study drug has not exceeded 5 half-lives, whichever is longer. 14. Subjects with obvious cognitive impairment. 15. The investigator believes that there are clinically significant medical or surgical diseases and subjects who are not suitable for participating in clinical trials.
Study Endpoint：	**Primary Endpoint:** Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 27th day. **Secondary Endpoints：** (1) Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 14th day. (2) Changes in MDS-UPDRS-II scores from the baseline to the 14th and 27th days.

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	(3) Changes in the MDS-UPDRS-III scores from the baseline to the 14th and 27th days. (4) To evaluate the pharmacokinetics and fluctuation index of levodopa of WD-1603 on the 28th day. (5) To evaluate the safety of WD-1603 in subjects with Parkinson's disease.

Statistical Analysis：

Population：

Full Analysis set (FAS)：All subjects who are randomized will be included in the full analysis set.

Per Protocol Set (PPS)：Including all subjects who have completed the pre-set sufficient test drug exposure in the full analysis set, obtained the primary endpoints in the test, and subjects who do not have a major violation of the trial.

Safety Set (SS)：Including all subjects who have received at least one dose and have a safety assessment.

Pharmacokinetic Analysis Set (PKS)：Any evaluable plasma concentration data from the safe population will be included in the pharmacokinetic analysis set.

Demographics：

Demographics and baseline characteristics (age, gender, race, weight, height, and BMI) will be summarized descriptively (n, mean, standard deviation, minimum, median, maximum, proportion of subjects for categorical variables). There will be no formal statistical comparison of the groups.

Pharmacokinetic Analysis:

Describe and compare the average values and pharmacokinetic parameters of levodopa and carbidopa plasma concentrations in each dose group on the 28th day and calculate the fluctuation index of levodopa plasma concentrations.

Efficacy Analysis：

Continuous variables will be summrairzed descriptively by the number of subjects, mean, standard deviation, median, 25% quantile, 75% quantile, minimum and maximum values; categorical variables will be summarized by frequency and percentage. Unless otherwise specified, all statistical tests will use a two-sided test with $\alpha=0.05$ to calculate a two-sided 95% confidence interval.

Primary Endpoint：

Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 27th day.

The statistical analysis of the primary endpoint will be based on FAS, and the last observation carried forward (LOCF) will be used to impute the data for subjects with missing primary endpoint of Day 27. Analysis of covariance (ANCOVA) method with baseline value as covariate and disease severity and treatment group as independent variables will be used to analyze the primary efficacy endpoint. The difference between the least squares mean of each dose group and the placebo group's and its 95% confidence interval and P value will be estimated. This statistical method will be repeated on the basis of PPS as a sensitivity analysis.

Mixed model repeated measures (MMRM) will be used as a sensitivity analysis. In the MMRM model, the change value of Day 27 from the baseline is used as the dependent variable, the baseline value is the covariate, and the disease severity, treatment group, visit, and interaction terms between treatment and visit are fixed effects, to estimate least squares mean and 95% confidence interval after the change of variables in each group.

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Secondary Endpoints：

1. Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 14th day.
2. Changes in MDS-UPDRS-II scores from the baseline to the 14th and 27th days.
3. Changes in the MDS-UPDRS-III scores from the baseline to the 14th and 27th days.
4. To evaluate the pharmacokinetics and fluctuation index of levodopa on the 28th day.
5. To evaluate the safety of WD-1603 in subjects with Parkinson's disease.

The statistical analysis of the secondary endpoints will be based on FAS, and the statistical model is similar to the primary endpoint.

Safety Analysis：

Safety assessment includes spontaneously reported adverse events (AEs), vital signs, clinical laboratory examinations, 12-lead electrocardiogram, orthostatic hypotension, Beck Depression Inventory-II (BDI-II) scale and physical examination. The safety will be listed by subjects and treatment and displayed in the summary table using descriptive statistics. Adverse events (AEs) will be coded and classified using the Medical Dictionary of Regulatory Activities (MedDRA) based on system organ class and preferred term. Treatment-emergent adverse events (TEAEs) refer to adverse events that occur for the first time after administration or exist before administration but worsen after administration. The number and percentage of subjects with Treatment-emergent adverse events (TEAE) will be summarized by system organ class, preferred terms and treatments, and by the maximum severity of each treatment and its relationship with the study treatment. Descriptive statistics of vital signs (blood pressure, heart rate and respiratory rate) will be calculated and presented at each time point by treatment. According to the judgment of investigators, abnormal vital signs will be classified as a sign of clinical significance.

The electrocardiogram results (absolute value and change from screening to clinical trial medication) will be summarized using descriptive statistics; frequency (number and percentage) will be overall evaluated based on the scheduled time and treatment.

Laboratory data will be summarized by laboratory test type and time periods. Investigators recognize abnormal findings in laboratory data base on their judgements and list specific data with clinical significance.

Abnormalities in the medical history will be coded as MedDRA terms using version 20.1 or later. Physical examination abnormalities will also be listed.

The original verbatim terms (input IRF) of concomitant medications will be coded into drug categories (ATC2 level) and preferred terms using the World Health Organization Drug Dictionary (WHODD), and these data will be listed.

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Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Plasma Concentration versus Time Curve
$AUC_{0\text{-}inf}$	Area Under the Plasma Concentration versus Time Curve Extrapolated from 0 to Infinity
$AUC_{0\text{-}t}$	Area under the Plasma Concentration versus Time Curve Calculated from 0 to the Last Measurable Observation
BMI	Body Mass Index
BDI–II	Beck Depression Inventory-II
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
C_{ave}	Average Plasma Concentration
CrCl	Creatinine Clearance
CTCAE	Common Terminology Criteria for Adverse Events
COMT	Catechol-O-methyltransferase
CPU	Clinical Pharmacology Unit
CRA	Clinical Research Associate
CRO	Contract Research Organization
DBS	Deep Brain Stimulation
DRM	Data Review Meeting
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Treatment

FDA	Food and Drug Administration
FAS	Full Analysis Set
GCP	Good Clinical Practice
eGFR	Estimated Glomerular Filtration Rate
β-hcg	β-Human Chorionic Gonadotropin
HbA1c	Glycated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCVAb	Hepatitis C Antibody
HIV	Human Immunodeficiency Virus
HIVAb	Human Immunodeficiencyvirus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward
MAO-B	Monoamine Oxidase-B
MAO	Monoamine Oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NMPA	National Medical Products Administration
pH	Potential of Hydrogen
PD	Pharmacodynamics
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PT	Preferred Term
PPS	Per-Protocol Set
QA	Quality Assurance
REM	Rapid Eye Movement
R&D	Research and Development
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SCr	Serum Creatinine
SOC	System Organ Classification
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SD	Standard Deviation
SS	Safety Set
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal Elimination Half-Life
t_{max}	Time to Maximum Plasma Concentration
TBIL	Total Bilirubin
TEAE	Treatment Emergent Adverse Events
TID	Three Times A Day
MDS-UPDRS	The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
WHODD	World Health Organization Drug Dictionaries

1 Study Background

1.1 Background Introduction

1.1.1 Disease Background and Epidemiology

Parkinson's disease, also known as paralysis agitans, is a degenerative disease of the central nervous system that occurs in middle-aged and elderly people. Clinically, it can be divided into primary Parkinson's disease (also known as Parkinson's disease) and secondary Parkinson's disease. Parkinson's disease (also known as Parkinson's syndrome) and is a common neurodegenerative disease. According to the epidemiology of the Parkinson's disease diagnosis and treatment guidelines released in 2019, the prevalence of Parkinson's disease in people over 65 years of age in China is 1700 per 100,000, which is similar to that of Western countries. The prevalence gradually increases with age, and the ratio of male to female is close to 1:1 or slightly more male than female. China has gradually entered an aging society. It is estimated that the number of subjects with Parkinson's disease in China has reached 2.6 million, accounting for about half of the global subjects. It is estimated that nearly 200,000 new subjects with Parkinson's disease will be added every year, and there will be 5 million by 2030 subjects with Parkinson's disease in China alone.

Existing studies have found that neurons in the substantia nigra and striatum of subjects with Parkinson's disease are damaged, and the secretion of gangliosides on nerve cell membranes is reduced, leading to insufficient dopamine production, while acetylcholinergic neurotransmitters are relatively increased, leading to imbalances of excitability and inhibitory neurotransmitter balance, causing symptoms including resting tremor, muscle rigidity, motor retardation, and cognitive decline. When subjects have 60%-80% of substantia nigra neurons damaged or 90% of striatal dopamine loss, symptoms and signs of Parkinson's disease begin to appear. Compared with healthy people, the uptake of dopamine in the striatum of Parkinson's disease subjects is significantly reduced.

1.1.2 Existing Treatment and Clinical Needs

According to the fourth edition of the Chinese Guideline of Parkinson's Disease released in December 2020, the severity of Parkinson's clinical symptoms is different, and Hoehn-Yahr grade 1.0-2.5 is defined as early. Once the disease occurs, it will gradually aggravate over time. The evidence suggests that the progress of the disease in the early stage is faster than that in the later stage. Therefore, once the early diagnosis is made, we should start early treatment and strive to grasp the opportunity of disease modification, which plays an important role in the long-term management of disease treatment. Although a series of new treatments have recently appeared in the treatment of Parkinson's disease, levodopa is still

the gold standard for the treatment of Parkinson's disease. The guidelines point out that for early subjects who do not deliberately delay the use of levodopa, especially for subjects with late-onset Parkinson's disease or younger subjects with high demand for motor function improvement, compound levodopa can be used as the first choice, but the effective dose should be kept as low as possible on the premise of meeting symptom control.

Oral administration of levodopa with which usually disintegrates in the stomach and be absorbed into the blood through the amino acid transporters in the upper part of the small intestine. About 1% of levodopa can eventually enter the midbrain through the blood-brain barrier and be taken up by substantia nigra neurons or other neurons. Under the action of dopa decarboxylase, it decarboxylates and becomes dopamine, thereby replenishing dopamine in the brain. In order to prevent levodopa from rapidly decarboxylating outside the brain and becoming dopamine, levodopa is currently combined with peripheral dopa decarboxylase inhibitors such as carbidopa or developed into a compound preparation, such as carbidopa, the so-called Compound levodopa. In peripheral blood, Catechol-O-methyltransferase (COMT) can catabolize dopamine. In order to inhibit the activity of this enzyme and allow more levodopa to enter the brain, COMT inhibitors are often used in conjunction with levodopa in the treatment of Parkinson's disease. Carbidopa-Levodopa tablets have undergone immediate release to sustained release. The compound product of COMT inhibitor and the compound products of carbidopa-levodopa further improves the blood concentration and effective action time of levodopa. A comparison of related products on China and US markets is summarized in Table 1.

Table 1 Comparison of Levodopa preparations in the China and US/Europe Markets

	Indications	US Market (European market)	China Market
Carbidopa-Levodopa Immediate Release (IR) Tablets	It is used to treat Parkinson's disease, post-encephalitic parkinsonism, and Parkinson's disease symptoms caused by carbon monoxide or manganese poisoning.	Sinemet®, listed in the United States in 1975 (NDA No.: 017555), with generic drugs	Not listed in China
Carbidopa-Levodopa Sustained Release (CR) Tablets	It is used to treat Parkinson's disease, post-encephalitic parkinsonism, and Parkinson's disease symptoms caused by carbon monoxide or manganese poisoning.	Sinemet®CR, listed in the United States in 1991 (NDA No.：019856), with generic drugs (discontinued in US)	Sinemet® Sustained-Release Tablets, imported and registered in 2015, no generic drugs
Levodopa and Benserazide Tablets	It is used to treat Parkinson's disease and symptomatic Parkinson's syndrome (post-encephalitic, arteriosclerosis or toxicity), but does not include Parkinson's syndrome caused by drugs.	Madopar®, listed in Europe (Switzerland) in 1973	Madopar®, imported and registered in 2011, with generic drugs (capsules)
Entacapone, Levodopa and Carbidopa Tablets	Used to treat spontaneous Parkinson's disease.	STALEVO®, listed in the United States in 2003 (NDA No.: 021485), with generic drugs	Stalevo®, imported and registered in 2012，no generic drugs
Carbidopa-	It is used to treat	Rytary®, listed in the	Not listed in China

Levodopa Sustained-Release Capsules	Parkinson's disease, Parkinson's disease caused by infection or inflammation of the brain, and Parkinson's disease symptoms caused by carbon monoxide or manganese poisoning.	United States in 2015 (NDA No.: 203312)	
Continuous Duodenal Infusions of Levodopa	It is used to treat dyskinesias of advanced Parkinson's disease.	DUOPA, listed in the United States in 2015 (NDA No.: 203952) (DUODOPA，listed in Europe in 2005)	Not listed in China
Levodopa Inhalation Powder	It is used to treat intermittent dyskinesias in Parkinson's subjects.	INBRIJA®, listed in the United States in 2018 (NDA No.: 2091840	Not listed in China

The first carbidopa-levodopa product, Sinemet® IR developed by Merck is an immediate-release formulation of carbidopa and levodopa. It was approved for marketing in the United States in 1975 for the treatment of Parkinson's disease. Sinemet® has high fluctuation of levodopa plasma concentrations and patients often develop motor fluctuations of symptoms and dyskinesia, an involuntary movement. The cause of the motor fluctuations may be partially attributed to the non-physiological, post-synaptic pulse-like stimulation of dopamine receptors by levodopa. Sinemet® CR, a carbidopa-levodopa sustained-release product developed by Merck was launched in the United States in 1991 and entered the Chinese market in 2015; compared with Sinemet®IR, its blood concentration fluctuations have been improved to some extent, but there are still relatively high blood concentration fluctuations, and its effective treatment time window is only 2-3 hours. In 2015, the FDA approved the marketing of Impax Laboratories' Rytary®, which is an extended-release formulationof carbidopa-levodopa. Rytary® uses tartaric acid to extend the absorption window of levodopa to 4-5 hours, and its fluctuation index is around 1.5, which improves the fluctuation of the blood concentration of levodopa compared to Sinemet®. The bioavailability of levodopa in Sinemet® CR and Rytary® is about 30% lower than that of Sinemet® IR, which increases the difficulty of dose conversion in clinical practice and requires a longer time of dosage titration. In addition, Rytary®

has a high content of hydrazine, a genetic toxic impurity, which has potential risks, and the drug has not been marketed in China.

Although there are many medications for early treatment of Parkinson's disease, there are two major problems: levodopa and its compound preparations directly provide dopamine, and theoretically, very good theoretical effects can be obtained. However, due to the impulsive fluctuations in the blood drug concentrations of oral administration of levodopa products, and the wide fluctuation of the drug concentration, such as dyskinesia and motor disability will occur, thus the use of levodopa was deliberately postponed for early Parkinson's subjects. The fourth edition of [the Chinese Guideline of Parkinson's Disease] in December 2020 points out that existing evidence suggests that early use of low-dose levodopa (within 400 mg/d) does not increase the occurrence of dyskinesia; it is not recommended to deliberately postpone the use of levodopa for early stage, especially for late-onset Parkinson's disease subjects or younger subjects with a high demand for improvement in motor function, and compound levodopa can be the first choice, but the effective dose should be maintained as low as possible under the premise of meeting symptom control. Although the current sustained-release tablets on the market have a relatively long maintenance time, they have a slow onset of action and low bioavailability. The levodopa immediate-release formulation has the characteristics of fast onset; when used, especially during the conversion of two different dosage forms, it takes longer time for dosage titration in clinical practice. In order to use a smaller effective dose clinically, levodopa tablets are often broken into two halves and taken in divided doses, so as to achieve the purpose of reducing the peak blood concentrations of levodopa and reducing the fluctuation of the blood concentrations.

1.2 Investigational Product

WD-1603 developed by WD-Pharma is a carbidopa-levodopa extended-release tablet.

WD-1603 is being developed under US FDA 505(b)(2) regulatory pathway, and its efficacy and safety highly rely on FDA's prior findings of Sinemet®.



Figure 1 Configuration of WD-1603

1.2.1 Non-Clinical Study

1.2.1.1 Pharmacology

Human Pharmacology Study

The preclinical pharmacology research refers to the similar product Sinemet® on the market in China. Carbidopa-Levodopa extended-release tablets are polymer-based compound tablets of carbidopa and levodopa, which is used to treat Parkinson's disease and Parkinsonism. Levodopa decarboxylates in the brain to form dopamine to alleviate the symptoms of Parkinson's disease. Carbidopa cannot pass through the blood-brain barrier, and only inhibits the decarboxylation of peripheral levodopa, so that more levodopa enters the brain and be converted into dopamine, which avoids frequent and high-dose levodopa. Small doses of carbidopa can reduce or may help eliminate adverse reactions in the gastrointestinal and

cardiovascular system, especially those related to the formation of dopamine in peripheral tissues.

1.2.2 Clinical Study

1.2.2.1 Human Pharmacokinetics

Up to now, WD-1603 has completed three phase I clinical PK trials in healthy people, and the main results are summarized as follows:

WD-1603-1001： This study evaluated the pharmacokinetic characteristics of a single-dose intra-oral and oral administration of WD-1603 62.5mg/250mg carbidopa/levodopa controlled-release tablet and Sinemet®. The results showed that WD-1603 62.5mg/250mg can produced a longer-lasting and less fluctuating plasma concentration of levodopa compared with Sinemet®. Compared with Sinemet® IR, the blood concentration of levodopa Cmax of WD-1603 is reduced, Tmax is prolonged, and the bioavailability is equivalent to that of Sinemet® IR. The reports show that the clinical advantages of WD-1603 are obvious, since most of the carbidopa-levodopa sustained-release products currently on the market have about 70% of the bioavailability of Sinemet® IR, which is hard for clinical dose conversion.

WD-1603-1002： The study mainly evaluated the effect of meals on the PK of a single-dose oral administration of a newly developed dose strength, WD-1603 25mg/100mg carbidopa-levodopa extended-release tablet in healthy subjects. The results showed that, compared with fasting, oral administration of WD-1603 tablets after a meal increased the blood concentration of levodopa, Tmax, Cmax, AUC as well as the increased utilization postprandial bioavailability.

WD-1603-1003： This study evaluated the dose proportionality of WD-1603 of four dose strengths in healthy subjects. By comparing the AUC curve of 25mg/75mg, 25mg/100mg, 25mg/150mg and 25mg/250mg Cabidopa-Levodopa Extended-Release tablets. The results showed that these four strengths were dose proportional.

1.2.2.2 Safety

Compound levodopa (carbidopa-levodopa) products have been on the market all over the world since 1975. WD-1603 has also completed three human PK studies in healthy subjects, in which subjects generally have good tolerance to the study drugs, and there are no serious adverse events, and all adverse events caused after treatment are mild.

2 Study Objectives

Primary objective

To investigate the effectiveness and safety of WD-1603 carbidopa-levodopa extended-release tablets in subjects with Parkinson's disease.

Secondary objective

To measure pharmacokinetic parameters and plasma fluctuation index of levodopa in subjects with Parkinson's disease.

2.1 Primary Endpoint：

Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 27th day.

2.2 Secondary Endpoints：

(1) Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 14th day.

(2) Changes in MDS-UPDRS-II scores from the baseline to the 14th and 27th days.

(3) Changes in the MDS-UPDRS-III scores from the baseline to the 14th and 27th days.

(4) To evaluate the pharmacokinetics and fluctuation index of levodopa on the 28th day.

(5) To evaluate the safety of WD-1603 in subjects with Parkinson's disease.

3 Study Design

3.1 Rationale

The objective of the study is to evaluate the efficacy of WD-1603 in subjects with early Parkinson's disease. Following EMA's clinical developemnt guidelines for Parkinson's drugs, as well as the consensus experts in the field, this clinical trial is designed as a phase II randomized, parallel, and double-blind, placebo-controlled multi-center study [1-3]. The results of this clinical trial will be used to estimate the sample size for a Phase III clinical study. This phase II clinical trial will enroll 40 subjects with early-stage Parkinson's disease and randomly divided them into four groups with different doses of WD-1603 and a placebo group in equal proportions (1:1:1:1). The treatment period is 28 days.

In the inclusion criteria, the diagnosis basis for Parkinson's disease is stipulated. The inclusion criteria are based on modified Hoehn & Yahr scale ≥1, ≤2.5and the sum of MDS-UPDRS-II+ MDS-UPDRS-III ≥18 points

3.2 Benefit- Risk Assessment

WD-1603's similar mechanism drug Sinemet® IR, Sinemet® CR, and Rytary® have been marketed for the treatment of Parkinson's diseaseHuman Phase I clinical study results suggest that WD-1603 has less fluctuations in the blood concentrations of levodopa than those similar drugs on the market, and it has similar bioavailability to Sinemet® IR, easier for dose conversion. WD-1603 has no obvious irritation and no obvious side effects. According to the results of the clinical studies of cabidopa-levodopa products, it is safe to use this type of drugproducts in general; adverse gastrointestinal system reactions such as nausea and vomiting, nervous system reactions such as dizziness, etc., most of the medication-related TEAEs are

Grade 1. Therefore, it is expected that the subjects in this study will tolerate well.

The safety of the subjects will be closely monitored throughout the study. For potential adverse drug reactions (ADR) of the study drug, the investigators should make comprehensive judgments based on the clinical conditions of the subjects and give corresponding clinical treatments.

3.3 Overall Study Design

This trial is a phase II, randomized, double-blind, parallel, fixed-dose, placebo-controlled clinical trail in subjects with early Parkinson's disease for a period of 4 weeks, which aims to evaluate the efficacy and safety of WD-1603 carbidopa-levodopa extended-release tablets in subjects with Parkinson's disease. Eligible subjects will be randomly divided into one of the four treatment groups at a ratio of 1:1:1:1: WD-1603 25mg/100 mg, 25mg/150 mg, 2 x 25/mg100 mg or placebo. The first oral administration is before breakfast, the second and third oral administration is after meal, and the oral administration is three times every 5 hours (only twice on the 28th day, and the blood samples for PK characteristic evaluation are collected after the second administration). Eligible subjects are 30 years and older, 75 years and younger who are diagnosed with early idiopathic Parkinson's disease and have not received levodopa-containing drugs for at least 4 weeks.

Study Treatment and Follow-up:

Screening Period: subjects will start the screening period after signing ICF. After completing the screening examination specified in the scheme and meeting the inclusion criteria in the screening period, the subjects who enter the baseline evaluation measurement (day - 1) will be randomly divided into groups in the proportion of 1:1:1:1, and the qualified subjects will be randomly assigned to each study group. The clinical trial process is shown in Figure 2 below:：

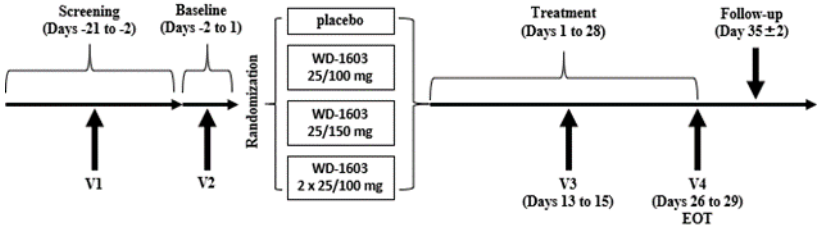


Figure 2 Clinical Trial Flow Chart

Baseline Evaluation Period: Subjects are admitted to the clinics on Day -2, and UPDRS-II as well as UPDRS-III evaluation will be performed on Day -1. For subjects who take regular anti-Parkinson's drugs with three times daily, UPDRS-III evaluation timepoints will be before the first morning drug

administration and 2.5 hours ± 15 minutes after the morning dose, before the second dose administration and 2.5 hours ± 15 minutes after the second dose administration, before the third dose administration and 2.5 hours ± 15 minutes after the third dose administration, and the MDS-UPDRS of subjects without drug treatment before the trial will be evaluated at the same time points as the drug treatment period (Visit 3). The baseline assessment included Baker Depression Self-Rating Scale and orthostatic hypotension assessment. Eligible subjects will be randomly assigned to each group in the treatment period. Subjects will be discharged from the clinics with test medications.

Drug Treatment Period: according to the specifications of randomly assigned drug treatment, subjects are given study drugs before meals for the first morning dose, after meals for the second and third doses orally three times daily, three tablets each time (the dose strenthswill be 25mg/100 mg, 25mg/150 mg, 2 x 25mg/100 mg or placebo). On Days 13-15 and Days 26-29, the subjects will return to the clinics for assessments.

After the treatment period, the subjects will have safety follow-up visit on the 7th day after the last dose in the treatment periods. For subjects who do not complete the 4-week treatment, the early termination visit must be completed.

Concomitant Medication:

During the trial, subjects can continue to use other Parkinson's disease drugs that do not contain levodopa, such as anticholinergic drugs, amantadine, or MAO-B inhibitors.

Scale Rater Requirements:

The Clinicians who assess MDS-UPDRS-II and MDS-UPDRS-III should remain blind to clinical trial grouping.

3.4 Study Endpoints

Primary Endpoint：

Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 27th day.

Secondary Endpoints：

1) Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 14th day.

2) Changes in MDS-UPDRS-II scores from the baseline to the 14th and 27th days.

3) Changes in the MDS-UPDRS-III scores from the baseline to the 14th and 27th days.

4) To evaluate the pharmacokinetics and fluctuation index of levodopa on the 28th day.

5) To evaluate the safety of WD-1603 in subjects with Parkinson's disease.

4 Study Population

4.1 Inclusion Criteria

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

1) Male/female subjects with early Parkinson's disease who are over 30 years old and under 75 years old, inclusive.

2) Able to understand and willing to sign an informed consent form (ICF) voluntarily.

3) The diagnosis of Parkinson's disease complies with idiopathic Parkinson's disease (2015 version of MDS Parkinson's disease diagnostic criteria).

4) Modified Hoehn & Yahr score ≥1, ≤ 2.5.

5) The sum of MDS-UPDRS-II and MDS-UPDRS-III ≥18 (subjects will be evaluated once before the administration of the test drugs).

6) Subjects must have not received levodopa drugs or catechol-O-methyltransferase inhibitors within 4 weeks before baseline or aredrug treatment-naive.

7) If subjects are currently receiving anticholinergic therapy, amantadine or monoamine oxidase B (MAO-B) inhibitors should maintain stable treatment regimens at least 4 weeks before baseline, and agree to maintain the same doses throughout the study.

8) Agree to use medically acceptable contraceptive methods throughout the study and within 1 month after completing the study.

9) Female subjects of non-fertility potential must be postmenopausal (postmenopausal refers to amenorrhea without other reasons for at least 1 year, and follicle stimulating hormone level ≥ 26IU/L) or surgical infertility (hysterectomy, bilateral oophorectomy) or bilateral tubal ligation).

4.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria cannot be selected for this study:

1) Have a history of severe allergic reactions or allergies to levodopa or carbidopa.
2) Pregnancy or breastfeeding.
3) Diagnosed as atypical Parkinson's disease or any known secondary Parkinson's syndrome.
4) Use dopamine receptor agonists within 30 days before screening.
5) The patient has been treated with one of the following drugs within 28 days before screening: non-selective MAO inhibitors, dopamine releasing agents (for example, amphetamine), reserpine, dopamine antagonists (for example, metoclopramide), antipsychotics or other drugs that may interact with dopamine function.

6) The investigator believes that the placebo treatment cannot be tolerated.
7) Acute psychosis or hallucinations, using any antipsychotic to treat psychosis or clinically obvious depression.
8) History of epilepsy or epilepsy.
9) A history of digestive system disease or digestive system surgery that interferes with the absorption of levodopa.
10) The history of narrow-angle glaucoma.
11) Subjects with a history of malignant melanoma.
12) Human immunodeficiency virus antibody (HIV)-1/2Ab, hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV-Ab) are positive.
13) Have received the clinical trial study drug within 30 days before the first dose administration of the test drug, or the treated study drug has not exceeded 5 half-lives, whichever is longer.
14) Subjects with obvious cognitive impairment.
15) The investigator believes that there are clinically significant medical or surgical diseases and subjects who are not suitable for participating in clinical trials.

4.3 Screening Failures

If there is evidence indicating that the reason for excluding a subject from the study has changed, or the investigatir believes that some non-conforming conditions are caused by accident, the subjects who do not meet the eligibility for inclusion can be screened again after communicating and agreeing with the sponsor and medical supervisor and determining the contents to be re-screened. In this study, each subject is allowed to repeat the screening only once. Whether the subjects can be screened repeatedly will be discussed and decided by the medical supervisor and the sponsor. There is no time limit for re screening, and the screening number needs to be reassigned.

4.4 Subjects Withdrawl

Subjects can decide to terminate the study treatment earlier at any time during the study, and it will not affect their continued acceptance of appropriate clinical treatment. If one of the following situations occurs, the investigator should arrange for the subject to terminate the study treatment earlier:

- During the study process, it is found that the subjects do not meet the important inclusion criteria while they are already enrolled in the study.
- Subject withdraws consent form.
- The treatment is inadequate, and the investigator judges the need to use other medications.

- Due to the occurrence of AE, the investigator judges that the subject is not suitable for continuing the study.
- Breaking blindness with study medications.
- Pregnancy.
- Serious non-compliance with the protocol's procedures including study treatment.

The investigator should arrange for the subject to terminate the study treatment earlier and complete the end of study treatment (EOT) assessment as much as possible:

- Vital signs examination (including blood pressure, heart rate, respiratory rate, body temperature).
- Adverse event monitoring.
- Concomitant medication

4.5 Subject Replacement

There is no replacement plan for subjects in this study.

5 Investigational Product

5.1 Investigational Product

The investigational products used in this study include the experimental drug (WD-1603) and placebo. See Table 2 for specific information. The above-mentioned drugs are provided by the sponsor.

Table 2 WD-1603 Dosing Information

	WD-1603 Cabidopa-Levodopa Extended-Release Tablet	Placebo
Manufacturer	[redacted]	[redacted]
Strength	25mg/100 mg, 25mg/150 mg	WD-1603 matching placebo tablets
Dose	25mg/100 mg, 25mg/150 mg, 2 x 25mg/100 mg	Three tablets: 2 x Placebo-1 and 1 x Placebo-2 tablets
Route of administration	Oral, TID for 4 weeks	Oral, TID for 4 weeks

Abbreviation：TID= three times daily

5.2 Package Insert and Labels

Packing: Single piece is packed in aluminum-plastic blister pack, 3 pieces in a small bag, 24 sachets in a box.

The label content includes clinical trial number, drug name, drug number, specifications, packaging

specifications, storage conditions, product batch number, expiration date, usage and dosage, and the name of the sponsor. The label must indicate "For clinical trial use only, keep out of reach of children".

5.3 Investigational Products Regimens

The administration methods of different dosage groups are shown in Table 3 below:

Table 3 Treatment Regimens in Different Dose Groups Treatment Regimens in Different Dose Groups

Treatment Group	Treatment Regimens
Treatment A: 25mg/100 mg	1×25mg/100 mg+1×Placebo-1+1×Placebo-2, orally administered once every five hours, three times a day
Treatment B: 25mg/150 mg	1×25/150 mg+2×Placebo-1, orally administered once every five hours, three times a day
Treatment C: 2 × 25mg/100 mg	2 × 25mg/100 mg+1×Placebo-2, orally administered once every five hours, three times a day
Treatment D: Placebo Tablets	2×Placebo-1 + 1×Placebo-2, orally administered once every five hours, three times a day

Note：[1] The size of Placebo-1 dosage form is the same as the 25mg/100 mg dosage form, and Placebo-2 dosage form is the same size as the 25mg/150 mg dosage form. The sizes of dosage formsin each treatment group is consistent in appearance.

[2] The morning dose administration is 30 minutes (± 5 minutes) before a meal, and the noon and evening dose administration will be within 5 minutes after a meal.

[3] The dose administration interval is every 5 hours ± 30 minutes.

5.4 Dose Modifications/Interruptions

5.4.1 Dose Modifications

During the treatment period of this trial, dose modifications is not allowed in principle.

5.4.2 Dose Interruptions

Dose interruption details will be recorded on the eCRF.

5.5 Allocation to Treatment(Randomization)

Allocation of subjects to treatment groups will proceed through the use of an Interactive Response Technology (IRT) System. A computer-generated randomization schedule will be used to assign subjects to the WD-1603 25mg/100 mg, 25mg/150 mg, 2 × 25mg/100 mg or placebo group at a ratio of 1:1:1:1.

The randomization plan and subject identification information will be included in the clinical study report.

5.6 Investigational Products Management, Distribution and Recall

Investigators are in charge of the drug management in the clinics. The investigator must ensure that all study drugs (including the study drug and placebos provided by the sponsor) are only used for subjects in this clinical trial, and their dosage and usage should follow the protocol. The above process shall be in the charge of a specially assigned person and recorded, and the study drugs shall be managed by a specially assigned person. Researchers are not allowed to transfer research treatment drugs to any non-clinical research participants. The container of the drug and the remaining treatment drugs must be recovered, and the number of recovered drugs shall be recorded in the original record and eCRF.

At the end of the study, all study drugs, including all unused and partially used study drugs and all recovered drug packaging, shall be returned to the sponsor or destroyed after being counted by the investigators accordance with the sponsor's instruction.

5.7 Transportation, Handling, Storage and Destruction/Return

All study drugs will be provided to investigators by the sponsor directly or through a supplier that has a cooperative relationship with the sponsor. The supplied medicines must be kept in a suitable safe area (e.g. locked medicine cabinet/pharmacy) and stored in accordance with the regulations on the medicine label.

Researchers must keep accurately and record timely the received study drugs, the study drugs issued to the subjects, the unused study drugs recovered from the subjects, and the unused or expired study drugs should be returned to the sponsor. At the end of the study, a copy of these records must be provided to the sponsor. Researchers shall not destroy the labels of any study drugs or any used or unused study drugs before receiving instructions from the sponsor or the designated personnel after the check-up.

Supply and inventory records must be backed up for inspection by the sponsor's designated representative or local regulatory authority.

5.8 Investigational Products Inventory/Compliance

During the study, the study medications and any medication events that deviate from the study protocol will be recorded in the eCRF, including the date and reason of medication. Researchers must explain to the subjects the importance of receiving research treatment according to the protocol, and require the subjects to take the drugs according to the protocol.

Investigators and researchers will be responsible for counting all clinical supplies and keeping records (distribution, inventory and return) according to the instructions of the sponsor and in accordance with the guidelines of GCP and applicable international and/or domestic relevant regulations. Subjects shall be

required to return all unused study drugs and used study drug packages at each visit to evaluate the study drug compliance. At each visit, investigators shall confirm and record the subject's compliance with the study medication.

5.9 Blinding and Unblinding

This is a double-blind study. During the entire study, the evaluators involved in the efficacy assessment and participated subjects are always blinded.

If the rater for efficacy assessments breaks the blind due to special reasons, they have to be replaced, and the date, time and reason for breaking the blind shall be recorded in detail.

6 Concomitant/Prohibited Medications and Therapies

6.1 Concomitant Medication and Trerapies

Any drug that is not banned and considered to be used to ensure the interests of subjects can be used and/or continued to be used under the supervision of the investigator.

All previous medications and treatments received by the subject within 30 days before the first dose of study medication, as well as any combined medications and treatments received by the subject during the study period (since sign the ICF) to the end of the study shall be recorded in the original data of the subject. Including over-the-counter drugs and non-drug therapies (such as physical therapy). It will be recorded in the concomitant medications section according to the eCRF guide. Any new therapies that change existing treatments will also be recorded on the eCRF concomitant medications page, and will be updated throughout the subject's participation in the study.

6.2 Restricted Concomitant Medication

The following drugs can be used in comcomitant, provided that there is no change in the drug dose in the 4 weeks before the baseline assessment, and the drug dose cannot be changed from the screening to the follow-up visit after the completion of 4-week treatment.

During the trial, subjects can continue to use anticholinergic drugs, amantadine, or MAO-B inhibitors.

6.3 Prohibited Medications

During the study from the screening to the post-treatment follow-up visit, the subjects are prohibited from using the following drugs and treatments:

Non-selective MAO inhibitors, dopamine releasing agents (for example, amphetamine), reserpine, dopamine antagonists (for example, metoclopramide), antipsychotics or other drugs that may interact with dopamine function.

The judgements from investigators that the medications may affect the objectivity of the assessments of

efficacy and safety.

7 Study Visits

The overall design of the clinical trial is shown in Figure 2. There are five visits in this clinical study. For details, please refer to Table 4 Schedule of Procedures

Table 4 Schedule of Procedures

Date / Procedure	Visit 1 Screening	Visit 2 Baseline Assessment	Visit 3 Interim Assessment	Visit 4 Endpoint Assessment	Visit 5 Follow-up/Early Termination
	Days -21 to -2	Days -2 to 1	Days 13 to 15	Days 26 to 29	Days 35±2
Informed Consent	X				
Medical/surgical history	X				
Medication history	X				
Review Inclusion and Exclusion Criteria		X			
Physical Examination	X				
Symptom directed Physical Examination		X	X	X	
Weight, Height, BMI	X				
Vital signs (blood pressure, orthostatic hypotension, heart rate, respiratory rate, and body temperature)）	X	X[1]	X[1]	X[1]	X
HIV、Hepatitis B and C	X				
12-lead ECG	X	X[2]	X[2]	X[2]	
Safety laboratory examination (blood routine, urine routine, blood biochemistry, coagulation function, glycosylated hemoglobin [HbA1c]) [3]	X			X	
Urine pregnancy test	X	X		X	
FSH（to confirm post-menopausal status）	X				
Adverse Events Assessments	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
MDS-UPDRS-II[4]	X	X	X	X	
MDS-UPDRS-III[5]	X	X	X	X	
Beck Depression Scale Assessment [6] [Beck Depression Inventory-II（BDI-II）]	X	X		X	

Date / Procedure	Visit 1 Screening	Visit 2 Baseline Assessment	Visit 3 Interim Assessment	Visit 4 Endpoint Assessment	Visit 5 Follow-up/Early Termination
	Days -21 to -2	Days -2 to 1	Days 13 to 15	Days 26 to 29	Days 35±2
WD-1603 administration		← X[7] →			
PK blood sample collection				X[8]	
Admission		X[9]	X[10]	X[11]	
Discharge from Clinics		X	X	X	

[1] Measured vital signs and orthostatic hypotension before the first dose administration, 1 hour and 4 hours after the first dose administration. Orthostatic hypotension will be monitoered: (1) to measure the blood pressure in the supine position, (2) to measure the blood pressure again in a standing position after 3 minutes, (3) if systolic blood pressure drops ⩾20mmHg or diastolic blood pressure drops ⩾10mmHg, orthostatic hypotension will be diagnosed; (4) if diagnosed, after one hour, ask the subject to repeat the above steps (1) to (3). Note: If necessary, please consult the principal investigator or designated personnel to give corresponding treatment.

[2] Performed 12-lead electrocardiogram on Day 1, Day 15 and Day 29.

[3] Collect fasting (8 hours) blood samples for chemical and hematological evaluation. The coagulation function and glycosylated hemoglobin are only tested during the screening period.

[4] MDS-UPDRS-II: Complete the MDS-UPDRS-II scale assessment in the morning of each visit period (Day -21--2, Day -1, Day 14 and Day 27).

[5] MDS-UPDRS-III: During the screening period, an outpatient evaluation is performed before any drug administration. In the other visit periods, 6 assessments of the MDS-UPDRS-III scale on the designated day will be carried out at the timepoints: Day -1: the following 6 timepoints will be for the subjects who take non-levodopa drugs: (1) at the time before the first drug administration, (2) 2.5 hours after the first dose administration, (3) 5 hours after the first dose administration or before the second dose administration, (4) 2.5 hours after the second dose administration at noon (7.5 hours after the first dose administration), (5) 10 hours after the first dose administration or before the third dose administration, and (6) 2.5 hours after the third dose administration (12.5 hours after the first dose administration). The timepoints for the subjects who are not treated with any drugs will be the same timepoints as those with the drug treatment period above.

For Day 14 and Day 27: the 6 timepoints are as follows: (1) before the first dose administration, (2) 2.5 hours after the first dose, (3) before the second dose at noon, (4) 2.5 hours after the second dose, (5) before the third dose, and (6) 2.5 hours after the third dose.

Each scale evaluation has a time window of ±15 minutes.

[6] Bake Depression Scale Evaluation: Evaluation at any time during the screening period, baseline evaluation period (Day-1) and endpoint evaluation period (Day 28).

[7] WD-1603 tablet 25mg/100mg or 25mg/150mg or 2 x 25mg/100mg or placebo orally three times a day, the first dose is every morning 30 minutes (±5 minutes) before breakfast, the second and third doses are taken after meals (within 5 minutes after a meal), three tablets each time (see Table 3 on page 35 for the tablet combinations), starting from Day 1, daily treatment for 4 weeks ; on Day 28, WD-1603 tablets or placebo will be taken orally twice, in the morning and at noon.

[8] Day 28, Blood sample collection time points include before the second dose (-15 to 0 minutes) and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 9.0 hours after the second dose (time window for each blood sample collection: ≤1 hour time window ±2 minutes, >1 hour time window ±5 minutes).

[9] Day -2, The subjects are admitted to the clinics in the afternoon or evening and are assessed with MDS-UPDRS on Day -1 and randomly assigned to one of the four treatment groups. On Day 1, they will discharge after oral taken of drug in the morning, vital signs measurement completion, and monitoring of orthostatic hypotension.

[10] Day 13, the subjects are admitted to the clinics in the afternoon or evening. On Day 14 for MDS-UPDRS evaluation, on Day 15 subjects discharge after oral administration of test drugs, measurement of vital signs, monitoring of orthostatic hypotension and 12 lead ECG.

[11] Day 26, subjects are admitted to the clinicsin the afternoon or evening, MDS-UPDRS assessment on Day 27, Baker depression scale assessment and blood drug concentration sampling are evaluated on Day 28, discharge after laboratory examination, vital signs measurement, orthostatic hypotension and 12-lead monitoring on Day 29 morning.

BMI= body mass index; ECG= electrocardiogram; PK= pharmacokinetic

Visit 1 Screening (Days -21 to- 2):

The screening will be conducted within 21 days before the start of treatment. Subjects are required to sign an informed consent form before conducting any research projects. Subjects who provide informed consent will receive standard medical screening. Subjects who meet all the selection criteria and do not meet any exclusion criteria will be eligible to participate in the study. Subjects need to complete the following procedures:

- Sign informed consent
- Ask about medical history/surgical history
- Ask about medication history
- Physical examination
- Measure weight and height, calculate BMI
- Measure vital signs (blood pressure, orthostatic hypotension, heart rate, respiratory rate and body temperature)
- 12-lead ECG
- Safety laboratory examination (blood routine, urine routine, blood biochemistry, blood coagulation function, glycosylated hemoglobin [HbA1c])
- Virological examination (HIV, hepatitis B, hepatitis C)
- Urine pregnancy test (women of childbearing age)
- FSH (postmenopausal women)
- MDS-UPDRS-II evaluation
- MDS-UPDRS-III evaluation
- Beck Depression Inventory Evaluation (BDI-II, Beck Depression Inventory-II)
- Concomitant medication record
- Adverse event monitoring

Visit 2 Baseline Assessment（Days -2 to 1）：

Eligible subjects will stay in the Clinicsin the afternoon or evening of Day -2, and stay in the Clinicsfor 2 nights and 3 days. Subjects need to complete the following test procedures:

On Day -1:

- Urine pregnancy test (women of childbearing age)
- MDS-UPDRS-II evaluation: once in the morning.
- MDS-UPDRS-III evaluation: 6 timepoints for evaluations will be performed: the subjects who

have used non-levodopa drugs before the test (1) before the first dose, (2) 2.5 hours after the first dose, (3) 5 hours after the first dose or before the second dose, (4) 2.5 hours after the second dose (7.5 hours after the first dose), (5) 10 hours after the first dose or before the third dose, (6) 2.5 hours after the third dose (12.5 hours after the first dose), the time window is ±15 minutes. The subjects who were not treated with medication before the trial are at the same time point as the medication period (Visit 3). Eligible subjects on Day 1 are randomly assigned to one of the four treatment groups; take the study drug orally 3 times a day, 3 tablets each time: 100 mg (one tablet of 100 mg plus two placebo tablets), 150 mg (one tablet of 150 mg plus two placebo tablets), 200 mg (two 100 mg tablets plus one placebo) or placebo group (three placebo tablets), three times a day, before and after meals.

- Beck Depression Inventory Evaluation (BDI-II, Beck Depression Inventory-II)
- Concomitant medication record
- Adverse event monitoring

On Day 1:

- Randomly distribute study drugs and instruct subjects to take
- Measure vital signs (blood pressure, orthostatic hypotension, heart rate, respiratory rate and body temperature)
- 12-lead ECG
- Concomitant medication record
- Adverse event monitoring
- Discharge

Visit 3（Days 13 to 15）：

Subjects stay in the Clinicsin the afternoon/evening on Day 13, for 2 nights and 3 days. Subjects need to complete the following test procedures：

On Day 14：

- Taking study drugs
- MDS-UPDRS-II evaluation: once in the morning.
- MDS-UPDRS-III evaluation: before the first dose and 2.5 hours ± 15 minutes after, before the second dose and 2.5 hours ± 15 minutes, and before the third dose and 2.5 hours ± 15 minutes after.
- Recover the remaining study drugs and issue new study drugs

- Concomitant medications record
- Adverse event monitoring

On Day 15：

- Taking study drugs
- Measure vital signs (blood pressure, orthostatic hypotension, heart rate, respiratory rate and body temperature)
- 12-lead ECG
- Concomitant medications record
- Adverse event monitoring
- Discharge

Visit 4（Days 26 to 29）：

Subjects will stay in the Clinics in the afternoon/evening on Day 26, for 3 nights and 4 days. Subjects need to complete the following test procedures:

On Day 27：

- Taking study drugs
- MDS-UPDRS-II evaluation: once in the morning.
- MDS-UPDRS-III evaluation: before the first dose and 2.5 hours ± 15 minutes after, before the second dose and 2.5 hours ± 15 minutes, and before the third dose and 2.5 hours ± 15 minutes after.
- Concomitant medications record
- Adverse event monitoring

On Day 28：

- Take the study drug (only twice, in the morning and noon)
- Beck Depression Inventory Evaluation (BDI-II, Beck Depression Inventory-II)
- Collect blood samples of subjects to detect the blood drug concentration. The blood sample collection time points are 0.25 hours before the second dose and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 9.0 hours after the dose (the time window for each blood sample collection: ≤1 hour time window ±2 minutes, >1 hour time window ±5 minutes).
- Concomitant medication record
- Adverse event monitoring

- Recover surplus study drugs

On Day 29：

- Safety laboratory examination (blood routine, urine routine, blood biochemistry)
- Urine pregnancy test (women of childbearing age)
- Measure vital signs (blood pressure, orthostatic hypotension, heart rate, respiratory rate and body temperature)
- 12-lead ECG
- Concomitant medication record
- Adverse event monitoring
- Discharge

Visit 5（Day 35±2）：

Safety follow-up. Approximately 7 days (±2) after the last dose, the subject will return to the Clinicsfor safety follow-up. Subjects need to complete the following test procedures:

- Measure vital signs (blood pressure, orthostatic hypotension, heart rate, respiratory rate and body temperature)
- Concomitant medication record
- Adverse event monitoring

8 Study Process and Assessments

8.1 Information Collection at Screening

8.1.1 Demographic Information

During screening, demographic data of the subjects must be collected, including ethnicity, age (date of birth), height, gender, etc.

8.1.2 Medical History/Surgery History/Allergy History Collection

During screening, the medical history, surgical history, and history of allergies must be recorded before the subject signs the ICF. During the baseline period, if applicable, medical history information can be supplemented and updated

8.1.3 Diagnosis and Treatment History of Target Disease

8.1.3.1 Diagnosis of Parkinson's disease

The diagnosis of Parkinson's disease is based on the 2015 version of MDS Parkinson's disease diagnostic criteria.

8.1.3.2 Treatment history of Parkinson's disease

History of levodopa drugs for Parkinson's disease.

History of non-levodopa drugs for Parkinson's disease.

8.2 Efficacy Assessment

（1）Subject's MDS-UPDRS-II and MDS-UPDRS-III scores

1）The change in the sum of MDS-UPDRS-II + MDS-UPDRS-III from the baseline (Day -1)to Day 27.

2）The change in MDS-UPDRS-II score from baseline (Day -1) to Day 27.

3) The change in MDS-UPDRS-III from baseline (Day -1) to Day 27.

8.3 PK measurement

Evaluation of fluctuations of levodopa plasma concentrations will be performedon Day 28.

On the 28th day, blood samples will be collected from the subjects, and about 4 mL of whole blood will be collected at each time point. On the 28th day, only two doses were taken, that is, in the morning and at noon, and the plasma concentrations of levodopa and carbidopa will be measured.

Fluctuation index=(Cmax-Cmin)/Cave.

All blood collection involving PK must record the blood collection, medication and meal time of the subject. Record the food composition (protein, carbohydrate, fat), weight, and calories of the noon lunch. For the collection, processing and transportation requirements related to PK blood sampling, please refer to the "Bioanalytical Laboratory Manual" for details.

8.4 Safety Assessment

Vital signs, physical examination, neurological examination, 12-lead ECG, laboratory examination, comparion of the mean change of the baseline (Day -1) to the 28th day of the Beck Depression Inventory-II (BDI-II) and collection All AEs are monitored for safety.

In addition to completing all planned safety assessments in accordance with the screening rate specified in the scheme in Table 4, investigators can arrange unplanned visits according to the clinical conditions of the subjects.

8.4.1 Vital Signs

Vital sign examinations include body temperature, blood pressure (systolic blood pressure, diastolic blood pressure), heart rate, and respiratory rate. During the baseline and treatment period, vital signs should be checked before the first medication on the day of the visit. The detailed schedules are shown in Table 4 Schedule of Procedures. The blood pressure in the sitting position and pulse rate are measured after the

subjects are in resting state. The pulse rate detection time is 1 minute. To measure the blood pressure of the subjects in the supine position, the blood pressure should be measured with the same arm, and the same examiner should try to measure the blood pressure during the study. The detection steps for orthostatic hypotension are as follows:

i. Measure the blood pressure of the subject in the supine position

ii. Record blood pressure

iii. Measure blood pressure again in a standing position after 3 minutes

iv. Record blood pressure

v. A decrease in systolic blood pressure ≥20 mmHg or a decrease in diastolic blood pressure ≥10 mmHg is orthostatic hypotension (the subject rests on the back for 1 hour and repeats the above steps i to iv)

Note: If necessary, please consult the principal investigator or designated personnel to give corresponding treatment.

8.4.2 Physical Examination

Physical examination mainly includes: general conditions, skin, mucous membranes, lymph nodes, head and neck (including thyroid), chest (heart, respiratory system), abdomen (liver, gallbladder, spleen, kidney), musculoskeletal system, etc., detailed examination plan See Table 4 Test Flow Table.

8.4.3 12--Lead Electrocardiogram (ECG)

Subjects need to get fully rest to a resting statue and then can be tested. The detailed examination plan is shown in Table 4 Test Flow Table.

During the study period, inspections should be conducted in accordance with the procedures specified in the protocol, and the operational requirements are consistent with the screening period. In addition, as far as possible, the same researcher should review all the 12-lead ECG examination results of a subject during the study to maintain the consistency of the before and after evaluation criteria.

If an abnormal ECG examination occurs during the visit, investigators and/or researchers can decide whether to retest based on the clinical condition of the subject and then evaluate the examination result. If clinical mainifestations prompt, an unplanned visit for 12-lead ECG examination can also be arranged.

8.4.4 Laboratory Assessments

Perform laboratory assessments (blood routine, blood biochemistry, HbA1c, urine routine, blood

coagulation function, blood pregnancy test and virological test) according to the schedule in Table 4 Test Flow Table.

A copy of the laboratory qualification certificate of the Clinics (if applicable) must be provided to the sponsor, and the normal range and unit of each parameter shall be collected in eCRF. The normal scope of laboratory inspection items and any change of units during the study must be updated in eCRF, and the date of reconfirmation of qualification certificate shall be indicated. Investigators need to review all laboratory test reports of subjects and evaluate the clinical significance of abnormal results. The laboratory inspection items are shown in Table 5.

Table 5 Laboratory Parameters

Tested Items	Clinical Laboratory Examination Parameters
Blood Routine Test	Red blood cell count, white blood cell count, hemoglobin, platelet and white blood cell differential count (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Blood biochemistry	Electrolytes: potassium, sodium, chlorine Liver function test: ALT, AST, alkaline phosphatase, glutamyl transpeptidase, TBIL, direct bilirubin Renal function test: urea/urea nitrogen, serum creatinine Others: glucose, calcium, magnesium, phosphorus, total protein, albumin, cholesterol, triglycerides, lactate dehydrogenase, amylase, uric acid Calculate CrCl according to the simplified MDRD formula: eGFR=186×SCr-1.154×(age) 0.203×0.742(female) eGFR: estimated glomerular filtration rate (mL/min/1.73m2); Scr: serum creatinine (mg/dL); unit conversion relationship of serum creatinine: 1mg/dL=88.4 μmol/L
Urine Routine Test	pH, specific gravity, protein, glucose, ketone bodies, occult blood, white blood cells, red blood cells, epithelial cells, bacteria, casts, crystals
Coagulation	Prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen and INR
Glycated hemoglobin	HbA1c
Pregnancy test	Urine β-hCG. If the investigator has doubts about urine pregnancy test result, a blood pregnancy test can be performed to confirm.
Virus Detection	Human immunodeficiency virus antibody (HIV)-1/2Ab, hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV-Ab). If HBsAg is positive or HCVAb is positive, test for HBV DNA or HCV RNA.

Abbreviations：ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase; β-hcg=β-Human chorionic gonadotropin; CrCl= Creatinine clearance; eGFR= Estimated glomerular filtration rate; HbA1c= Glycated hemoglobin; INR=International normalized ratio; pH= potential of hydrogen; SCr= Serum creatinine; TBIL= Total bilirubin.

9 Adverse Events

9.1 Definition of Adverse Events

AE：Referring to all adverse events in clinical study, which can be manifested as symptoms and signs, diseases, or abnormal laboratory tests, but they may not have a causal relationship with the study drug. Therefore, AE can be any unfavorable, unexpected indicator, symptom, or disease (new occurrence or exacerbation of the original disease).

The AE that occurs after the subject uses the study drug is defined as TEAE.

AE does not include：

- Non-aggravated chronic diseases before participating in the clinical study.
- Elective medical examination or surgery before entering the clinical study.
- Overdose of the study drug or concomitant medications, that causes no symptoms or signs.

Abnormal laboratory examinations that need to be regarded as AE：

Laboratory abnormal values (blood biochemistry, blood routine, and urine routine) or other abnormal values (such as ECG) must be recorded as AE when they meet at least one of the following criteria.

Clinical outliers that meet any of the following criteria should be reported as AEs:

- Accompanying symptoms and signs.
- The results of the examination require other diagnostic examinations or treatment measures (such as surgical intervention).
- The results of the examinations lead to changes in the dosing schedule of the study drug (such as: dose change, dosing delay, discontinuation) or termination of the study;
- The investigator believes that the test result has clinical significance.

If the investigators believe that the abnormal (or obviously abnormal) laboratory test value has no clinical significance, the reason must be clearly recorded in the original file (such as normal fluctuations of the disease).

The following are not AE: only for repeating an abnormal examination but does not meet any of the above conditions; or abnormal laboratory examination due to past medical history or current medical history. Any abnormal results that are judged to be wrong or abnormal values that are normal after re-examination or abnormal values with no clinical significance are not reported as AEs.

Diagnostic or therapeutic invasive (such as surgery), non-invasive operation "operation itself" should not be reported as AEs, but when the disease condition that caused this operation meets the definition of AE (or SAE), it should be reported as AE (or SAE). If acute appendicitis occurred during the AE reporting period, it should be reported as an AE, and the appendectomy should be recorded as the AE treatment.

SAE： Referring to AE that meets any of the following criteria：

- cause death.
- Life-threatening (refers to the immediate risk of death, not the possibility of death when it is assumed to be severe in the future).
- Lead to hospitalization or prolong hospitalization time.

- Cause permanent or severe disability/loss of function.
- Cause congenital malformations or birth defects.
- Important medical events.

An important medical event refers to a medical event that does not appear immediately but requires medical measures to prevent the occurrence of the above result. Such medical events include cancer, bronchial allergic spasm that requires intensive treatment in the emergency room or at home, and non-hospitalized cachexia or convulsions, drug dependence or addiction, etc.

Hospitalization not required to be recorded as SAE：

- Hospitalization or prolonged hospitalization that is not related to AE deterioration is not an SAE in itself and does not need to be recorded as an SAE, i.e.:
- The hospitalization of their own disease conditions is not caused by new AE or aggravation of existing disease conditions (e.g. to check the laboratory test abnormalities that continue to exist before the start of the study);
- Hospitalization not related to AE, (such as cosmetic surgery);
- Surgery or hospitalization planned or arranged before entering the study;
- Temporary stay in hospital for observation (less than 24h duration);
- Admission for management reasons (such as annual routine physical examination).

ADR： Referring to any harmful or undesired reaction to the human body that may be related to the study drug in a clinical trial. There is at least one reasonable possibility that the causal relationship between the study drug and AEs, that is, the correlation cannot be ruled out.

Suspicious and Unexpected Serious Adverse Reactions (SUSAR)： Referring to suspicious and unexpected serious adverse reactions whose nature and severity of clinical manifestations exceed the existing data and information such as the investigator's manual of the trial drug, the instructions of the marketed drug, or the summary of product characteristics.

Adverse Events Report

AE Collection Time Range： AEs should be collected from the time the subjects receive the study drug for the first time until the end of the follow-up period. All AEs should be recorded in the original document and the adverse event table in eCRF. Diseases and abnormal baseline values that occurred before signing the ICF to the administration of the study drug are generally recorded as medical history.

AE Names： AE Name of AE should be medical terms. The diagnostic term is preferred; if there is no

clear diagnosis, choose symptoms/signs; if there is no diagnosis, symptoms, or signs, choose laboratory abnormalities. If the abnormal value reflects the aggravation of the underlying disease, the name of the AE is recorded as "a disease aggravated".

Investigators should make judgments on the severity of the AE and its relevance to the test drug, and should pay attention to AE development, and take appropriate medical measures, when necessary, until the AE is cured or stabilized. Investigators ensure that the later follow-up includes a supplementary investigation of the nature or causality of the AE (or SAE).

After learning about AE (or SAE), investigators need to collect all event-related data (such as medical records, laboratory tests, and diagnostic reports) of the subjects, and record the relevant information in the original file and eCRF adverse event table. It should be reported in accordance with Section 9.3 if the case is SAE.

Severity Assessment：

If an AE that is not described in the Common Adverse Event Evaluation Criteria (CTCAE) 5.0, investigators can refer to the general principles in Table 6 to do severity classification.

Table 6 Severity Classification of Adverse Events

Grade	Description
1 (Mild)	Asymptomatic or mild; only clinically or diagnostically seen; no treatment needed.
2 (Moderate)	Requires minor, topical or non-invasive treatment; age-appropriate instrumental restriction of activities of daily living*.
3 (Severe)	Severe or medically significant but not immediately life-threatening; cause hospitalization or prolong hospitalization; cause disability; restrict self-rational activities of daily living**。
4 (Life-threatening)	Urgent treatment is needed.
5 (Death)	Death related to adverse events.

*: Instrumental activities of daily living refer to cooking, buying clothes, using the phone, managing finances, etc.
**: Self-rational activities of daily living refer to bathing, dressing and undressing, eating, washing, taking medicine, etc., without being bedridden.

Pay attention to distinguish the severity of AE. "Severe" is used to describe the severity, not necessarily SAE. For example, headache may be severe in severity, but it cannot be included in the SAE just because of "severe" headache, unless it meets SAE criteria.

Evaluation of Correlation between AE and Study Drug：

The investigator needs to determine the correlation between each AE and the study drug. According to the five criteria of AE analysis, the causal relationship between AE and study drugs can be divided into "definitely related", "probably related", "may related", "may not be related", and "definitely not related". Among them, the judgment of “definitely related, very likely related, and possibly related” related to the study drug is ADR.

The investigator (or a qualified clinician designated by the investigator) evaluates the correlation between AE and the study drug through medical judgment. Classification provided in Table 7 can be referred to evaluate the relationship between AEs and study drugs or research procedures. Other factors that need to be considered include underlying diseases, concomitant treatments, and other incentives. At the same time, Investigator Brochure or product information can be referred to complete the judgment.

Table 7 Reference for Determining the Correlation between Adverse Events and Investigational Products

Index	Definitely Related	Probably Related	May Related	May Not Be Related	Definitely Not related
Reasonable sequence of events	Yes	Yes	Yes	Yes	No
Type of reaction of known test drug	Yes	Yes	Yes	No	No
It can be improved by stopping the study drug	Yes	Yes	Yes or No	Yes or No	No
Reappearance of study drug can be repeated	Yes	?	?	?	No
The AE can be explained separately	No	No	Yes	Yes	Yes

9.2 Follow-up of Adverse Events

All AEs occurr from the beginning of the subject's first acceptance of the study drug to the end of the follow-up period shall be followed up to recovery, return to the baseline level, the investigator judges that there will be no change in the continued follow-up, the subject refuses to follow up, the subject loses the follow-up, the subject dies or can make other reasonable explanations for the event.

If the AE progresses to "SAE" during AE follow-up, the investigator shall immediately report according to SAE.

9.3 Serious Adverse Event

SAE collection will start from the subject's first receipt of the test drug until the end of the follow-up period. Once an SAE occurs during this period, the investigator should immediately make a comprehensive evaluation of the incident, take relevant treatment measures, complete the SAE report form, describe in detail about the time and severity of the AE and the relationship with the study drug and the actions taken, and also sign and date on the report. The investigator shall report to the sponsor's clinical pharmacovigilance department in written form by email within 24 hours (no later than 72 hours in case of special circumstances) after being informed of any SAE, email:_____ and pharmacovigilance CRO:_____ and copy to relevant personnel. A detailed and written follow-up report should be provided in a timely manner.

The original serious adverse event report form and the record file reported to the sponsor must be kept in the study center.

For reports involving deaths, investigators should provide the sponsor and the Ethics Committee with other required materials, such as autopsy reports and final medical reports.

After the follow-up period, if the investigator knows the SAE and judges that it is "definitely related / likely related / possible related" to the test drug, it can be reported to the sponsor's clinical pharmacovigilance department in the form of spontaneous report.

9.4 Overdose

It refers to the intentional or accidental taking of more than the test drug dose or frequency specified in the study protocol, regardless of whether it is accompanied by AE or sequelae.

If the drug overdose is accompanied by an AE (or SAE), it needs to be reported in the original document and the adverse event table in eCRF; if it meets SAE criteria, it also needs to be reported in accordance with the requirements of Section 9.4.

9.5 Pregancy

If a female subject or a male subject’s partner has pregnancy during the study period (using the test drug at least once), the investigator must fill in the Pregnancy Report Form after being notified, report to the clinical pharmacovigilance department within 24 hours (no later than 72 hours in case of special circumstances), and report to the ethics committee according to the requirements of the ethics committee of clinical research institutions. If the female subjects become pregnant, they have to immediately withdraw from the study due to the violation of the protocol; if the male subjects’ partners become pregnant, they are not required to withdraw from the study, but their partners need to be treated in accordance with the female subjects’ ways of pregnancy to record, report, and follow-up. When collecting the pregnancy information of male subject partners, the informed consent of their partners is required.

If a female subject or a male subject’s partner has pregnancy during the study period (using the test drug at least once), the investigator must fill in the Pregnancy Report Form after being notified, report to the clinical pharmacovigilance department within 24 hours (no later than 72 hours in case of special circumstances), and report to the ethics committee according to the requirements of the ethics committee of clinical research institutions. If the female subjects become pregnant, they have to immediately withdraw from the study due to the violation of the protocol; if the male subjects’ partners become pregnant, they are not required to withdraw from the study, but their partners need to be treated in accordance with the female subjects’ ways of pregnancy to record, report, and follow-up. When collecting

the pregnancy information of male subject partners, the informed consent of their partners is required.

9.6 Sponsor SUSAR Report

The sponsor shall report to the National Center for Drug Evaluation (CDE), the State Drug Administration and the National Health Commission in accordance with the relevant guidelines of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use(ICH) and the requirements of China GCP:

- Fatal or life-threatening SUSAR

The sponsor should report to the above-mentioned agency as soon as possible within 7 days after first being notified and submit a follow-up report within the next 8 days.。

- All other SUSAR

The sponsor shall report to the above-mentioned agency within 15 days after being notified.

Minimum Requirements of the Report

The final description and evaluation of the report may not be available within the time limit required. However, for management purposes, the initial report must do the following within the specified time limit: ①identifiable subjects; ②suspicion drugs; ③determined reporting source; ④the name, severity and correlation of the AE. The follow-up information should be actively obtained and reported in time.

Sponsors report to investigators, clinical trial institutions, and ethics committees in accordance with the requirements of local China GCP：

- SUSAR：Quickly report to all investigators participating in clinical trials, clinical trial institutions, and ethics committees.

Note: After receiving the relevant safety information of the clinical trial provided by the sponsor, the investigator should sign and read it in time, and consider the treatment of the subject and whether to make corresponding adjustments. If necessary, the investigator should communicate with the subject as soon as possible, and report SUSAR provided by the sponsor to the ethics committee.

9.7 Security Update Report during R&D

The sponsor shall prepare a safety update report (DSUR) during the study every year in accordance with regulatory requirements and submit it to CDE within the prescribed time limit. The sponsor shall simultaneously report DSUR to all investigators participating in clinical trials, clinical trial institutions, and ethics committees.

9.8 Measures to Prevention and Control of Risks

The combination of carbidopa and levodopa can reduce the peripheral reactions (nausea, vomiting) caused by levodopa decarboxylation; however, carbidopa does not reduce the adverse effects of levodopa on the central nervous system (CNS). Because carbidopa can increase the concentration of levodopa in the brain, thereby converting more dopamine, some central nervous system adverse effects such as dyskinesia (involuntary movement) will occur at lower doses.

All subjects should be carefully observed to prevent depression with suicidal tendencies.

Subjects with severe cardiovascular, pulmonary diseases, bronchial asthma, kidney, liver, and endocrine diseases should use it with caution.

Like levodopa, subjects with a history of myocardial infarction and atrial, nodular or ventricular arrhythmia outside the sinus node should use this product with caution. For such subjects, during the initial dose adjustment period, attention should be paid to monitoring the heart function which should be carried out in a place with cardiac intensive care equipment.

Like levodopa, treatment with this product increases the risk of upper gastrointestinal bleeding in subjects with a history of peptic ulcer.

- **Orthostatic Hypotension**

Orthostatic hypotension is one of the common non-motor symptoms of Parkinson's disease. Generally speaking, the longer the course of the disease, the older the age or the greater the dosage of Parkinson's disease, the higher the incidence of orthostatic hypotension. The more past diseases and the more complicated the medication history, the greater the possibility of inducing orthostatic hypotension. Some common chronic diseases, such as diabetes, essential hypertension, congestive heart failure, etc. have a certain relationship with the occurrence of orthostatic hypotension.

- **Angle-closure Glaucoma**

Angle-closure glaucoma is a common disease in middle-aged and elderly people. The intraocular pressure increases due to the closure of the angle of the chamber. Therefore, drugs that may cause the angle of the chamber to be closed should be banned or used with caution, including levodopa, which may also induce acute attack of chronic angle-closure glaucoma due to increased intraocular pressure.

- **Falling Asleep and Drowsiness in Daily Activities**

There have been reports that when subjects use this product alone or in combination with other dopaminergic drugs, sudden sleep attacks will occur during daily activities without warning signs (including operating motor vehicles). There are reports of road traffic accidents caused by falling asleep

suddenly. Although many subjects report drowsiness during dopaminergic drug treatment, there are still subjects who have sudden sleep attacks without sensing the warning signs, such as excessive drowsiness, leading to reports of road traffic accidents, and they believe that the incident occurred immediately after they were awakened. Sudden sleep was reported one year after starting treatment.

Sudden sleep attacks during daily activities usually occur in subjects who have experienced drowsiness, although some subjects may not have experienced sudden sleep attacks. For this reason, and especially because some events do occur after the start of treatment, the prescribing physician should re-assess the patient for drowsiness or falling asleep. The prescribing doctor should be aware that the patient may not admit to being drowsy or falling asleep until he/she is directly asked if he/she is drowsy or falling asleep during a specific activity. Subjects should be informed of this situation, and advised to drive or operate machinery carefully during treatment. During treatment, subjects who have experienced drowsiness and/or sudden sleep episodes must avoid such activities.

Before the start of treatment, inform the patient of the possibility of drowsiness, and ask about specific factors that may increase the risk of drowsiness, such as the combined use of sedative drugs and the presence of sleep disorders. If the patient reports significant drowsiness or falling asleep during activities that require active participation (such as talking, eating, etc.) during the day, consider stopping this product treatment. If continue the treatment with this product, it is recommended that the patient not drive and avoid other potentially dangerous activities that may cause injury to the patient due to drowsiness. There is not enough information to prove that reducing the dose can eliminate sudden sleep attacks from daily activities.

- **High Fever and Coma**

According to reports, sporadic cases of syndromes similar to antipsychotic drugs for neuroleptic malignant syndrome (NMS) areare associated with the reduction or withdrawal of certain antiparkinsonian drugs, such as levodopa, levodopa carbidopa, or levodopa carbidopa controlled-released tablets. NMS is a rare but life-threatening syndrome characterized by fever or high fever, muscle stiffness, involuntary movements, changes in consciousness/mental status, delirium, autonomic dysfunction, tachycardia, shortness of breath, sweating, high blood pressure or low blood pressure, and abnormal laboratory results (such as increased creatine phosphokinase, leukocytosis, myoglobinuria, and increased serum myoglobin). Therefore, subjects should be closely monitored when the dosage is suddenly reduced or stopped, especially those who are receiving neurorelaxant treatment.

10 Data Management

The clinical trial data management process of this study will follow the SOP of the data management department according to the requirements of GCP and corresponding regulations to ensure the authenticity, accuracy, integrity, reliability and traceability of clinical trial data. The details of clinical trial data management will be specified in the data management plan.

10.1 Data Collection and Entry

The data entry of this study is directly entered into the eCRF, and the investigator or clinical research coordinator fills in the subject information in eCRF accurately and timely, completely and standardized it according to the subject's original data information.

The main responsibility of the investigator is to ensure that the data reported in eCRF or other forms is accurate, complete, and timely, and make sure that the data on the eCRF is derived from the original data of the subject, and explain any differences.

Clinical research associates (CRA) should supervise whether clinical trials follow the protocol, conduct original data verification, and confirm that all eCRF fillings are consistent with original data. In case of errors and differences, CRA shall notify the investigators and record the corresponding queries according to the errors or differences found, so as to ensure that all data records and reports are correct and complete.

10.2 Database Management and Query Management

Clinical trial data management personnel conduct data verification according to the data verification plan, which mainly includes manual verification and logical verification of computer systems. Questions generated by the verification must be answered by the investigators or the authorized personnel. If the investigator's answer solves the question, the data manager will close the question, and if the question is not resolved, the question will be issued again. This process continues until the data cleaning is completed.

10.3 Database Lock

According to the database lock process, once all the steps before the lock are completed, the database lock shall be approved in writing, the data editing authority of the database shall be revoked, and the database shall be locked. If the problems found after the database is locked need to be modified, the data should be modified strictly in accordance with the process of unlocking and relocking.

11 Statistical Analysis

Detailed statistical analysis strategy and steps will be described in a separate statistical analysis plan (SAP). When the trial starts, if there is a change in the statistical analysis method, it will be revised in SAP and the final version will be finalized before the database is locked. When the database is locked, the protocol

and additional exploratory analysis not involved in SAP need to be described in detail in the statistical analysis report.

11.1 General Considerations in Statistics

The study will use statistical analysis software (SAS) version 9.4 or above for statistical programming and analysis. Unless otherwise specified, all test tables are summarized based on treatment groups.

All data will be statistically described. The statistics used include the number of cases (missing cases), mean, standard deviation (SD), median, minimum and maximum for continuous variables; frequency, percentage etc. for cateforical variables. Descriptive statistics for measurement data mainly include the following: the number of measurement data cases that meet or approximate the normal distribution (including the number of missing cases), mean, SD, minimum, maximum, and 95% CI of data; mean; median, upper quartile, lower quartile, minimum, maximum and interquartile of measurement data in non-normal distribution. Unless otherwise specified, the decimal places of the minimum and maximum values are consistent with the original data recorded in the database. The number of decimal places for mean and median is one more decimal place than the original data recorded in the database, and the SD retains two more decimal places than the original data recorded in the database. The number of decimal places for all statistical data cannot exceed four digits at most. Calculate frequency and relative numbers for qualitative and quantitative data. For counting indicators, descriptive statistics include the number of cases and percentages. Percentage is reserved to one decimal place, and the percentage with a frequency of 0 is not reported.

11.2 Handling of Missing Values

Efficacy Index Data: The missing data index involved in the curative effect analysis shall be filled with Multiple Imputation for Missing Data method.

Safety Data: Unless otherwise specified, the missing data will not be filled in, and the missing data will be filled and summarized only when the summary analysis needs to divide the time. The dates in the list are listed in accordance with the conditions filled in on CRF.

Outliers will be judged from two aspects of medicine and statistics, especially based on medical industry knowledge.

11.3 Analysis Sets

Full Analysis Set (FAS): All subjects participating in randomization will be included in the full analysis set.

Per Protocol Set (PPS): Including all subjects who have completed the pre-set sufficient test drug exposure

in the full analysis set, obtained the primary endpoints in the test, and subjects who do not have a major violation of the trial.

Safety Set (SS): Including all subjects who have received at least one treatment and have a safety assessment.

Pharmacokinetic Analysis Set (PKS): Any evaluable plasma concentration data from the safe population will be included in the pharmacokinetic analysis set.

11.4 Protocol Deviations

PD refers to fail to follow the protocol to conduct the test. PD is divided into mild PD and major PD according to its severity. Mild PD means that PD does not affect the safety of subjects and the integrity of the research data, but should be handled appropriately. Significant PD refers to the presence of obvious PD, which may affect the subject's rights, safety, willingness to continue participating in the trial, and/or the completeness, accuracy, and reliability of research data. If there is a major PD, the subject may be excluded from the PPS. Details will be discussed and decided at the Data Review Meeting (DRM) before the database is locked, including but not limited to:

(1) Does not meet the selection/exclusion criteria.

(2) Non-compliance with research treatment, such as using wrong research medication/treatment.

(3) Use any prohibited combined drugs and treatments.

11.5 Sample Size Estimation

The number of subjects in this trial is mainly determined based on past experience and related clinical trials of similar products.

11.6 Subjects Distribution

Enrolled population: All subjects participating in the study will be included in the Enrolled Population.

Safety Population: All subjects in the enrolled population who have received more than one study drug will be included in the Safety Population.

Full Analysis set (FAS)：All subjects participating in randomization will be included in the Full Analysis set.

Per Protocol Set (PPS)：Including all subjects who have completed the pre-set sufficient test drug exposure in the full analysis set, obtained the primary endpoints in the test, and subjects who do not have a major violation of the trial.

Safety Set (SS)：Including all subjects who have received at least one treatment and have a safety assessment.

Pharmacokinetic Analysis Set (PKS)：Any evaluable plasma concentration data from the safe population will be included in the Pharmacokinetic Analysis Set.

Summarize the distribution of subjects for all subjects. The enrollment and randomization of subjects, the screening failure, the reason for screening failure, the dropout, and the completion of the test will be described in accordance with the group. For subjects who drop out, classify and summarize them according to the main reasons for dropping out.

Provide the distribution list of subjects arranged by group and subject serial number.

11.7 Demographics/Baseline Analysis

Demographics and baseline characteristics (age, gender, race, weight, height, and BMI) will use descriptive statistics (n, mean, standard deviation, minimum, median, and maximum, as well as proportion of subjects for categorical variables) to summarize. There will be no formal statistical comparison of the groups.

For demographic data and baseline characteristics such as medical history/allergic history/surgery history, etc., descriptive statistical analysis will be performed on each treatment group in accordance with general principles. The medical history/allergic history/surgical history will also be summarized according to the treatment group according to the system organ classification (SOC) and preferred term (PT) classification in the Medical Dictionary of Regulatory Activities (MedDRA) version 23.0 or later.

Provide a list of demographic/baseline data results arranged by group and subject number.

11.8 Analysis of Pharmacokinetic Parameters and Drug Fluctuation Index

Pharmacokinetic Parameters：Cmax, Cmin, AUC and other commonly used PK parameters and relative bioavailability between doses. Plasma levodopa is summarized according to the blood sampling time point of the protocol; describe and compare mean of the blood concentration of levodopa and carbidopa in each dose group, and calculate the fluctuation index ([Cmax-Cmin]/Cavg, Cavg= AUC0-t/t).

11.9 Efficacy and Pharmacodynamic Analysis

In general, continuous variables will be statistically described by the number of cases, mean, standard deviation, median, 25% quantile, 75% quantile, minimum value and maximum value; classification variables will be described by frequency and percentage. Unless otherwise specified, all statistical tests will use a two-sided test with α=0.05 to calculate a two-sided 95% confidence interval.

Primary Endpoint:

Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 27th day.

The statistical analysis of the primary endpoint will be based on FAS, and the last observation carried forward (LOCF) will be used to fill in the missing data for subjects who lack the primary endpoint of Day 27. Analysis of covariance (ANCOVA) method with baseline value as covariate and disease severity and treatment group as independent variables will be used to analyze the change from baseline on Day 27 of treatment. The difference between the least squares mean of each dose group and the placebo group's 28-day treatment relative to the baseline change and its 95% confidence interval and P value are calculated by the ANCOVA model. This statistical method will be repeated on the basis of PPS as a sensitivity analysis.

Mixed model repeated measures (MMRM) will be used as a sensitivity analysis. In the MMRM model, the change value of Day 14 and Day 27 from the baseline is used as the dependent variable, the disease severity, treatment group, visit, and interaction terms between treatment and visit are fixed effects, to estimate least squares mean and 95% confidence interval after the change of variables in each group.

Secondary Endpoints:

(1) Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 14th day.
(2) Changes in MDS-UPDRS-II scores from the baseline to the 14th and 27th days.
(3) Changes in the MDS-UPDRS-III scores from the baseline to the 14th and 27th days.
(4) To evaluate the pharmacokinetics and fluctuation index of levodopa on the 28th day.
(5) To evaluate the safety of WD-1603 in subjects with Parkinson's disease.

The statistical analysis of the secondary endpoints will be based on FAS, and the statistical model is similar to the main indicators.

11.10 Compliance

Compliance analysis will be conducted in FAS.

Summarize the percentages and reasons of dose reduction, interruption, or termination of the different treatment groups, so as to evaluate the compliance of the trial drug.

Compliance calculation:

Drug exposure compliance (%) = (the actual number of drugs taken by the subjects during the study treatment period/the number of drugs planned to be taken) x100%

Compliance with the number of medications (%) = (the actual number of medications taken by the subject during the study treatment period/the number of planned medications) x100%

Compliance will be classified and summarized by group according to <80%, 80-120%, >120%. Provide a checklist for all drug exposures.

11.11 Concomitant Medication

The concomitant medication data will be summarized in the FAS.

The latest version of the World Health Organization Drug Dictionary (WHODD, version SEP, 2019) will be used for coding classification, and an 11-digit code will be assigned to the drug. Use appropriate Anatomy-Therapeutics-Chemical $AUC_{0\text{-}inf}$ (ATC) codes to further code the drugs to show the treatment classification.

The start and end dates recorded by the eCRF relative to the administration date of the first and last dose of the trial drug will be used to define the pre-treatment, concomitant and post-treatment medications. Pre-treatment medication is defined as any medication used before (excluding the date) the start date of the treatment of the trial drug. Concomitant medication will be defined as any drug that continues to be used at the start date of the treatment of the trial drug, or on or after the first dose of the trial drug until the day of the last dose of the trial drug. Post-treatment medication will be defined as any medication administered on or after the last dose of the test drug. This study will summarize any previous or concomitant medications and important non-drug treatments of subjects before or after the start of the trial drug treatment according to each treatment group, and summarize them in accordance with ATC terminology (Anatomy-Therapy-Chemical Classification System).

11.12 Primary Endpoint

In FAS and PPS, superiority trials will be applied on treatment groups and placebo group of the primary endpoints. If the results in the two data sets are inconsistent, they will be discussed in the statistical analysis report.

The primary endpoint is the changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 27th day.

11.13 Secondary Endpoints：

1. To Changes in the sum of MDS-UPDRS-II and MDS-UPDRS-III from the baseline to the 14th day.
2. Changes in MDS-UPDRS-II scores from the baseline to the 14th and 27th days.
3. Changes in the MDS-UPDRS-III scores from the baseline to the 14th and 27th days.
4. To evaluate the pharmacokinetics and fluctuation index of levodopa on the 28th day.

5. To evaluate the safety of WD-1603 in subjects with Parkinson's disease.

11.14 Sensitivity analysis

The missing data of the efficacy index involved in the efficacy analysis will be filled, and sensitivity analysis needs to be added for comparison before and after the missing data is filled.

11.15 Safety Analysis

Safety assessment variables include AE, ECG, laboratory test values, changes in the Beck Depression Inventory-II (BDI-II) scale from baseline and vital signs on the 28th day, etc. In SS, the safety data will be summarized by each treatment group, and all subjects will be listed.

11.15.1 Adverse Event Analysis

All AEs and TEAEs are summarized by treatment groups.

Use MedDRA version 23.0 or higher to encode all AEs to provide the SOC and PT of each event.

The number and percentage of subjects in the following categories are summarized by treatment group:

- Any AE
- Any TEAE
- Any related TEAE
- Any severe TEAE
- Severe TEAE related to any study medication
- Any SAE
- Any SAE related to study medication
- Any death
- Any TEAE that leads to early termination of the study

The number and percentage of subjects with TEAE according to SOC and PT will be summarized by each treatment group.

TEAE will be summarized according to severity and relevance to the test drug. In addition, deaths, SAEs, TEAEs that lead to the termination of study medication and early termination of the study are summarized by each treatment group.

11.15.2 Laboratory Test Value

The clinical laboratory data that should be summarized include: blood routine, blood biochemistry, urine routine.

For each laboratory parameter, changing values from the baseline to the end of the study of the record at

each time point (screening, baseline, each visit and the end of the study), and each vist will be summarized. The parameters will be summarized by each treatment group.

Assign LNH (L: lower than normal value, N: within normal value range, H: higher than normal value) classification for laboratory test results according to the normal value range set by the local laboratory or central laboratory. The change table (L, N, H) is used to evaluate the changes of various laboratory parameters from baseline to the end of the study for the results of baseline and after medication.

If necessary, a scatter plot or box plot will be drawn based on the selected laboratory parameters, and the baseline and post-dose results will be compared.

11.15.3 Vital Signs

The vital signs parameters that should be summarized include blood pressure (systolic blood pressure, diastolic blood pressure), heart rate, respiration rate, and body temperature.

For each vital sign parameter, the change from vital sign values (systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate and body temperature) recorded at each time point (screening, baseline, each visit and the end of the study), each visit and study from baseline to the end study will be summarized. The parameters will be summarized by treatment group.

Assign the LNH (L, N, H) classification to the vital sign results according to the normal value range. The change table (L, N, H) is used to evaluate the changes in vital signs parameters from baseline to the end of the study for the results of baseline and after medication.

If necessary, a scatter plot or box plot will be drawn based on the selected laboratory parameters to compare the changes between the baseline and the results after medication.

11.16 Other Special Examinations

Not planned.

12 Ethics and Supervision

The implementation of this study will be in accordance with the SOP of the sponsor and cro, which are designed to ensure compliance with the GCP guidelines. When signing the protocol, investigators will agree to follow the instructions and processes described in the protocol, and follow the GCP principles and relevant domestic laws and regulations.

12.1 Ethics Committee

Before the start of the study, the investigator is responsible for providing the ethics committee with the protocol, ICF, and information provided to the subjects (subject recruitment advertisements, etc.) in order to obtain the approval of the ethics committee and obtain approval for the implementation of clinical

research. The approval document of the ethics committee must be sent to the investigator in written form, and the investigator will provide a copy of the approval document to the sponsor. The approval document of the ethics committee must be accompanied by a list of all committee members participating in the discussion of the approval document and their respective professional backgrounds.

In the process of clinical research, any issues related to the safety of clinical research, such as changes in protocol or subject ICF and SAEs in clinical research, must be reported to the ethics committee in a timely manner. The end or early termination of clinical research must also be reported to the ethics committee in time.

12.2 Informed Consent

The rights, safety and physical and mental health of subjects are the most important considerations, taking priority over scientific and social interests. The investigator must clearly and fully inform each subject or to the guardian if the subject is unable to give opinions in the informed consent, of the nature, purpose, related procedures, expected time, and expected time of the research, potential risks and benefits, and any discomfort that may arise. Each subject must be aware that participation in this study is voluntary and can withdraw from the study and revoke the informed consent at any time, without affecting their subsequent treatment and their relationship with the treating doctor. ICF shall comply with the regulatory requirements of the regulatory authority and be given in a standard writing format, and use non-professional language as far as possible. Each ICF must include all the relevant content mentioned above and include a voluntary declaration. ICF needs to be submitted to the relevant ethics committee for approval.

After explaining the basic contents of the study and confirming that the subjects understand the purpose of the study, the investigator shall ask each subject to sign his name and date on the ICF. The subjects should carefully read and consider the statement before signing the name and date, and obtain a signed ICF. Before starting any operating procedures related to clinical research, ICF signed by the subjects must be obtained, including the informed consent of any screening process that is used to determine the subjects' eligibilities to participate in the research. Subjects are not allowed to enter the study without obtaining informed consent.

For subjects who cannot sign the ICF for any reason, their guardian must sign.The ICF signed and dated by the subjects and the investigators must be properly kept by the investigator and recorded in the original records of the relevant study.

12.3 Investigator

Before the subjects are enrolled in the study, investigators should explain the significance of the study to

the selected persons or guardian, obtain their consent and sign ICF. When an AE occurs, research staff need to investigate the cause and deal with it accordingly, and report to the investigator at the same time. If the subject dies, investigators shall be responsible for providing histopathology and related data of the subject. Investigators shall input the data into the medical records and eCRF truthfully, accurately, completely, timely and legally. The investigators cooperate with the clinical research associates appointed by the sponsor for regular inspections. It is necessary to keep complete laboratory examination records, clinical records and original medical records of subjects. In addition, AEs need to be followed up (see section 9.3).

12.4 Data Protection and Human Tissue Sampling

Data protection will be implemented in accordance with the Principles of the Data Protection Act (1998) 95/46/EC, which will also apply to all research data collected and recorded in any format.

Any scan data, images, 12-lead ECG and other examination results collected in this study will be retained in the subject's medical record held by the investigator.

The samples used for safety analysis (urine and blood samples) will not be retained after the analysis is completed.

12.5 Quality Assurance and Inspection Requirements

The sponsor is responsible for establishing and maintaining a quality control and quality assurance system to ensure that the test implementation and data generation, recording and reporting in accordance with the process meet the requirements of the current GCP and local applicable regulations.

The sponsor will ensure that appropriate monitoring is implemented before the start of the study, during the study, and after the end of the study. The sponsor representative will review the research center, the storage location of the trial drug, eCRF, the investigator's source file and all other research documents to ensure that they are accurate and in compliance with the protocol and GCP.

The source file verification will compare the eCRF record content with the corresponding source file to ensure accuracy. Any discrepancies will be reviewed with the researcher and/or related researchers. If corrections are needed, the researcher and/or related researchers will directly correct or issue a questioning form on eCRF. The monitoring procedure requires verification of informed consent, compliance with inclusion/exclusion criteria, SAE documents and SAE correct records. Other monitoring activities may be listed in the research-specific monitoring plan.

In addition to routine monitoring procedures, the sponsor or the designated CRO's quality assurance department may conduct audits of clinical research work to assess whether it complies with clinical trial

norms, guidelines and regulations. Investigators need to allow reviewers of ethics committees, regulatory agencies (such as NMPA, etc.), and authorized representatives of the company to enter the Clinicsto directly access source documents, eCRF, and applicable supporting records. During the audit and/or inspection, investigators should be present as much as possible. If the investigators receive an inspection notice from the regulatory agency, they should immediately contact the sponsor or its authorized personnel. This study will be organized, carried out and reported in accordance with the SOP requirements of the plan, sponsor and CRO. In ICH E6, Quality Assurance (QA) is defined as "all planned and systematic actions aimed at ensuring that test implementation and data generation, recording and reporting comply with GCP and applicable regulatory requirements." Sponsor’s QA activities will be conducted in accordance with the regulations of the research audit plan. Section 5.19.3(b) of ICH E6 points out that the formulation of the audit plan and the trial audit process should be affected by the importance of the trial in the information submitted to the competent authority, the number of subjects, the type of trial, and the degree of complexity. the subject's risk level and guidance for any problems found. QA work can be outsourced to a CRO or an independent organization. The investigators are required to support the audit activities, present as required by the auditors and allow the auditors to directly access the original data/documents.

Qualified regulatory agencies/or authorized third parties may also conduct inspections (during or after the research is completed). If an inspection request is made by a regulatory authority, the investigator must immediately notify the sponsor of receiving the inspection request.

12.6 Training

According to GCP principles, CRA should have qualifications recognized by the sponsor. Before the start of the clinical research, investigators should be trained on the protocol. Investigators need to read and understand the content of the protocol, master GCP principles, eCRF unified recording methods and standards, and implement clinical research in strict accordance with the plan.

12.7 Monitoring

The CRO and qualified personnel of the sponsor will conduct the clinical monitoring of this study, and the corresponding clinical monitoring implementation plan will detail the process. In accordance with relevant regulations, investigators will allow supervision, inspection and inspection of clinical, laboratory and pharmacy facilities to ensure compliance with GCP. eCRF and the original medical records (original data) of the subjects should all be provided to the CRO/sponsor representative for regular review. These reviews will verify the compliance of the protocol and the accuracy of the data in accordance with

domestic regulations and GCP regulations. All records of the Clinicswill be inspected by the local competent authority.。

The medical monitoring work content of this study will be specified in a separate clinical monitoring implementation plan (MMP), including important contents such as the definition of clinical monitoring, the main participants and their division of responsibilities, the medical monitoring process of this study, and the time limit for completion. The preparation of the MMP will start from the finalization of the research protocol, and will be completed at the latest before the first visit of the first subject, and will be further updated if necessary, during the follow-up medical monitoring work to ensure the the medical monitoring work of this study in a scientific and reasonable way. The contact information and information of the research medical monitor and other contact persons will be listed in the clinics file.

13 Study Management Records and Publication

13.1 Protocol Revision

Without the consent of the sponsor, review and approval by the ethics committee, the investigators must strictly abide by the current protocol and must not change the protocol (Section 4.5.2 of ICHE6).

Any changes to the protocol require a protocol revision. The revision of the protocol that clearly affects the safety of the subjects and the quality of the research must be approved by the ethics committee of all research centers. In order to protect the safety and benefit of all research subjects, investigators or sponsor is allowed to take any emergency measures to ensure the safety of the subjects. If the investigators believe that the protocol needs to be modified urgently for safety reasons, they must immediately notify the medical supervisor of the study and obtain his/her approval, and must notify the Clinics ethics committee at the same time. If the protocol revision only involves the content of research management, there is no need the approval of the ethics committee, but it needs to be filed.

Any possible appropriate revisions to the protocol during the course of the study will be communicated and agreed between the sponsor and the investigator. The sponsor shall ensure that the protocol revision is submitted to the management agency in a timely manner.

13.2 Record Maintenance and Retention

In order to protect the subject’s privacy, the subject’s name or the abbreviations must not appear on the documents sent to the sponsor.

In order to provide the sponsor/CRO with accurate, complete and clear data, the following standards must be followed:

- Researchers should prepare original documents for each subject entering the study. The content

should be comprehensive and accurate, so that all inspection results and related data can be recorded, and these documents should be properly stored.

- eCRF entry should be as close as possible to the subject's visit.

When completing or terminating the research, investigators still have the responsibility to retain all research documents, including but not limited to: protocol, eCRF, IB, regulatory agency registration documents, ICF, and communication letters with the ethics committee.

The Clinicsshould plan to retain the research documents after the research is completed until 5 years after the end of the clinical research. The sponsor will specify in the contract the time, cost and treatment after expiration of the documents with investigators and their medical institutions. The study documents shall be approved by the sponsor before final destruction.

At the end of the required retention period or the investigator retires or transfers, the investigator is required to contact the sponsor, allowing the sponsor to choose to keep research records permanently. The retained records shall be kept independently, and the sponsor shall not have direct access to this data.

13.3 Protocol Compliance

Investigators should implement the research strictly in accordance with the protocol. The protocol is written to enable the investigators to complete the research in compliance with the requirements of Chapter 4 of ICH E6.

Any subjects whose study medications deviate from the protocol or who do not meet the study inclusion and exclusion criteria may be excluded from a certain analysis set and may affect the results of the study. If any PD or violation is found, it should be reported to the sponsor or CRO immediately. Any deviation or violation that may affect the safety of the subject or the suitability of participating in this study should be reported to the medical monitor for medical advice.

Subjects who have not signed ICF approved by the ethics committee will not be able to receive treatment with test drugs.

Investigators and research teams must comply with GCP principles and all applicable domestic laws and regulations.

13.4 Study Termination

The sponsor will make every effort to complete this study but reserves the right to terminate the study at any time due to medical or administrative reasons. Reimbursement will be made for subject recruitment, laboratory examinations and other research expenses.

The investigator has the right to terminate the research after sufficient medical judgment. If the study is

terminated, the investigator should notify the ethics committee and the study record must be kept.

14 Study Results Registration and Publication

The results of this research belong to the sponsor. Investigators should keep confidential the information and data related to this research. Without the written consent of the sponsor, relevant research results may not be cited or published.

The sponsor has the right to publish or publish the research-related information or data, or report it to the drug administration department. If the sponsor needs to publish the research information or data, it shall negotiate with the investigators on the author's signature order; if the name of the investigators appear in the sponsor or advertising content, the consent of the researcher shall be obtained.

With the written consent of the sponsor, investigators can publish the clinical research information or results in scientific journals or other publications, or use it for teaching or other scientific research activities. After completing the entire study, if relevant research papers need to be published publicly, the sponsor and the clinical research unit should agree before publishing the papers, and the order of signatures shall also be determined after consultation between the two parties.

15 References

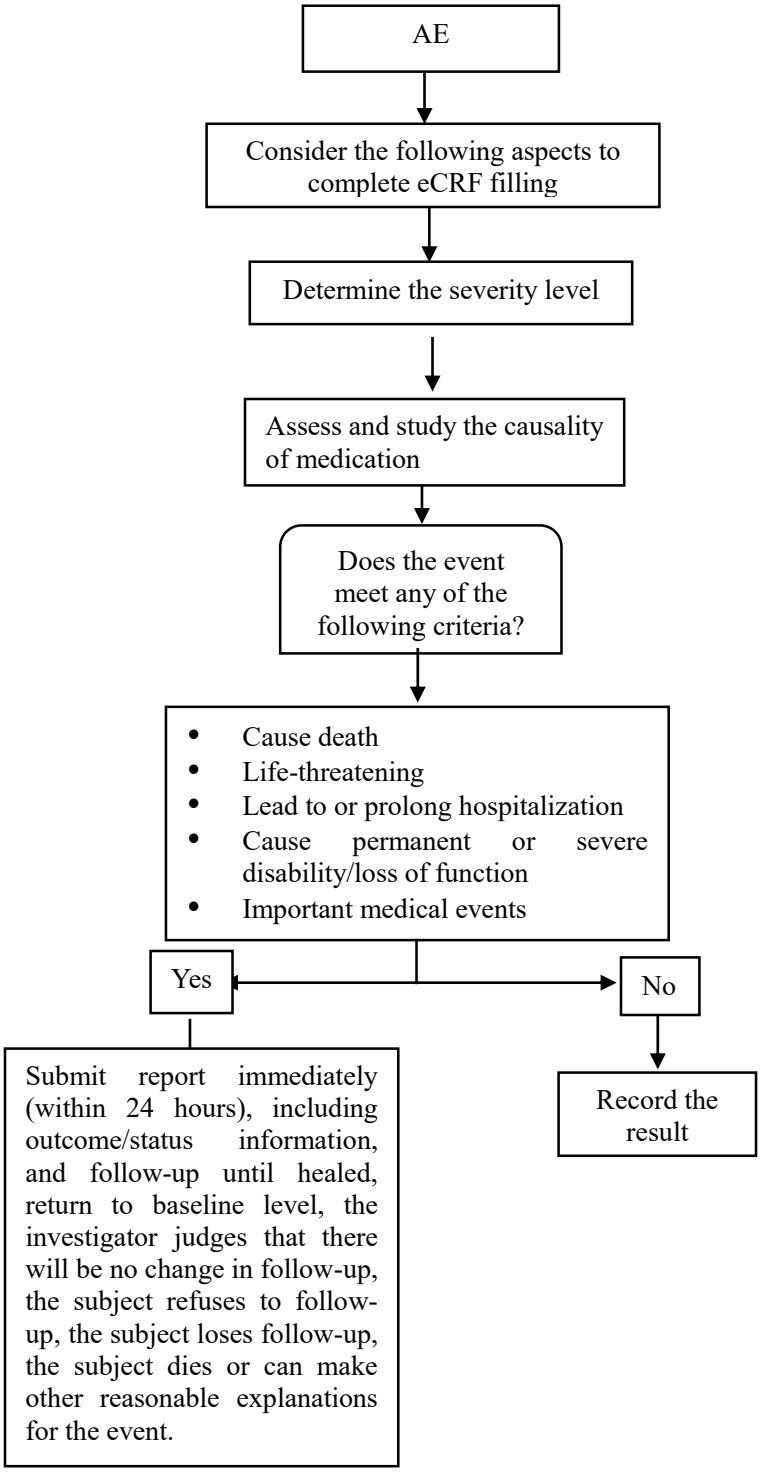
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16 Appendix

16.1 Appendix A Adverse Event Reporting Process



16.2 Appendix B MDS Diagnostic Criteria for Parkinson's Disease （2015）

MDS Diagnostic Criteria for Parkinson's Disease（2015）

The primary core criterion for diagnosis is to clear Parkinson’s syndrome, which is defined as: the presence of motor retardation and at least one of the two main signs of resting tremor or rigidity. The examination of all core signs must be carried out in accordance with the method described in the MDS-Unified Parkinson's Disease Assessment Scale (MDS-UPDRS).

Once Parkinson's syndrome is clearly diagnosed, it shall be diagnosed according to the following criteria:

The clinical diagnosis of Parkinson's disease (PD) requires:

1. Does not meet the absolute exclusion criteria;
2. At least two supporting standards, and;
3. No warning signs (red flags).

Diagnosed as probable PD requires:

1. Does not meet the absolute exclusion criteria;
2. If there are red flags that need to be offset by supporting standards:

If there is 1 warning sign, at least 1 supporting standard must be required;

If there are 2 warning signs, at least 2 supporting standards must be required;

Note: No more than 2 warning signs are allowed under this category.

Explanation of the above terms:

1. Supporting standards

（1）It has a clear and significant effective response to dopaminergic drug treatment. During the initial treatment, the patient's function returns to normal or close to normal. In the absence of a clear record, a significant response to initial treatment can be divided into the following two situations:

a. The symptoms are significantly improved when the dose of the drug is increased, and the symptoms are significantly aggravated when the dose of the drug is decreased; slight changes are not included. The above changes are recorded through objective scores (UPDRS-III score improved by more than 30% after treatment) or subjective records (reliable subjects or caregivers provide clear evidence of significant changes);

b. Clear and significant "on/off" period fluctuations; must include predictable end-of-dose phenomena to

some extent.

（2）Dyskinesia induced by levodopa

（3）Single limb static tremor recorded in clinical physical examination (previous or current examination)

（4）There is loss of sense of smell or cardiac MIBG scintillation imaging shows the presence of cardiac de-sympathetic innervation

2. Absolute exclusion criteria

The presence of any of the following can rule out the diagnosis of PD:

(1) Definite cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar eye movement abnormalities (nystagmus induced by continuous gaze, huge square wave jerks, hyperrhythmic saccades);

(2) Downward vertical supranuclear gaze palsy, or selective downward vertical saccade slows down

(3) In the first 5 years of the onset, diagnosed as likely behavioral variant frontotemporal dementia or primary progressive aphasia (according to the consensus criteria published in 2011);

(4) Manifestations of Parkinson's syndrome that has been confined to the lower limbs after the onset of more than 3 years

(5) Treat with dopamine receptor blockers or dopamine depleting agents, and the dose and time course are consistent with drug-induced Parkinson’s syndrome

(6) Although the condition is at least moderate severity, there is a lack of observable treatment response to high-dose levodopa treatment

(7) Clear cortical sensory loss (such as impairment of skin writing and entity discrimination when the main sensory organs are intact), clear motor apraxia or progressive aphasia

(8) The functional neuroimaging of the presynaptic dopaminergic system is normal

(9) Clearly recorded other diseases that can cause Parkinson's syndrome or suspected to be related to the patient's symptoms, or based on the overall diagnostic evaluation, the professional evaluation doctor feels that it may be other syndromes instead of PD.

3. Warning signs（Red Flags）

(1) Rapidly progressing gait disorder occurs within 5 years of onset and requires regular wheelchair use

(2) Onset for 5 years or more, no progress in motor symptoms or signs at all; unless this stabilization is related to treatment

(3) Early ball dysfunction: severe dysphonia or dysarthria (most of the time speech is difficult to understand) or severe dysphagia (need to eat soft food, or nasogastric tube, gastrostomy eating)

(4) Inspiratory respiratory dysfunction: Inspiratory wheezing or frequent inspiratory sighs during the day or night

(5) Severe autonomic dysfunction appears within 5 years of onset, including:

a. Orthostatic hypotension-within 3 minutes after standing up, the systolic blood pressure drops at least 30 mmHg or the diastolic blood pressure drops at least 15 mmHg, and the patient does not have dehydration, other medications or diseases that may explain autonomic dysfunction;

b. Severe urinary retention or urinary incontinence occurred within 5 years of onset (excluding long-term or small stress urinary incontinence in women), and it is not a simple functional urinary incontinence. For male subjects, urinary retention is not caused by prostate disease and must be related to erectile dysfunction.

(6) Repeated (>1 time/year) falls due to balance impairment within 3 years of onset

(7) Disproportionately anterior neck (dystonia) or hand-foot contracture occurred within 10 years of onset

(8) Even if the course of the disease reaches 5 years, there will be no common non-motor symptoms, including sleep disorders (maintenance sleep disorder insomnia, excessive daytime sleepiness, rapid eye movement sleep behavior disorder), autonomic nerve dysfunction (constipation, daytime urgency, symptomatic orthostatic hypotension), hyposmia, mental disorders (depression, anxiety, or hallucinations)

(9) Pyramidal tract signs that cannot be explained by other reasons are defined as pyramidal tract limb weakness or clear pathological active reflexes (including mild reflex asymmetry and isolated metatarsophalangeal reactions)

(10) Bilateral parkinsonism. The patient or caregiver report bilateral onset without any lateral advantage, and no obvious laterality is observed on the objective physical examination.

Standard application:

1. According to the MDS criteria, can this patient be diagnosed with Parkinson's syndrome?

If the answer is no, neither the probable PD nor the clinically confirmed PD can be diagnosed;

If the answer is yes, proceed to the next evaluation:

2. Are there any absolute exclusion criteria?

If the answer is yes, neither the probable PD nor the clinically confirmed PD can be diagnosed;

If the answer is no, proceed to the next evaluation:

3. To evaluate the presence of warning signs and supporting standards, the methods are as follows:

(1) Record the number of warning signs;

(2) Record the number of supporting standards;

(3) Are there at least 2 supporting standards and no warning signs?

If the answer is yes, the patient meets the criteria for clinical diagnosis of PD;

If the answer is no, proceed to the next evaluation:

(4) Are there more than 2 warning signs?

If the answer is yes, it cannot be diagnosed as probable PD;

If the answer is no, proceed to the next evaluation:

(5) Is the number of warning signs equal to or less than the number of supporting standards?

If the answer is yes, the patient meets the diagnostic criteria for probable PD.