Statistical Analysis Plan, SAP
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History of revision of statistical analysis plan

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V1.0/2022-10-26	Finalize

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Abbreviations

abbreviations	account for
AE	Adverse event
ANCOVA	(math.) Analysis of variance
ATC	Anatomical Therapeutics and Chemical Classification System
BQL	Below the lower limit of quantification
FAS	Full Analysis Set
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
LLOQ	lower limit of quantification
LOCF	Final data carried forward
MedDRA	Medical Dictionary of Regulatory Activities
MMRM	Mixed effects modeling of repeated measurements
OC	Observational data
PKS	Pharmacokinetic Analysis Collection
PT	Preferred terminology
PPS	Compliance with the program set
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SOC	Classification of system organs
SS	Security Analysis Set
TEAE	Adverse events during treatment
TFL	Tables, charts, lists
WHODRUG	World Health Organization Drug Dictionary

1. Preamble

This Statistical Analysis plan (SAP) is prepared in accordance with ICH E9 (Statistical Principles for Clinical Trials), ICH E3 (Structure and Content of Clinical Study Reports), and relevant national regulations[1-4]. It follows the Statistical Analysis Plan (Version 1.0, 2022-10-26) for the Phase II, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of WD-1603 (Carbidopa/Levodopa Controlled-Release Tablets) in Patients with Parkinson's Disease.

This Statistical Analysis Plan (SAP) describes the rules for presenting and analyzing the efficacy data and safety evaluation data specified in the protocol, and provides a detailed description of the data and variables to be summarized and analyzed, as well as the statistical methods to be used. The content of this SAP document includes trial objectives, trial design, evaluation indicators, statistical analysis sets, statistical analysis methods, reference materials, appendices, etc.

This SAP is established and finalized before the clinical trial database of the protocol is locked.

2. Study Objectives

Primary Objective: To assess the proof-of-concept efficacy of WD-1603 in Parkinson's disease (PD) patients.

3. Study Design

3.1. Overall Design

This study was a 4-week, Phase II, randomized, double-blind, parallel-group, fixed-dose, placebo-controlled clinical trial in patients with early-stage Parkinson's disease, designed to evaluate the proof-of-concept efficacy of WD-1603 (carbidopa/levodopa controlled-release tablets). Eligible patients were randomized 1:1:1:1 to one of four treatment groups: WD-1603 25/100 mg, 25/150 mg, 2×25/100 mg, or placebo. The first daily dose was administered pre-meal, while the second and third doses were administered post-meal, with three doses given at 5-hour intervals (on D28, only two doses were administered, and

pharmacokinetic [PK] blood sampling was conducted after the second dose). Eligible patients were aged 30-75 years, diagnosed with early-stage idiopathic Parkinson's disease, and had not received levodopa-containing medications for at least 4 weeks.

Study treatment and follow-up：

Screening period: Following the signing of the ICF, subjects entered the screening phase. During this period, subjects who completed protocol-specified screening procedures and met the inclusion/exclusion criteria proceeded to baseline assessments (D-1). Eligible subjects were then randomized in a 1:1:1:1 ratio to the respective treatment groups. The clinical trial flow is illustrated in Figure 1 below:

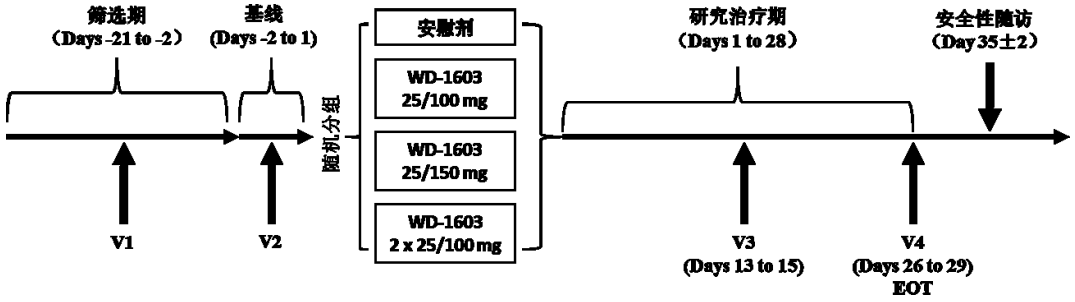


Figure 1 Clinical trial flow chart

Baseline assessment period: Subjects will be admitted to the Clinical Center on D-2 and will undergo UPDRS-II+UPDRS-III assessments on D-1. UPDRS-III assessments will be performed at the following timepoints: Pre-dose and 2.5 ± 0.25 hours post-dose for the first administration, Pre-dose and 2.5 ± 0.25 hours post-dose for the second administration, and Pre-dose and 2.5±0.25 hours post-dose for the third administration. For subjects not receiving prior pharmacotherapy, MDS-UPDRS assessments followed the same schedule as the treatment period (Visit 3). Baseline evaluations included the Beck Depression Inventory (BDI) and orthostatic hypotension monitoring. Eligible subjects were randomized into treatment groups for the medication phase. On D1, subjects were discharged with study medication.

Treatment period: Subjects will be randomly assigned to medication in the form of 3 tablets (25/100 mg, 25/150 mg, 2x25/100 mg, or placebo) to be administered orally 3 times per day, the first time before a meal, and the second and third times after a meal. Subjects will return to the clinical site for visits on days 13-15 and 26-29 of the period.

Post-Treatment Follow-Up: a safety follow-up visit was conducted 7 days after the last dose of study medication. Subjects who discontinued prior to completing the 4-week treatment period underwent an early termination visit.

Concomitant medications:

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

Scoring requirements:

Clinicians scoring MDS-UPDRS-II and MDS-UPDRS-III should remain blinded to the treatment allocation.

3.2. Comparison Type

Was placebo-controlled.

3.3. Sample Size

The predicted sample size for this study was 10 cases per group, and 10 cases were actually enrolled in each group, for a total of 40 cases. The sample size was extrapolated based on experience with this type of clinical trial and not based on having statistical significance.

3.4. Randomization Method

Randomization in this study was conducted using an Interactive Response Technology system, which automatically assigned treatment groups based on randomization numbers. According to the randomization plan, eligible subjects were stratified by study site and randomized in a 1:1:1:1 ratio to receive WD-1603 25/100 mg, 25/150 mg, 2×25/100 mg, or placebo.

3.5. Blinding

This study utilized a double-blind design. Throughout the study period, the evaluators involved in the efficacy evaluations as well as the subjects participating in the trial were always in a maintained blinding .

If the efficacy evaluator becomes unblinded for a specific reason, immediate replacement by a blinded evaluator shall occur and detailed documentation must be maintained of the date, time, specific rationale for this unblinding event.

3.6. Pharmacokinetic (PK) Blood Sampling

Blood samples will be collected from all subjects on D28. Blood samples will be collected at time points including prior to the second dose administration (-15 to 0 minutes).

The blood samples were collected at 0.5h, 1.0h, 2.0h, 3.0h, 4.0h, 5.0h, 6.0h, and 9.0h (±2 min (for sampling windows≤1 h) and ±5 min (for>1 h)) after administration of levodopa/carbidopa.) Blood samples will be analyzed using validated bioanalytical methods for both levodopa and carbidopa concentrations.

4. Efficacy Endpoints

4.1. Primary Endpoint

（1）Compare the changes from baseline to D27 in the combined MDS-UPDRS-II and MDS-UPDRS-III scores between each dose group and the placebo group.

4.2. Secondary Endpoints

（1）Comparison the changes from baseline to D14 in the combined MDS-UPDRS-II and MDS-UPDRS-III scores between each dose group and the placebo group.

（2）The longitudinal changes in MDS-UPDRS Part-II scores from baseline to D14 and D27 will be compared between each dose group and the placebo group.

（3）The longitudinal changes in MDS-UPDRS Part-III scores from baseline to D14 and D27 will be compared between each dose group and the placebo group.

4.3. Security Evaluation Indicators

4.3.1. Adverse Event

AE: Refers to all adverse medical events that occur in a clinical trial participant, which may be manifested as signs and symptoms, disease, or abnormal laboratory tests, temporal association with investigational medicinal product（IMP）use is not required. Therefore, an AE can be any unfavorable, unintended sign, symptom, or disease (new occurrence or exacerbation of a pre-existing condition)

TEAE: AE that occurs after the subject has used the test drug.

TEAE (also known as ADR) related to the test drug: refers to noxious and unintended reaction that occurs in a clinical trial that may be related to the test drug. A TEAE that is "definitely related, probably related, or possibly related" to the test drug is recognized as an ADR.

SAE: means an AE that meets any of the following criteria:

- Resulting in death;
- Life-threatening (meaning that there is an immediate risk of death, not that death is assumed to be possible in the future if the development is severe)
- Resulting in hospitalization or prolonged hospitalization;
- Resulting in permanent or severe disability/loss of function;
- Causes congenital malformations or birth defects;
- Important Medical Events.

An important medical event is a medical event that does not result in an immediate occurrence of the above outcomes, but that requires medical measures to prevent the occurrence of an outcome such as the above, which include: cancer, bronchial allergic spasms requiring intensive treatment in the emergency room or at home, malaise or convulsions in the absence of hospitalization, and drug dependence or addiction. See the clinical study protocol for a detailed description.

Summarize the number of instances, cases, and percentages of the following adverse events by actual treatment group:

- ✓ Any AE
- ✓ TEAE
- ✓ TEAE with CTCAE grade≥ 3 levels
- ✓ SAE
- ✓ TEAE leading to withdrawal from the trial
- ✓ TEAE leading to permanent discontinuation of investigational drug
- ✓ TEAE leading to a reduction in the dose of the investigational drug
- ✓ TEAE leading to a temporary suspension of the investigational drug
- ✓ TEAE that is orthostatic hypotension
- ✓ TEAE related to the investigational drug
- ✓ TEAE related to the investigational drug with CTCAE grade ≥ 3
- ✓ SAE related to the investigational drug
- ✓ TEAE related to the investigational drug leading to withdrawal from the trial
- ✓ TEAE related to the investigational drug leading to permanent discontinuation of the investigational drug
- ✓ TEAE related to the investigational drug leading to a reduction in the dose of the investigational drug
- ✓ TEAE related to the investigational drug leading to a temporary suspension of the investigational drug
- ✓ TEAE related to the investigational drug that is orthostatic hypotension

4.3.2. Vital signs

Vital signs assessment parameters included body temperature, blood pressure (systolic, diastolic), heart rate, respiratory rate measurements and their clinical determination of significance.

4.3.3. Laboratory tests

The evaluation indexes of clinical laboratory tests include routine blood, blood biochemistry, urine routine laboratory test results and their clinical significance.

4.3.4. Electrocardiography

The electrocardiogram assessed parameters were heart rate, PR interval, QRS interval, QT interval, QTc interval measurements and their clinical significance.

4.4. Pharmacokinetic (PK) Parameters

PK parameters at steady state after multiple dosing: Tmax,ss, Cmax,ss, Cmin,ss, Cav,ss, t1/2,ss, AUC0-τ, AUC0-∞,ss, λz,ss, fluctuation index, and fluctuation amplitude. The definitions of each parameter are given in the following table.

Table 4.4.1 Definitions of PK parametersd for multiple-dose administration

Parameters	define
Tmax,ss	Time to first observed peak concentration following multiple-dose administration at steady state
Cmax,ss	Steady-state peak concentration refers to the maximum blood drug concentration when reaching steady state after multiple administrations
Cmin,ss	Steady-state trough concentration refers to the lowest blood drug concentration when steady state is reached after multiple administrations
Cav,ss	"Average steady-state plasma drug concentration" refers to the quotient of the area under the plasma drug concentration curve within a dosing interval when the plasma drug concentration reaches a steady state divided by the time interval
t1/2,ss	Elimination half-life when multiple administrations reach steady state, elimination half-life $t1/2 = Ln(2)/\lambda z,ss$
λz,ss	The elimination rate constant of plasma drug concentration in the terminal phase. It is the negative value of the slope obtained by performing a linear regression of the logarithm of the plasma drug concentration against time.
AUC0-τ	At steady state, the area under the plasma drug concentration-time curve within a dosing interval (τ) is calculated using the linear trapezoidal area method.
AUC0-∞,ss	Area under the plasma concentration-time curve extrapolated from the start of the last dose to infinity
Volatility Index	Percentage fluctuation at steady state = 100% × (Cmax,ss-Cmin,ss)/Cav,ss
Amplitude of Fluctuations	Fluctuation at steady state = 100% × (Cmax,ss-Cmin,ss)/Cmin,ss

5. Statistical Analysis Set

In this trial, the following analysis sets are defined for statistical analysis:

FAS: all subjects participating in randomization will be included in the full analysis set.

Per-Protocol Set (PPS): It includes all subjects in the Full Analysis Set who have completed a pre-set sufficient exposure to the investigational drug, obtained the primary efficacy indicators in the trial, and have not made major violations of the trial protocol.

Safety Set (SS): includes all subjects who received at least one treatment with a safety assessment .

Pharmacokinetics Analysis Set (PKS): all subjects in the safety population with any assessable plasma concentration data will be included in the pharmacokinetic analysis set.

6. Methods of Statistical Analysis

6.1. General Agreement

The pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin® Version 8.3. Other statistical analyses excluding PK parameter calculations will be performed using SAS® Version 9.4. In general, continuous variables will be summarized using the number of subjects, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum. Categorical variables will be summarized using frequency counts and percentages. Unless otherwise specified, statistical tests will employ two one-sided tests at α=0.025 to calculate two-sided 95% confidence intervals. In the absence of specific instructions, the following conventions for decimal places retention will be applied throughout this statistical analysis:

Table 6.1.1 Requirements for the retention of decimal places in data

Statistic	Decimal places requirement
Individual data	Measured data (such as laboratory tests): retain the actual number of decimal places.
Arithmetic mean, median, Q1, Q3	One decimal place more than the maximum number of decimal places for individual data.

standard deviation	1 decimal place more than the arithmetic mean, up to a maximum of 4 decimal places.
Minimum and maximum values	Same as individual data.
Frequency, incidence rate, constituent ratio	Retain 1 decimal place in the form of a percentage, results with a frequency of 0 are shown as "0", results with 100% are shown as "100%".
Test statistic (such as chi-square or t-value, etc.)	Retain 4 decimal places.
P-value	4 decimal places are reserved, and specific values less than 0.0001 will be indicated by "<0.0001".

Baseline for the safety assessment indicators was defined as the last non-missing test, evaluation, or calculation prior to the first administration of the test medication during the treatment period. Baseline was defined as the result of the most recent central laboratory test (including unscheduled visits) prior to the first administration of the drug for central laboratory testing programs; and the most recent local laboratory test (including unscheduled visits) prior to the first administration of the drug for local laboratory testing programs.

The baseline for the efficacy assessment indicator is defined as the measured or derived value prior to the first use of the investigational drug in the treatment period (D-1 by default). Its specific derivation rules are described in detail at 6.1.4.

6.1.1. Processing of Data from Unscheduled Visits

The conventions for processing data from unscheduled visits are as follows:

When establishing baseline measurements, it is crucial to incorporate data obtained during both planned and unscheduled visits. Specifically, the most recent non-deficient test result recorded before the initial medication administration was selected as the baseline measurement.

Safety analyses were stratified by study visit and assessment category (including laboratory evaluations, vital sign monitoring, and electrocardiographic assessments), with metric-based summarization restricted to protocol-specified scheduled visit data during the treatment period.

For efficacy endpoint analyses employing post-LOCF imputation methodology, longitudinal data integration encompassed protocol-defined scheduled visits, protocol-deviated unscheduled visits, and premature

discontinuation visits. However, formal statistical characterization was strictly limited to pre-specified study timepoints as delineated in the Statistical Analysis Plan (SAP).

All unscheduled visit data are tabulated.

6.1.2. Handling of Out-of-window Data

For all types of test data with a per-protocol-specified window, any data exceeding the window is regarded as a minor protocol deviation. This does not affect population segmentation and summary analysis. Meanwhile, the data exceeding the window should be listed in a separate list.

6.1.3. Handling of Missing Dates for Various Events

For various event categories (current medical history, past/concomitant diseases, adverse events, prior medications/non-drug therapies, concomitant medications/non-drug therapies, etc.), specify the rules for determining start/end dates (and/or) imputation methods for missing dates based on the definitions and nature of each event type. Detailed specifications can be found in Appendix 2 at the end of the separate SAP document.

6.1.4. Derivation of Data

Duration of Parkinson's disease (months)=(date of signing informed consent-date of first diagnosis+1)/30.4375.This precisely calculated variable was taken 1 decimal place.

MDS-UPDRS-III Baseline, D14, and D27 Values are defined as the average of multiple MDS-UPDRS-III assessments conducted pre-dose (D-1), on D14, and D27, respectively. By default, MDS-UPDRS-III is assessed six times at each visit (Baseline, D14, and D27), with the final score calculated as:(MDS-UPDRS-III Assessment 1+Assessment 2+Assessment 3+Assessment 4+Assessment 5+Assessment 6) / 6.This derived variable is rounded to the nearest integer.

MDS-UPDRS-II+MDS-UPDRS-III Baseline, D14, and D27 Values are defined as the sum of the single MDS-UPDRS-II assessment and the average of multiple MDS-UPDRS-III assessments (as above) at each corresponding time

point (Baseline/D-1, D14, and D27). The total score is calculated as:MDS-UPDRS-II Score+(MDS-UPDRS-III Assessment 1+Assessment 2+Assessment 3+Assessment 4+Assessment 5+Assessment 6) / 6.This derived variable is rounded to the nearest integer.

6.2. Study Population

6.2.1. Subject Disposition

Number and percentage of subjects who underwent screening, successfully screened, randomized, completed the study, discontinued (including premature withdrawal) with reasons for discontinuation.

6.2.2. Protocol Deviation

Summary of protocol deviations by category and major protocol deviations (number and incidence) by category; detailed listing of protocol deviations by subject.

6.2.3. Demographics and Baseline Characteristics

Summary statistics were generated for the FAS population across treatment groups, with categorical organization of demographic characteristics and baseline parameters:

（1） Quantitative demographic indicators: age (years), height (cm), weight (kg), BMI (kg/ m^2)；

（2） Demographically disaggregated indicators: sex (male and female）.ethnicity (Han and other)；

（3） Baseline characteristics of Parkinson's disease: disease duration, modified Hoehn &Yahr score, MDS-UPDRS-II score, MDS- UPDRS-III score, MDS-UPDRS-II+ MDS-UPDRS-III score, and Beck Depression Self-Rating Scale total score;

（4） Other baseline characteristics include surgical history, medical history.

The above indicators were summarized descriptively. Continuous variables were calculated for their number of cases, arithmetic mean, standard deviation, median, 25th percentile (Q1) ,75th percentile （Q3），minimum and maximum values. Frequencies and component ratios were calculated for count and rank

data.

The list describes in detail the demographic information and baseline characteristics of the subjects.

If FAS and PPS subjects were different, the descriptive summaries of demographics and baseline Parkinson's disease characteristics were repeated on the basis of the PPS.

6.2.4. Prior/Concomitant Illnesses

Definitions of prior/concomitant illnesses, and rules for filling in missing values are detailed in [redacted] at the end of the separate SAP document. Based on the FAS set, prior/concomitant illnesses will be coded according to MedDRA (version V25.1) and then summarized into groups according to the systematic organ classification and preferred terminology.

The list describes in detail the subject's prior/concomitant illnesses.

6.2.5. Prior/Concomitant Medications

Definitions of prior/concomitant medications, and rules for filling in missing values are detailed in Appendix 2 at the end of the text of the separate SAP document. based on FAS, prior/concomitant medications were coded using the world health organization drug dictionary (WHODRUG) (version: September 2022) and summarized by group according to the ATC classification (ATC02 and ATC04), and the frequency and percentage of prior/concomitant medications were counted.

The list describes in detail the subject's past/concomitant medications.

6.2.6. Prior/Concomitant Non-medicinal Treatments

Definitions of prior/concomitant non-medicinal treatments, and rules for filling in missing values are detailed in Appendix 2 at the end of the separate SAP document. Based on the FAS, prior/concomitant non-medicinal treatments were coded for subjects using MedDRA (version V25.1). prior/concomitant non-medicinal treatments were only tabulated.

6.2.7. Medication Compliance

Based on the FAS set, grouped and aggregated analysis of medication compliance for the IMP(WD-1603).

Calculation formula for medication compliance: medication compliance= actual quantity of medicinal product used (tablets)/planned quantity of medicinal product (tablets)× 100%. The method of calculating the actual quantity of medicinal product used and the planned quantity of medicinal product used in the formula is as follows:

actual quantity of medicinal product used (tablets):calculated according to the pages for drug dispensation and return in the eCRF: quantity of drug dispensed (tablets)-quantity of drug returned (tablets)-quantity of drug lost (tablets).

planned quantity of medicinal product (tablets):daily dosage (tablets) following the protocol*duration of drug exposure (days). duration of drug exposure (days)=date of last drug administration-date of first drug administration+1.

Classification of medication compliance: number of cases and percentage by group for <80%, ≥80% to ≤120%, and >120% classifications.

Describe in a list the quantity of the IMP(WD-1603) used (in tablets), medication compliance, and compliance classification for each subject.

6.3. Primary Efficacy Analysis

6.3.1. Primary Analysis Method

The primary efficacy endpoint of this study is the change in MDS-UPDRS-II+MDS-UPDRS-III relative to the baseline on D27 (a lower-is-better indicator). The difference method (RD) is used to conduct a superiority test on the change in MDS-UPDRS-II+MDS-UPDRS-III relative to the baseline on D27 for each dose group and the placebo group. The superiority margin is set at 0. The hypothesis testing is as follows:

H0: T-C≥0, H1: T-C<0

Test level $\alpha = 0.025$ (one-sided)

T and C the mean values of the primary efficacy endpoints (the change in the

total score of MDS-UPDRS-II+MDS-UPDRS-III relative to the baseline on D27) for each dose group and the placebo group, respectively.

Primary analyses will be conducted based on the FAS. For subjects with missing primary endpoint data on D27 or D14, the Last Observation Carried Forward method will be used to impute the missing data. A statistical description will be provided for the changes in MDS-UPDRS-II+MDS-UPDRS-III relative to the baseline on D27 or D14. Within the same treatment group, a paired-samplet-test for a single group will be used to test the differences in the paired-design samples for the changes in MDS-UPDRS-II+MDS-UPDRS-III from the baseline on D27 or D14 and the changes in MDS-UPDRS-II+MDS-UPDRS-III from D14 to D27. Between the different treatment groups, analysis of variance (ANOVA) will be used to test the differences in the multiple independent samples for MDS-UPDRS-II+MDS-UPDRS-III at baseline, on D14, or on D27.

The reference procedure for the single-group t-test for quantitative indicators was as follows:

```
PROC TTEST
VAR CHG1 CHG2 CHG3
 RUN
```

Note: Within a specific group , CHG1, CHG2, and CHG3 represent the change from baseline on D14, the change from baseline on D27, and the change from D14 to D27, respectively.

The ANOVA reference procedure for multiple independent samples for quantitative indicators is as follows:

```
PROC ANOVA;
CLASS GROUP;
MODEL AVAL=GROUP;
RUN;
```

Primary analyses will be conducted based on the FAS.For subjects missing primary endpoint data on Day 27, the LOCF method will be used to impute the

missing data. ANCOVA with the baseline value as the covariate and the treatment group as the independent variable will be used to analyze the change from baseline on D27 of treatment. The difference in the least-squares means of the change from baseline after 27 days of treatment between each dose group and the placebo group, along with its 95% confidence interval and P-value, will be calculated using the ANCOVA model .

The reference procedure for the analysis of covariance of quantitative indicators is as follows:

PROC MIXED;

CLASS GROUP;

MODEL CHG= GROUP BASELINE <SPECIFIC VAR>;

LSMEANS GROUP /pdiff cl diff=control(“C”) ;

RUN;

Note: CHG represents the change in indicator values relative to baseline; BASELINE refers to the baseline value of MDS-UPDRS-II+MDS-UPDRS-III during the baseline period .

6.3.2. Sensitivity Analysis Method

For the main primary evaluation indicators, in order to explore the robustness of the statistical inference results obtained from the primary analysis method, the following two types of sensitivity analyses should be performed.

The same analysis model based on the PPS population

Repeat the original ANCOVA model analysis based on the PPS population.

Different analysis model based on FAS population

Based on the FAS population, on the basis of the original ANCOVA model, the disease severity during the baseline period (Modified Hoehn & Yahr Scale score) will be additionally introduced as a categorical covariate for analysis.

Different analysis model based on FAS population

Based on the FAS population, without imputing missing data, a MMRM will be used as a sensitivity analysis. In the MMRM, the changes from baseline on D14

and D27 are used as the dependent variables, the baseline value is used as the covariate, and the treatment group, visit, and the interaction term between treatment and visit are considered as fixed effects. The maximum likelihood estimation method is used for parameter estimation. The covariance matrix of the model adopts an unstructured (UN) form, and the Kenward-Roger correction is applied to the denominator degrees of freedom of the fixed effects. The adjusted least-squares means of the changes in each group and their 95% confidence intervals are estimated.

The reference procedure for the analysis of the mixed linear model of repeated-measures data is as follows:

PROC MIXED method=REML;

CLASS VISIT GROUP.

MODELCHG=GROUP VISIT GROUP*VISIT BASELINE / solution ddfm=kr;

REPEATEDVISIT/ type=UN RCORR.

LSMEANS GROUP*VISIT /pdiff cl;

RUN.

Note: When the UN form is selected as the variance-covariance structure of the residuals, if the model fails to converge, the information criteria (AIC and BIC) will be calculated through posterior inspection to determine the most appropriate variance-covariance structure of the residuals for analysis.

6.4. Secondary Efficacy Analysis

The data processing and analysis methods shall be consistent with those specified in the primary analysis method for the primary efficacy endpoints.

6.5. Security Analysis

Based on SS, a summary analysis will be conducted on the drug exposure, adverse events, physical examination, vital signs, laboratory tests, and electrocardiograms examinations for each treatment group.

6.5.1. Drug Exposure

Summarize the exposure of the IMP by treatment group , using the mean, standard deviation, median, quartiles, maximum and minimum for description.Provide a statistical description of the treatment duration of the study drug, the number of days of study drug exposure, the cumulative exposure dose，and the average daily exposure dose during the treatment period. The relevant calculation formulaes are as below.

Duration of exposure(days)= date of last drug administration-date of first drug administration+1 (ignoring possible interruption days in between)

Average daily exposure=cumulative exposure dose of the drug(tablets)/ duration of exposure (days), where the cumulative exposure dose of the drug(tablets)=amount of drug dispensed (tablets)-amount of drug returned(tablets)-amount of drug lost（tablets）.

6.5.2. Adverse Events

The grading criteria for adverse events (AEs) refer to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and are classified into Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death). Generally, according to the conservative principle: if the severity of an AE is missing, it will be recorded as "Grade 3" in the summary description; if the relationship between a TEAE and the IMP is missing, it will be recorded as a TEAE related to the IMP in the summary description. Based on the conservative principle, some missing start dates of AEs will be imputed for calculation purposes, while the end dates of AEs will not be imputed. The rules for imputing missing values of AE start dates are detailed in Appendix 2 at the end of the separate SAP document. The adverse events recorded in this trial will be coded according to the MedDRA version 25.1.

The analysis for AE is described below:

（1）Summarize and describe the number of subjects (occurrence frequency) and the number of occurrences of each type of TEAE defined in "4.3.1 Adverse events" for each treatment group.

（2）For each type of TEAE defined in "4.3.1 Adverse events", summarize by each treatment group and describe the number of subjects (incidence rate) and the number of occurrences based on the SOC and PT classifications .

（3）For each type of TEAE defined in "4.3.1 Adverse events", summarize by each treatment group. Based on the SOC, PT classification, and severity, describe the number of subjects (incidence rate) and the number of occurrences for each classification and different severities. If an adverse event under the same SOC/PT occurs multiple times in the same subject, for that specific SOC/PT, only the data related to the most severe case of this subject will be included in the summary statistics of the number of subjects in the table, while the number of occurrences will be summarized based on the actual observed data.

（4）List all types of TEAEs defined in "4.3.1 Adverse events". The list shall include, but not be limited to, the names of various TEAEs, occurrence times, severities, and relationships with the IMP.

6.5.3. Vital Signs

Summarize and describe the results of each vital sign indicator and their changes relative to the baseline for each treatment group at each scheduled visit. Summarize, in the form of a cross - tabulation, the changes relative to the baseline in the clinical significance assessment results of each indicator examination for each treatment group at each scheduled visit. All examination results and abnormal examination results of each vital sign indicator for each subject will be listed.

Summarize, in the form of a cross - tabulation, the changes relative to the baseline in orthostatic hypotension (present or absent) for each treatment group at each scheduled visit. All examination results of each orthostatic hypotension indicator for each subject will be listed.

6.5.4. Laboratory Tests

Summarize and describe the results of laboratory tests, including complete blood count, urinalysis (quantitative indicators only), and blood biochemistry, and

their changes relative to the baseline for each treatment group at each scheduled visit. Summarize, in the form of a cross-tabulation, the changes relative to the baseline in the clinical significance assessment results of laboratory tests for each treatment group at each scheduled visit. All examination results and abnormal examination results of complete blood count, urinalysis, and blood biochemistry for each subject will be listed.

6.5.5. Electrocardiogram Examination

Summarize and describe the results of heart rate, PR interval, QRS interval, QT interval, and QTc interval and their changes relative to the baseline for each treatment group at each scheduled visit. Summarize, in the form of a cross - tabulation, the changes relative to the baseline in the overall clinical significance assessment results of electrocardiogram for each treatment group at each scheduled visit. All examination results and abnormal examination results of each electrocardiogram indicator for each subject will be listed.

6.5.6. Beck Depression Inventory

Summarize and describe the total scores of the BDI and their changes relative to the baseline for each treatment group at each scheduled visit. List and describe the total scores of the BDI and the scores of each examination item.

6.6. Pharmacokinetic Analysis

6.6.1. Handling of Results BQL

（1） When statistically summarizing and plotting the mean plasma concentration-time curve, unless otherwise specified :

- All concentration values BQL will be treated as 0, represented as "BQL" in the data list, and the number of BQLs at each time point will be indicated ;

（2） When calculating pharmacokinetic (PK) parameters, unless otherwise specified :

- BQLs occurring before Tmax, ss are treated as 0;
- BQLs occurring after Tmax,ss were treated as missing;

（3） When plotting the individual plasma concentration-time curve, unless otherwise specified:

- All concentration values BQL will be treated as 0.

In this analysis plan, only the pharmacokinetic analysis methods for intensive sampling are stipulated.

6.6.2. Plasma Concentration Analysis

Based on the Pharmacokinetic System (PKS), list and describe the plasma concentration data of levodopa and carbidopa for each subject at each scheduled blood sampling time point by different treatment groups (the placebo group is not applicable). Conduct a statistical description of the plasma concentration data of levodopa and carbidopa at each scheduled blood sampling time point .

Based on the plasma concentration statistics (mean and standard deviation) at each blood sampling time point, plot the linear graph of the mean plasma concentration - time curve and the semi - logarithmic graph of the mean plasma concentration-time curve for levodopa and carbidopa according to the scheduled blood sampling time points. The standard deviation of the plasma concentration at each scheduled blood sampling time point in the graph is represented by upper and lower standard deviation lines. Note: The mean concentration-time (C-T) graphs of the three treatment groups should be presented in one graph to facilitate intuitive comparison between treatment groups .

Based on the plasma concentration statistics of each subject at each blood sampling time point, plot the linear graph of the individual plasma concentration-time curve and the semi-logarithmic graph of the individual plasma concentration-time curve for levodopa and carbidopa according to the actual blood sampling time points .

6.6.3. Pharmacokinetic Parameter Analysis

Among the subjects included in the Pharmacokinetic System (PKS), based on the administered dose of each subject and the plasma concentration - actual blood sampling time point data, use Phoenix WinNonlin version 8.3 software to calculate the pharmacokinetic (PK) parameters of levodopa and carbidopa after multiple administrations by the linear trapezoidal linear interpolation method in

the non-compartmental model approach (NCA module) .

Among the subjects included in the PKS, conduct the following analyses by different treatment groups:

(1) List and describe the PK parameter data of levodopa and carbidopa for each subject.

(2) Conduct a statistical description of the PK parameters of levodopa and carbidopa.

(3) For the PK parameters Cmax,ss and AUC0 - τ of levodopa and carbidopa, divide the PK parameters of subjects in each group by the planned administered dose of each group to obtain the individual data of Cmax,ss/dose and AUC0 - τ/dose. After natural logarithm transformation, using WD - 1603 25/100 mg or WD - 1603 25/150 mg as the reference, perform an inter - group difference comparison. Then, after anti - natural logarithm transformation, obtain the relative bioavailability (F) value and its 90% confidence interval (CI).

Reference procedure for the inter-group relative bioavailability (F) value and its 90% CI:

```
proc mixed
class ARMN RANDNO
model LOGAVAL = ARMN /ddfm=KR
lsmeans ARMN /pdiff cl alpha=0.10
run
```

6.7. Exploratory Subgroup Analysis

f the data permit, subgroup analysis can be conducted based on the background medications for Parkinson's disease (whether combined with anticholinergic drugs, amantadine, MAO-B inhibitors, etc.)

6.8. Planned Changes in Analysis

There are no analytical changes to the plan.

7. Statistical Analysis Results

7.1. Table, Figure and List Formats

See the separate document of TFL Mockup.

8. Amendment to the Protocol Analysis Plan

None.

9. References

[1]Former State Food and Drug Administration. Code for Quality Management of Drug Clinical Trials, 2003.9.

[2]Former State Food and Drug Administration.Guidelines on the Structure and Content of Clinical Study Reports on Chemical Drugs,2005.3.

[3]Former State Food and Drug Administration. Guidelines on Biostatistics for Drug Clinical Trials, 2016.6

[4]Former State Food and Drug Administration. Plan and Report on Data Management and Statistical Analysis of Drug Clinical Trials. Guiding Principles for Reporting, 2016.7

10. Attachment

Annex 1 Tables, Test Flow Table

Date / Protocol Activity	Visit 1 Screen	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]	

Date / Protocol Activity	Visit 1 Screen	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
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	
Baker Depression Scale Assessment [6] [Beck Depression Inventory-II（BDI－II）]	X	X		X	
WD-1603 administration		← X[7] →			
PK blood sample collection				X[8]	
Admission		X[9]	X[10]	X[11]	
Discharge from CPU		X	X	X	

[1] Measured vital signs and orthostatic hypotension before the first administration, 1 hour and 4 hours after the first administration. Orthostatic hypotension will be measured during these vital signs: (1) measure the blood pressure in the supine position, (2) measure the blood pressure again in a standing position after 3 minutes, (3) systolic blood pressure drop ≥20mmHg or diastolic blood pressure drop ≥10mmHg is orthostatic hypotension (4) after one hour, ask the subject to repeat the above steps (1) to (3) in the supine position. 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 administration. In the other visit periods, 6 assessments of the MDS-UPDRS-III scale are carried out at the time point of the clinical trial administration: Day -1: The subjects who takk non-levodopa drugs before the trial are given the first administration, 2.5 hours after the administration, 5 hours after the first administration or before the second administration, 2.5 hours after the second administration(7.5 hours after the first administration),10 hours after the first administration or before the third administration, and 2.5 hours after the third administration (12.5 hours after the first administration). The subjects who are not treated with drugs before the test

Date / Protocol Activity	Visit 1 Screen	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
	are treated at the same time point as the drug treatment period (Visit 3). Day 14 and Day 27: Before the first dose administration, 2.5 hours after the first dose, before the second dose and 2.5 hours after the second dose, before the third dose, and the third dose 2.5 hours after the dose. Each scale evaluation has a time window of ±15 minutes. [6] Baker 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 25/100mg or 25/150mg or 2x25/100mg 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, 4 weeks and 28 days; on the 28th day orally twice, in the morning and noon. [8] Day 28, Blood sample collection time points include before the second dose (-15 to 0 minutes) and after the second dose 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 9.0 hours (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 hospital in the afternoon or evening, and are assessed by 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 hospital 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 hospital in 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				

Annex 2 Definitions of Various Events, Date Missing Filling Rules

Event Name	Definition of the Event	Imputation Rules for Missing Start/End Dates
Concomitant Medications/Non-Drug Therapies	Medications/non-drug therapies that were discontinued before (and not including) the start date of the investigational product treatment.	Missing start dates shall not be imputed. Imputation for missing end dates: If the corresponding field on the CRF indicating "Is it ongoing?" is "Yes", the event shall be determined as concomitant medication/non-drug therapy without imputing the end date. If the corresponding field on the CRF indicating "Is it ongoing?" is "No", the end date shall be imputed according to the following logic before determining the event: • If the "year", "month", and "day" are all missing, impute with the day prior to the start date of the investigational product treatment.

		• If the "month" and "day" are missing but the year is known and the same as the start date of the investigational product treatment, impute with the day prior to the start date of the investigational product treatment. • If the "month" and "day" are missing but the year is known and different from the start date of the investigational product treatment, impute as December 31st of that year. • If only the "day" is missing and the year/month match the start date of the investigational product treatment, impute with the day prior to the start date of the investigational product treatment. • If only the "day" is missing and the year/month differ from the start date of the investigational product treatment, impute as the last day of that month. No imputation shall be performed if the imputed end date is earlier than the start date or contradicts the event definition.
Concomitant Medications/Non-Drug Therapies	Any medications/non-drug therapies that are still ongoing at the start date of the investigational product treatment, or used on or after the day of the first dose of the investigational product.	Imputation for missing start dates: • If the "year", "month", and "day" are all missing, impute with the start date of the investigational product treatment. • If the "month" and "day" are missing but the year is known and the same as the start date of the investigational product treatment, impute with the start date of the investigational product treatment. • If the "month" and "day" are missing but the year is known and different from the start date of the investigational product treatment, impute as January 1st of that year. • If only the "day" is missing and the year/month match the start date of the investigational product treatment, impute with the start date of the investigational product treatment. • If only the "day" is missing and the year/month differ from the start date of the investigational product treatment, impute as the 1st day of that month. Missing end dates shall not be imputed.
Pre-existing/Concomitant Diseases	Diseases other than Parkinson's that occurred in subjects before or during the	No imputation

	trial.	
History of Present Illness	Date of First Diagnosis of Parkinson's Disease	Imputation for missing first diagnosis dates: • If the "year", "month", and "day" are all missing, or the "year" is missing, no imputation shall be performed. • If both the "month" and "day" are missing, impute as July 1st. • If only the "day" is missing, impute as the 15th day of that month. • If the imputed date occurs after the informed consent date, impute as the informed consent date.
AE	The definition is described in the safety analysis section.	Partial missing AE start dates will be imputed based on conservative principles for calculation purposes, while AE end dates will not be imputed. Imputation for Missing Start Dates: • If the "year", "month", and "day" are all missing, impute with the study start date (i.e., the first administration date of the investigational product). • If both the "month" and "day" are missing and the year matches the study start date's year, impute with the study start date. • If both the "month" and "day" are missing but the year differs from the study start date's year, impute as January 1st of that year. • If only the "day" is missing and the year/month match the study start date's year/month, impute with the study start date. • If only the "day" is missing but the year/month differ from the study start date's year/month, impute as the 1st day of that month. • If the AE end date is not missing and the imputed AE start date falls after the AE end date, impute the AE start date as the AE end date. No imputation shall be performed if the imputed date contradicts the event definition.