Statistical Analysis Plan

NCT Number: NCT04668157

Title: A Phase 3, Open-label, Multicenter, Long-term Study to Evaluate the Safety, Efficacy and Pharmacokinetics of TAK-536 in Pediatric Subjects from 2 to Less Than 6 Years of Age with Hypertension

Study Number: Azilsartan-3004

Document Version and Date: Version 2.0 / 06-Jun-2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: Azilsartan-3004

Study Title: A Phase 3, Open-label, Multicenter, Long-term Study to Evaluate the Safety, Efficacy and Pharmacokinetics of TAK-536 in Pediatric Subjects from 2 to Less Than 6 Years of Age with Hypertension

Phase: 3

Version: 2.0

Date: 06-Jun-2023

Prepared by: [redacted]

Based on:

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	01-Feb-2021	Not Applicable
Version 2.0	06-Jun-2023	To add some analysis

TABLE OF CONTENTS

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BMI	Body mass index
BUN	blood urea nitrogen
CCB	calcium channel blocker
CI	confidence interval
CRF	case report form
COVID-19	coronavirus disease 2019
DRI	direct renin inhibitors
ECG	electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FAS	full analysis set
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
LLN	lower limit of normal
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term (MedDRA)
PTE	pretreatment event
Q1	25th percentile
Q3	75th percentile
RAS	renin-angiotensin-system
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To evaluate the safety of TAK-536 in pediatric subjects with hypertension aged 2 to less than 6 years

1.1.2 Secondary Objective(s)

To evaluate the efficacy and pharmacokinetics of TAK-536 in pediatric subjects with hypertension aged 2 to less than 6 years

1.2 Endpoints

1.2.1 Primary Endpoint(s)

Safety:

- *Adverse events (AEs)*
- *Resting 12-lead electrocardiogram (ECG) parameters*
- *Anthropometric measurements (weight, height, and body mass index [BMI])*
- *Laboratory test values*
- *Vital sign measurements (office sitting pulse rate* and home sitting blood pressure*)*

  **These should be measured in a sitting position. For subjects who are unable to assume a sitting position, blood pressure measurements can be obtained while in other positions such as a supine position. In this case, all measurements should be conducted in the same position during the study.*

1.2.2 Secondary Endpoint(s)

Efficacy:

- *Change from baseline in office trough sitting diastolic and systolic blood pressure at Week 12 and 52 (last observation carried forward [LOCF])*
- *Proportion of subjects who achieve the target blood pressure at Week 12 and 52 (LOCF)*

Note: The target blood pressure is <95th percentile for essential hypertension and <90th percentile for subjects with secondary hypertension. The values are shown in Table 1.

Table 1 Reference Blood Pressure Values of Children by Gender and Age

Age (years)	Male			Female		
	90th	95th	95th + 12 mmHg	90th	95th	95th + 12 mmHg
2	102/56	106/59	118/71	103/60	106/64	118/76
3	103/59	107/62	119/74	104/62	108/66	120/78
4	105/62	108/66	120/78	106/65	109/69	121/81
5	106/65	109/69	121/81	107/67	110/71	122/83
6	107/68	111/71	123/83	108/69	111/72	123/84

Systolic/diastolic blood pressures (mmHg), Guidelines on the Clinical Examination for Decision Making of Diagnosis and Drug Therapy in Pediatric Patients with Cardiovascular Diseases and Cardiovascular Disorder by the Japanese Circulation Society (JCS2018) [3]
The 90th and 95th indicate 90th and 95th percentile, respectively.

Pharmacokinetics:

Plasma concentrations of TAK-536

1.3 Estimand(s)

Not Applicable.

2.0 STUDY DESIGN

This is a phase 3, open-label, multicenter study to evaluate the safety, efficacy, and pharmacokinetics of long-term administration of TAK-536 once daily for 52 weeks in pediatric patients with hypertension aged 2 to less than 6 years.

The study consists of a 2-week Run-in Period, a 52-week Treatment Period, and a 2-week Follow-up Period (56 weeks in total).

Screening and Run-in Period:

Subjects eligible at screening will begin to receive the placebo in a single-blinded fashion at the start of the Run-in Period.

The duration of the Run-in Period will be 2 weeks. However, at the earliest, the subjects should enter the Treatment Period 1 week after starting to receive placebo if his/he blood pressures meet the inclusion criteria. In addition, for the subjects who are treated with any antihypertensive drugs before the Run-in Period, the Run-in Period can be extended up to 4 weeks if blood pressures do not meet the inclusion criteria.

Subjects who were treated with renin-angiotensin-system (RAS) inhibitors (ACE inhibitors, ARB and direct renin inhibitors [DRI]) must discontinue these medications at the start of the Run-in Period.

Subjects who were treated with antihypertensive drugs other than RAS inhibitors until the start of the Run-in Period can continue to receive a single antihypertensive drug in addition to the

study drug if the subjects are considered to need the additional treatment for hypertension in the Treatment Period by the investigator or subinvestigator. The dose of the antihypertensive drug used before the Run-in period should be the same once the Run-in period starts.

If termination of antihypertensive drugs other than RAS inhibitors requires a gradual down-titration, this can be accomplished while subjects are in the Run-in Period. In the case of the down-titration, the antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period. Antihypertensives, in particular beta-blockers (BBs), should be tapered off gradually, as it may cause withdrawal syndrome, in which symptoms such as palpitations, restlessness, hypertension, headache would be observed upon abrupt discontinuation.

Treatment Period:

Study drugs will be dosed according to the subject's body weight. In the Treatment Period, the initial dose of TAK-536 will be 0.1 mg/kg (not exceeding 2.5 mg/day). After the initial dose, TAK-536 will be titrated to 0.2 mg/kg (not exceeding 5 mg/day), 0.4 mg/kg (not exceeding 10 mg/day), and 0.8 mg/kg (not exceeding 20 mg/day) if the subjects do not achieve the target blood pressure and no concerns are found in safety and tolerability. The target blood pressure is <95th percentile for essential hypertension and <90th percentile for subjects with secondary hypertension (Table 1)

TAK-536 will be titrated at the visits of Weeks 2, 4, or 8. Between the visits of Week 4 and 8, an additional unscheduled visit of Week 6 may be requested at the investigator's or subinvestigator's discretion in order to titrate the dose of the study drug in the subjects when the further decrease in blood pressure is needed. Even if the dose is not titrated to the maximum dose (0.8 mg/kg) by Week 8, TAK-536 may be titrated to 0.2 mg/kg, 0.4 mg/kg, or 0.8 mg/kg in a stepwise order after Week 8 if the subjects do not achieve the target blood pressure and there are no concerns regarding safety and tolerability.

During the Treatment Period before Week 12, change in the dosage of any concomitant antihypertensive drug is not allowed in the subjects who are treated with a single antihypertensive drug other than RAS inhibitors. TAK-536 dose can be reduced to 0.4 mg/kg, 0.2 mg/kg, or 0.1 mg/kg at the investigator's or subinvestigator's discretion if there are any concerns in safety and tolerability with upward titration of TAK-536 (ie, in case of occurring any AEs associated with titration of TAK-536).

During the Treatment Period after Week 12, when the subjects do not achieve the target blood pressure with the maximum dose (0.8 mg/kg) of TAK-536, the subjects can receive additional antihypertensive drugs (other than RAS inhibitors) or can change in dose of the antihypertensive drug in addition to TAK-536 at the investigator's or subinvestigator's discretion. TAK-536 dose can be reduced to 0.4 mg/kg, 0.2 mg/kg, or 0.1 mg/kg at the investigator's or subinvestigator's discretion if there are any concerns in safety and tolerability with upward titration of TAK-536 (ie, in case of occurring any AEs associated with titration of TAK-536). When the antihypertensive drugs require dose reduction or interruption because of concerns in safety and tolerability with titration, dosing of the antihypertensive drugs other than TAK-536 should be

reduced or interrupted first. Thereafter, dose reduction or interruption of TAK-536 should be considered.

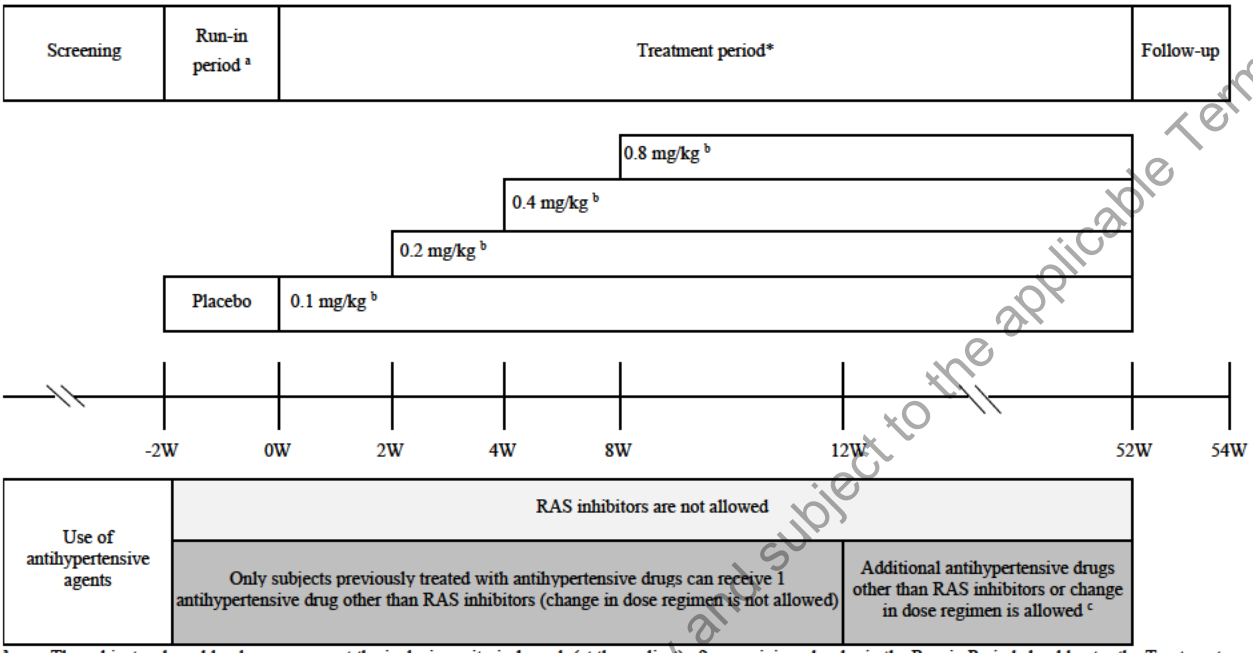
Follow-up Period:

Follow-up Period will last 2 weeks from the day following the final dose of TAK-536, that is at Week 54 after the start of the Treatment Period. Safety will be evaluated up to that time.

Sites will employ all efforts to see subjects in the clinic for assessments. In unavoidable circumstances (eg, a widespread disease outbreak such as the coronavirus disease 2019 [COVID-19] pandemic or natural disaster), exceptions may be consulted for alternative visits or assessments for conducting subject visits with approval by the Medical Monitor and/or sponsor. Such instances will be documented in the study records as related to COVID-19.

A schematic of the study design is included as Figure 1. A schedule of assessments is listed in Appendix A in the protocol.

Figure 1 Schematic of Study Design



[a] The subjects whose blood pressure meet the inclusion criteria 1 week (at the earliest) after receiving placebo in the Run-in Period should enter the Treatment Period. Only for the subjects who were treated with antihypertensive drugs before the Run-in Period, the Run-in Period could be extended up to 4 weeks if blood pressures do not meet the inclusion criteria.

[b] During the Treatment Period, if the subjects do not achieve the target blood pressure and no concern are found in safety and tolerability, TAK-536 will be titrated every 2 or 4 weeks by Week 8. TAK-536 can be reduced at the investigator's or subinvestigator's discretion if there are any concerns in safety and tolerability with upward titration of TAK-536 (ie, in case of occurring any AEs associated with titration of TAK-536). Even if the dose is not titrated to the maximum dose (0.8 mg/kg) by Week 8, TAK-536 may be titrated to 0.2 mg/kg, 0.4 mg/kg, and 0.8 mg/kg in a stepwise order after Week 8 if the subjects do not achieve the target blood pressure and there are no concerns regarding safety and tolerability.

[c] Change in the dosage of any concomitant antihypertensive drug is not allowed until TAK-536 is titrated to the maximum dose (0.8 mg/kg) in the subjects who are treated with a single antihypertensive drug other than RAS inhibitors at the start of the Treatment Period.

* Between the visits of Week 4 and 8, an additional unscheduled visit of Week 6 may be requested at the investigator's or subinvestigator's discretion in order to titrate the dose of the study drug in the subjects when the further decrease in blood pressure is needed.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

Total of 10 subjects to enter the Treatment Period was set in consideration of feasibility.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set will consist of all subjects who were enrolled and received at least 1 dose of study drug for the Treatment Period.

5.2 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who were enrolled and received at least 1 dose of study drug for the Treatment Period. Subjects in this analysis set will be used for efficacy summaries.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

- Day of last observation/test or contact, whichever comes later: Last date of SDTM.SV
- Treatment-emergent adverse event (TEAE): Any AE occurring after the start of TAK-536 administration, and until the end of Follow-up Period (or the test performed at early termination)
- Pretreatment event (PTE): Any AE occurring after obtaining informed consent but before the first study drug administration for the Run-in Period
- Adverse event during the Run-in Period: For subjects who enter the Treatment Period, any AE occurring after the first study drug administration for the Run-in Period until the first study drug administration for the Treatment Period. For subjects who do not enter the Treatment Period, any AE occurring after the first study drug administration for the Run-in Period
- Duration of exposure to study drug for the Treatment Period: Date of the last study drug administration for the Treatment Period − Date of the first study drug administration for the Treatment Period + 1
- Study period after the study drug administration for the Treatment Period: Date of last observation/test or contact − Date of the first study drug administration for the Treatment Period + 1
- Study Drug Compliance for Treatment Period: Total number of doses of study drug for the Treatment Period (Amount of study drug dispensed for the Treatment Period − Amount of study drug returned for the Treatment Period) / Duration of exposure to study drug for the Treatment Period × 100
- Office trough sitting diastolic and systolic blood pressures on each measuring day: The mean of 3 values with rounding to integer on a given measuring day is used as the representative value of that measuring day. If only 2 measurements are obtained on a given measuring day, the mean of the 2 values is used. If only one measurement is obtained on a given measuring day, that value is used.
- Achievement of target blood pressure on each measuring day: Subjects are determined to have achieved their target blood pressures if their office trough sitting diastolic/systolic blood pressures are the <95th percentile (both diastolic and systolic) shown in Table 1 for essential hypertension or <90th percentile (both diastolic and systolic) shown in Table 1 for secondary hypertension. If either systolic or diastolic blood pressure is missing, it will be handled as missing data. The age at the time of informed consent will be used.

- Disease duration (years): (Date of informed consent [year and month] − date of onset [or diagnosis] of underlying disease [year and month]) / 12
  For the date of informed consent, only the year and month will be used. If the year of onset (or diagnosis) of underlying disease is unknown, it will be classified as "Unknown." If only the month of onset (or diagnosis) of underlying disease is unknown, the disease duration will be calculated with the month of onset (or diagnosis) of underlying disease as January.
- QTcF interval: Fridericia's formula (QT interval / [RR interval$^{0.33}$])

6.1.1 Analysis Approach for Continuous Variables

Continuous variables will be summarized using the descriptive statistics (n, mean, standard deviation [SD], minimum, Q1, median, Q3, and maximum) unless stated otherwise in the section specific to an endpoint. The confidence intervals of the mean will be calculated using t-distribution.

6.1.2 Analysis Approach for Binary Variables

Binary and categorical variables will be summarized using the number and percentage of subjects unless stated otherwise in the section specific to an endpoint. The confidence intervals of the proportion will be calculated using Clopper-Pearson method.

6.2 Disposition of Subjects

6.2.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date of First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

6.2.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variables:

Age (years) at Informed Consent [2, 3, 4, 5]

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

6.2.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status [Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]

Primary Reason for Subject Not Being Eligible [Adverse Event, Lost to Follow-up, Screen Failure, Study Termination by Sponsor, Withdrawal by Subject, Other]

Analytical Methods:

(1) Eligibility for Entrance into the Treatment Period

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

6.2.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Status of Entrance into the Treatment Period [Entered]

Category:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Entered the Treatment Period by Site

Frequency distribution will be provided by site.

6.2.5 Disposition of Subjects

6.2.5.1 Treatment of Subjects

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Study Drug Administration Status [Eligible but Not Treated]

Reason for Not Being Treated [Adverse Event, Lack of Efficacy, Lost to Follow-up, Protocol Deviation, Study Terminated by Sponsor, Voluntary Withdrawal, Other]

Analytical Methods:

(1) Treatment of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

6.2.5.2 Disposition of Subjects

Analysis Set:

All Subjects Who administered the Study Drug

Analysis Variables:

Completed study treatment [Completed, Discontinued]

Reason for Discontinuation of Study Treatment [Adverse Event, Death, Lack of Efficacy, Lost to Follow-up, Protocol Deviation, Study Terminated by Sponsor, Voluntary Withdrawal, Other]

Completed study [Completed, Discontinued]

Reason for Discontinuation of Study [Adverse Event, Death, Lack of Efficacy, Lost to Follow-up, Protocol Deviation, Study Terminated by Sponsor, Voluntary Withdrawal, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

6.2.6 Protocol Deviations and Analysis Sets

6.2.6.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Significant Protocol Deviation [Categories by Takeda Controlled Terminology]

Analytical Methods:

(1) Protocol Deviations

The significant protocol deviations are defined as major or critical ones based on the Protocol Deviations Management Plan.

Frequency distribution will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

A listing of all protocol deviations (not only major or critical, but also minor ones) will be provided with the severity and the category by Takeda Controlled Terminology and Protocol Deviations Management Plan.

6.2.6.2 Analysis Sets

Analysis Set:

All Subjects Who Administered the Study Drug

Analysis Variables:

Handling of Subjects	[Subject Evaluability List]	
Analysis Sets	Full Analysis Set	[Included]
	Safety Analysis Set	[Included]

Analytical Methods:

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Other Baseline Characteristics

Analysis Set:

Safety Analysis Set

Analysis Variables:

Age (years) at Informed Consent [2, 3, 4, 5]

Age (years) at Week 0 [2, 3, 4, 5]

Gender [Male, Female]

Height (cm) at Week 0 [Min≤ - <80, 80≤ - <90, 90≤ - <100, 100≤ - <110, 110≤ - <120, 120≤ - ≤Max]

Weight (kg) at Week 0 [Min≤ - <10.0, 10.0≤ - <15.0, 15.0≤ - <20.0, 20.0≤ - <25.0, 25.0≤ - ≤Max]

BMI (kg/m^2) at Week 0 [Min≤ - <15.0, 15.0≤ - <18.0, 18.0≤ - <21.0, 21.0≤ - <24.0, 24.0≤ - <27.0, 27.0≤ - ≤Max]

Disease duration (years) [Min≤ - <0.5, 0.5≤ - <1.0, 1.0≤ - <1.5, 1.5≤ - <2.0, 2.0≤ - <2.5, 2.5≤ - <3.0, 3.0≤ - ≤Max]

Type of hypertension [Essential hypertension, Secondary hypertension]

Drug Induced Hypertension [Yes, No]

History of kidney transplantation [Yes, No]

Antihypertensive drugs prior to Run-in Period [Yes, No]

ACE inhibitors [Yes, No]

ARB [Yes, No]

DRI [Yes, No]

CCB [Yes, No]

Diuretics [Yes, No]

Alpha-blockers [Yes, No]

Beta-blockers [Yes, No]

Other [Yes, No]

RAS inhibitors (ACE inhibitors, ARB, and DRI) prior to Run-in Period [Yes, No]

Antihypertensive drugs at the start of Treatment Period [Yes, No]

CCB [Yes, No]

Diuretics [Yes, No]

Alpha-blockers [Yes, No]

Beta-blockers [Yes, No]

Other [Yes, No]

Steroids at the start of Treatment Period [Yes, No]

Central nervous system stimulants or non-central nervous system stimulants at the start of Treatment Period [Yes, No]

Office sitting blood pressure (systolic) (mmHg) at Week 0 [Min≤ - <110, 110≤ - <120, 120≤ - <130, 130≤ - <140, 140≤ - <Max]

Office sitting blood pressure (diastolic) (mmHg) at Week 0 [Min≤ - <70, 70≤ - <80, 80≤ - <90, 90≤ - <100, 100≤ - <Max]

eGFR (mL/min/1.73 m^2) at Week 0 [Min≤ - <30, 30≤ - <60, 60≤ - <90, 90≤ - <Max]

Analytical Methods:

(1) Summary of Demographics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

Age at Week 0 is defined as the age at date of the first study drug administration for the Treatment Period.

6.3.2 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Underlying Diseases of Secondary Hypertension

Medical History (other than the underlying disease of secondary hypertension)

Concurrent Medical Conditions (other than the underlying disease of secondary hypertension)

Analytical Methods:

(1) Underlying Diseases of Disease Induced Secondary Hypertension by System Organ Class and Preferred Term

(2) Underlying Diseases of Disease Induced Secondary Hypertension by System Organ Class and Preferred Term by Steroids at the Start of Treatment Period

(3) Medical History by System Organ Class and Preferred Term

(4) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

6.4 Medication History and Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medication History

Concomitant Medications [antihypertensive drugs, steroids, central nervous system stimulants or non-central nervous system stimulants, others]

Analytical Methods:

(1) Medication History by Preferred Medication Name

(2) Concomitant Medications by Drug Categories and Preferred Medication Name

(3) Antihypertensive Drugs Except for RAS inhibitors by Drug Categories and Preferred Medication Name in Treatment Period

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication name and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

The concomitant medications will be categorized based on the observed data.

6.5 Efficacy Analysis

6.5.1 Secondary Endpoint(s) Analysis

6.5.1.1 Derivation of Endpoint(s)

Refer to section 6.1.

6.5.1.2 Main Analytical Approach

Analysis Set:

Full Analysis Set

Analysis Variables:

Office trough sitting diastolic blood pressure

Office trough sitting systolic blood pressure

Proportion of subjects who achieved the target blood pressure

Visit:

Week 0, 2, 4, 8, 12, 16, 20, 24, 32, 40, 52, 54 (Follow-up), Week 12 (LOCF), Week 52 (LOCF)

Analytical Methods:

(1) Summary of observed value and change from baseline for office trough sitting diastolic and systolic blood pressure by visit

Descriptive statistics and 95% CI for mean values of observed values and changes from baseline will be provided by visit. Means and standard deviations will be plotted.

(2) Case plot of observed value office trough sitting diastolic and systolic blood pressure over time for each subject

The case plots of observed value over time for each subject will be presented.

(3) Summary of observed value and change from baseline for office trough sitting diastolic and systolic blood pressure in Week 12 (LOCF) with data which are obtained before dosage of the medications permitted with conditions in protocol section 7.3.2 is changed.

Descriptive statistics and 95% CI for mean values of observed values and changes from baseline will be provided in Week 12 (LOCF). The time window in section 9.2.2 will be applied for the data which are obtained until the day of dosage of the medications permitted with conditions in protocol section 7.3.2 is changed.

(4) Proportion of subjects who achieved the target blood pressure by visit

Frequency distributions and 95% CI of proportions will be provided by visit.

(5) Proportion of subjects who achieved the target blood pressure in Week 12 (LOCF) with data which are obtained before dosage of the medications permitted with conditions in protocol section 7.3.2 is changed.

Frequency distributions and 95% CI of proportions will be provided in Week 12 (LOCF). The time window in section 9.2.2 will be applied for the data which are obtained until the day of dosage of the medications permitted with conditions in protocol section 7.3.2 is changed.

6.5.2 Subgroup Analyses

Analysis Set:

Full Analysis Set

Analysis Variables:

Change from baseline for office trough sitting diastolic blood pressure

Change from baseline for office trough sitting systolic blood pressure

Proportion of subjects who achieved the target blood pressure

Visit:

Week 12 (LOCF), Week 52 (LOCF)

Subgroups:

Age (years) at Informed Consent [Min≤3, 4≤Max]

Gender [Male, Female]

Weight (kg) at Week 0 [Min≤ - <15.0, 15.0≤ - ≤Max]

Type of hypertension [Essential hypertension, Secondary hypertension]

RAS inhibitors (ACE inhibitors, ARB, and DRI) prior to Run-in Period [Yes, No]

Antihypertensive drugs at the start of Treatment Period [Yes, No]

Steroids at the start of Treatment Period [Yes, No]

Central nervous system stimulants or non-central nervous system stimulants at the start of Treatment Period [Yes, No]

eGFR (mL/min/1.73 m^2) [Min≤ - <60, 60≤ - <90, 90≤ - ≤Max]

Analytical Methods:

(1) Summary of change from baseline for office trough sitting diastolic and systolic blood pressure by visit by each stratum

Descriptive statistics and 95% CI for mean values of observed values and changes from baseline will be provided by visit by each subgroup.

(2) Proportion of subjects who achieved the target blood pressure by visit by each stratum

Frequency distributions and 95% CI of proportions will be provided by visit by each subgroup.

6.6 Safety Analysis

6.6.1 Adverse Events

6.6.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Relationship to Study Drug [Related, Not Related]

Intensity [Mild, Moderate, Severe]

Analytical Methods:

The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of Serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)

8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum toxicity grade.

- Summaries other than 2), 3), and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

6.6.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Intensity [Mild, Moderate, Severe]

Time of onset (day) [1≤ - ≤14, 15≤ - ≤28, 29≤ - ≤42, 43≤ - ≤56, 57≤ - ≤70, 71≤ - ≤84, 85≤ - ≤Max] [1≤ - ≤84, 85≤ - ≤168, 169≤ - ≤252, 253≤ - ≤336, 337≤ - ≤420, 421≤ - ≤Max]

Analytical Methods:

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(10) Non-serious Treatment-Emergent Adverse Events whose incidence summarized by PT is ≥2% by SOC and PT

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (5), (6) and (9)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

- Summary table for (9)

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.
  When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of

subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

6.6.1.3 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

PTE

Analytical Methods:

The following summaries will be provided using frequency distribution according to section 6.6.1.2.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

6.6.1.4 Displays of Run-in Adverse Events

Analysis Set:

All subjects who received the study drug for the Run-in Period

Analysis Variables:

AEs during the Run-in Period

Analytical Methods:

The following summaries will be provided using frequency distribution according to section 6.6.1.2.

(1) Run-in Adverse Events by System Organ Class and Preferred Term

(2) Serious Run-in Adverse Events by System Organ Class and Preferred Term

6.6.2 Adverse Events of Special Interest

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hypotension-related TEAE

Renal dysfunction-related TEAE

Hyperkalemia-related TEAE

Categories:

Intensity [Mild, Moderate, Severe]

Analytical Methods:

The following summaries will be provided using frequency distribution according to section 6.6.1.2.

(1) Hypotension-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Drug-Related Hypotension-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(3) Renal dysfunction-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(4) Drug-Related Renal dysfunction-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Hyperkalemia-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Drug-Related Hyperkalemia-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

Hypotension-related TEAE, Renal dysfunction-related TEAE and Hyperkalaemia-related TEAE are defined in section 9.2.3.

6.6.3 Clinical Laboratory Evaluations

6.6.3.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Red blood cell, White blood cell count with differential (%) (neutrophil, basophil, eosinophil, lymphocyte, monocyte), Hemoglobin, Hematocrit, Platelets

Serum Chemistry

ALT, Albumin, Alkaline phosphatase, AST, Bilirubin (Total bilirubin), Blood urea nitrogen (BUN), Calcium, Chloride, Creatinine, Creatine kinase, Cystatin C, Estimated Glomerular Filtration Rate (eGFR), Gamma-Glutamyl transferase (GGT), Glucose, Cholesterol (Total cholesterol), Triglyceride, Phosphate, Potassium, Sodium, Protein (Total protein), Lactate dehydrogenase (LDH)

Categories:

Results of determination based on normal reference range [Low, Normal, High]

Visit:

Week 0, 2, 4, 8, 12, 24, 52

Analytical Methods:

The following summaries will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline will be provided by visit.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results by Visit

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

(4) Number and Percentage of Subjects with Markedly Abnormal Values of Serum Chemistry

Overall frequency distributions of MAV during treatment period will be provided. If a laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in section 9.2.4.

6.6.3.2 Urinalysis

Analysis Set:

Safety Analysis Set

Analysis Variables:

Quantitative tests

Protein, Creatinine, Albumin, Protein/creatinine ratio, Albumin/creatinine ratio, Specific Gravity

Qualitative tests

Glucose	[-, +-, 1+, 2+, 3+, 4+, 5+]
pH	[Min <= - <= 8.0, 8.0 < - <= Max]
Protein	[-, +-, 1+, 2+, 3+, 4+, 5+]
Occult blood	[-, +-, 1+, 2+, 3+, 4+, 5+]

Ketones [-, +-, 1+, 2+, 3+, 4+, 5+]

Visit:

Week 0, 2, 4, 8, 12, 24, 52

Analytical Methods:

For quantitative tests, summaries (1), (2) and (3) will be provided.

For qualitative tests, summaries (4) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline will be provided by visit.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results by Visit

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

(4) Number of Subjects in Categories of Urine Laboratory Test Results by Visit

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

6.6.4 Vital Signs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Height, Weight, BMI

Office sitting pulse rate

Home sitting systolic and diastolic blood pressures

Visit:

Weight: Week 0, 12, 24, 40, 52

Height, BMI: Week 0, 24, 52

Office sitting pulse rate: Week 0, 2, 4, 8, 12, 16, 20, 24, 32, 40, 52

Home sitting systolic and diastolic blood pressures: Week 0, 2, 4, 8, 12

Analytical Methods:

The following summaries will be provided.

(1) Summary of Vital Signs and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline will be provided by visit.

(2) Case Plots

Plots over time for each subject will be presented.

6.6.5 12-Lead ECGs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Heart Rate

PR Interval

RR Interval

QRS Interval

QT Interval

QTcF Interval

Interpretation [Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit:

Screening, Week 12, 24, 52

Analytical Methods:

For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided.

For 12-lead ECG interpretation, summary (3) will be provided.

(1) Summary of ECG Parameters and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (screening) will be provided by visit.

(2) Case Plots

Plots over time for each subject will be presented.

(3) Summary of Shift of 12-lead ECG Interpretation by Visit

Shift table showing the number of subjects in each category at baseline (screening) and each post-baseline visit will be provided.

6.6.6 Extent of Exposure and Compliance

6.6.6.1 Extent of Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Duration of Exposure to Study Drug for Treatment Period (days)[1≤ - ≤84, 85≤ - ≤168, 169≤ - ≤252, 253≤ - ≤336, 337≤ - ≤420, 421≤ - ≤Max]

Study Drug Compliance for Treatment Period (%) [Min≤ - <70.0, 70.0≤ - <80.0, 80.0≤ - <90.0, 90.0≤ - ≤Max]

Analytical Methods:

(1) Study Drug Exposure and Compliance

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

6.6.6.2 Dose Corresponding to Each Visit Assessment

Analysis Set:

Safety Analysis Set

Analysis Variables:

Dose (mg/kg) [0.1, 0.2, 0.4, 0.8]

Visit:

Week 0, 2, 4, 8, 12, 16, 20, 24, 32, 40, and End of Treatment Period

Analytical Methods:

(1) Dose on The One Day before Visit

Frequency distributions will be provided.

For the dose at Week 0, the dose on the day of first study drug administration for the Treatment Period will be used. For the dose at Week 2, 4, 8, 12, 20, 24, 32 and 40, the dose on one day before the visit day will be used. For the dose at end of Treatment Period, the dose at the date of the last study drug administration for the Treatment Period will be used.

6.6.6.3 Dose Escalation

Analysis Set:

Safety Analysis Set

Analysis Variables:

Dose (mg/kg) [0.1, 0.2, 0.4, 0.8]

Visit:

Week 0, 2, 4, 8, 12, 16, 20, 24, 32, 40, and End of Treatment Period

Analytical Methods:

(1) Dose by Visit

Frequency distributions will be provided.

For the dose at Week 0, the dose on the day of first study drug administration for the Treatment Period will be used. For the dose at Week 2, 4, 8, 12, 20, 24, 32 and 40, the dose on the visit day will be used. For the dose at end of Treatment Period, the dose at the date of the last study drug administration for the Treatment Period will be used.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Analysis Set:

Subjects who have adequately measured plasma concentration of TAK-536 in FAS

Analysis Variable(s):

Plasma Concentrations of TAK-536, M-I and M-II

Visit:

Week 2 predose, Week 2 postdose, Week 4 predose, Week 4 postdose, Week 8 predose, Week 8 postdose, Week 12 predose, Week 12 postdose, Week 16 postdose,

Analytical Method(s):

The following summaries will be provided. The scheduled visit will be used. Any hours after dose (0.25 hours, 0.5 hours etc.) will be handled as “postdose”.

(1) Summary of Plasma Concentrations by Visit

Descriptive statistics will be provided by visit.

6.8 Interim Analyses

At the time when all subjects complete Week 24 in the Treatment Period, the data until Week 24 in the Treatment Period will be analyzed after being locked. This analysis is not intended to inform the trial for any decisions such as to continue or discontinue this study.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

No changes to protocol planed analyses.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Section	Before Change	After Change	Reason
6.1	Office trough sitting diastolic and systolic blood pressures on each measuring day: The mean of 3 values on a given measuring day is used as the representative value of that measuring day.	Office trough sitting diastolic and systolic blood pressures on each measuring day: The mean of 3 values with rounding to integer on a given measuring day is used as the representative value of that measuring day. If only 2 measurements are obtained on a given measuring day, the mean of the 2 values is used. If only one measurement is obtained on a given measuring day, that value is used.	To clarify the calculation
6.1.1		The confidence intervals of the mean will be calculated using t-distribution.	To specify the method
6.1.2		The confidence intervals of the proportion will be calculated using Clopper-Pearson method.	To specify the method
6.2.2	Age at Informed Consent (years)	Age (years) at Informed Consent	Correction
6.2.6.1	Significant Protocol Deviation [Entry Criteria, Concomitant Medication,	Significant Protocol Deviation [Categories by Takeda Controlled Terminology]	To change the analysis category

	Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]		
6.2.6.1		The significant protocol deviations are defined as major or critical ones based on the Protocol Deviations Management Plan.	To clarify
6.2.6.1		A listing of all protocol deviations (not only major or critical, but also minor ones) will be provided with the severity and the category by Takeda Controlled Terminology and Protocol Deviations Management Plan.	To clarify
6.3.1		Age (years) at Week 0 [2, 3, 4, 5]	To add this analysis
6.3.1	Disease duration (years) [Min≤ - <0.5, 0.5≤ - <1.0, 1.0≤ - <1.5, 1.5≤ - <2.0, 2.0≤ - <2.5, 2.5≤ - <3.0, 3.0≤ - <Max]	Disease duration (years) [Min≤ - <0.5, 0.5≤ - <1.0, 1.0≤ - <1.5, 1.5≤ - <2.0, 2.0≤ - <2.5, 2.5≤ - <3.0, 3.0≤ - ≤Max]	Correction
6.3.1		Drug Induced Hypertension [Yes, No]	To add this analysis
6.3.1	eGFR (mL/min/1.73 m^2) [Min≤ - <30, 30≤ - <60, 60≤ - <90, 90≤ - <Max]	eGFR (mL/min/1.73 m^2) <u>at Week 0</u> [Min≤ - <30, 30≤ - <60, 60≤ - <90, 90≤ - <Max]	To clarify
6.3.1		Age at Week 0 is defined as the age at date of the first study drug administration for the Treatment Period.	To clarify
6.3.2	(1) Underlying Diseases of Secondary Hypertension by System Organ Class and Preferred Term (2) Underlying Diseases of Secondary Hypertension	(1) Underlying Diseases of <u>Disease Induced</u> Secondary Hypertension by System Organ Class and Preferred Term (2) Underlying Diseases of <u>Disease Induced</u> Secondary Hypertension by	To clarify

	by System Organ Class and Preferred Term by Steroids at the Start of Treatment Period	System Organ Class and Preferred Term by Steroids at the Start of Treatment Period	
6.4		(3) Antihypertensive Drugs Except for RAS inhibitors by Drug Categories and Preferred Medication Name in Treatment Period	To add this analysis
6.5.2	Age (years) at Informed Consent [<3, >4] eGFR (mL/min/1.73 m^2) [Min≤ - <60, 60≤ - <89, 90≤ - ≤Max]	Age (years) at Informed Consent [Min≤3, 4≤Max] eGFR (mL/min/1.73 m^2) [Min≤ - <60, 60≤ - <90, 90≤ - ≤Max]	Correction
6.6.1.4	(1) Pretreatment Events by System Organ Class and Preferred Term (2) Serious Pretreatment Events by System Organ Class and Preferred Term	(1) Run-in Adverse Events by System Organ Class and Preferred Term (2) Serious Run-in Adverse Events by System Organ Class and Preferred Term	Correction
6.6.6.2	Dose Escalation	Dose Corresponding to Each Visit Assessment	To clarify this analysis
6.6.6.2	(1) Dose by Visit	Dose on The One Day before Visit	To add this analysis
6.6.6.3		Added this section	To add this analysis
9.2.2		Updated Table 2, and added "*3 If there would be a value that can be used as both of Week 52 and Week 54 (Follow-up Period) by applying the above rule, the value will be used only as Week 52."	Correction
9.2.2	Next, based on Table 3, the mean of the representative values on each measuring day within each time window will be used as the values for each visit.	Next, based on Table 3, the mean of the representative values with rounding to integer on each measuring day within each time window will be used as the values for each visit.	To clarify

9.2 Data Handling Conventions

9.2.1 Definition of Baseline

Baseline values are defined as the last observed value before the first dose of study drug for Treatment Period.

9.2.2 Definition of Visit Windows

For efficacy endpoints in section 6.5, the below time windows will be applied.

When calculating Study Day relative to a reference date (i.e., date of first dose for Treatment Period [Day 1]) , if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

When calculating Follow-up Day relative to a reference date (i.e. date of last dose [Follow-up Day 0]), it will be calculated as: date of observation - reference date. Hence, reference day is always Follow-up Day 0.

All evaluable data (i.e., non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time window will be used. If more than one observation lies within the same time window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used. This does not apply to Week 12 (LOCF) and Week 52 (LOCF).

For Week 12 (LOCF) and Week 52 (LOCF), the last observation obtained in the corresponding time window will be used.

Table 2 Time Window of Office Sitting Blood Pressure

Visit	Scheduled Study Day	Time Window	
		Study Day	Follow-up Day
Week 0	Study Day: 1	−28 to 1	
Week 2	Study Day: 15	2 to 22	< 4
Week 4	Study Day: 29	23 to 43	< 4
Week 8	Study Day: 57	44 to 64	< 4
Week 12	Study Day: 85	65 to 99	< 4
Week 16	Study Day: 113	100 to 127	< 4
Week 20	Study Day: 141	128 to 155	< 4
Week 24	Study Day: 169	156 to 183	< 4
Week 32	Study Day: 225	184 to 253	< 4
Week 40	Study Day: 281	254 to 323	< 4
Week 52	Study Day: 365	324 to 379*3	< 4
Week 54 (Follow-up Period)	Study Day: 379	373 to 393*3	> 0
Week 12 (LOCF)		2 to 99	< 4
Week 12 (LOCF) before Protocol 7.3.2 *1		2 to 99	< 4
Week 52 (LOCF) *2		2 ≤	< 4

*1 Data obtained after the earliest day of addition or dose change of antihypertensive drugs other than RAS inhibitors during the Treatment Period will not be used for summaries.
*2 The condition of *1 will not apply to this handling.
*3 If there would be a value that can be used as both of Week 52 and Week 54 (Follow-up Period) by applying the above rule, the value will be used only as Week 52.

For the safety endpoints in section 6.6 except for home blood pressure, time windows will not be applied, the CRF visits will used for the analyses.

For home blood pressure, the mean of 2 values on a given measuring day will be used as the representative value of that measuring day. If only one measurement is performed on a given measuring day, that value will be used as the representative value. Next, based on Table 3, the mean of the representative values with rounding to integer on each measuring day within each time window will be used as the values for each visit. However, if the representative values on the measuring day within the time window include values for 3 days or less, this visit will be handled as missing. If the time window overlaps at different visits, the value will be included in the earlier visit and excluded from the later visit.

Table 3 Time Window of Home Blood Pressure

Visit	Reference Day	Time Window	
		Number of Days from Reference Day*	Follow-up Day
Week 0 (predose)	Visit day for Week 0	−7 to −1	

Visit	Reference Day	Time Window	
		Number of Days from Reference Day*	Follow-up Day
Week 0 (postdose)	Visit day for Week 0	2 to 8	< 4
Week 2	Visit day for Week 2	2 to 8	< 4
Week 4	Visit day for Week 4	2 to 8	< 4
Week 8	Visit day for Week 8	2 to 8	< 4
Week 12	Visit day for Week 12	−7 to −1	< 4

*: The day before the Reference Day will be defined as Day −1 and the Reference Day as Day 1.

9.2.3 AEs of Special Interest

[Hypotension-related AE]

Hypotension, blood pressure decreased, orthostatic hypotension, blood pressure orthostatic decreased, dizziness, dizziness postural, vertigo, circulatory collapse, shock, loss of consciousness, syncope, and presyncope

[Renal dysfunction-related AE]

Renal failure, acute renal failure, renal impairment prerenal failure, acute prerenal failure, anuria, oliguria, nephropathy toxic, acute phosphate nephropathy, and azotaemia

[Hyperkalemia-related AE]

Blood potassium increased, Hyperkalaemia

9.2.4 Criteria for Markedly Abnormal Values

1) Hematology, Serum Chemistry, Urinalysis, Vital Signs, and 12-lead ECG (except Upper MAV Criteria of QTcF Interval)

For each parameter, all evaluable data (i.e., non-missing data) obtained will be classified as a MAV or not. The criteria in the table below will be used. The lower limit of the normal range and the upper limit of the normal range are abbreviated as LLN and ULN.

Table 4 MAV Criteria for Serum Chemistry

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
ALT (IU/L)	-	-	-	>3×ULN
Albumin (g/dL)	-	-	<2.5	-
Alkaline Phosphatase (IU/L)	-	-	-	>3×ULN
AST (IU/L)	-	-	-	>3×ULN
Bilirubin (mg/dL)	-	-	-	>2.0
Blood Urea Nitrogen (mg/dL)	-	-	-	>30
Calcium (mg/dL)	-	-	<7.0	>11.5

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Chloride (mEq/L)	-	-	<75	>126
Creatinine (mg/dL)	-	-	-	>2.0
Creatine Kinase (CPK) (IU/L)	-	-	-	>5×ULN
Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73m^2)			<30	
Gamma Glutamyl Transferase (GGT) (IU/L)	-	-	-	>3×ULN
Glucose (mg/dL)	-	-	<50	>350
Cholesterol (mg/dL)	-	-	-	>300
Triglycerides (mg/dL)	-	-	-	>2.5×ULN
Phosphate (mg/dL)	-	-	<1.6	>6.2
Potassium (mEq/L)	-	-	<3.0	>6.0
Sodium (mEq/L)	-	-	<130	>150
Protein (g/dL)	-	-	<0.8×LLN	>1.2×ULN

Classifying Subjects for the Overall Treatment Period

For each parameter and subject, classifications will be made according to the conditions i) to iii) provided below. The lower and the upper criteria will be considered separately.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that doesn't meet the MAV criteria will be considered as a subject without MAV.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV for that parameter.

9.3 Analysis Software

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.