Title: A Phase 3, Open-label, Multicenter, Long-term Study to Evaluate the Safety, Efficacy and Pharmacokinetics of TAK-536 in Pediatric Patients 6 to Less Than 16 Years of Age with Hypertension

NCT Number: NCT02791438

Statistical analysis plan Approve Date: 05-OCT-2018

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-536/OCT-101

A Phase 3, Open-label, Multicenter, Long-term Study to Evaluate the Safety, Efficacy and Pharmacokinetics of TAK-536 in Pediatric Patients 6 to Less Than 16 Years of Age with Hypertension

PHASE 3

Version: 1.0

Date: 05 October 2018

Prepared by:

PPD

PPD

Based on:

Protocol Version: Amendment 02

Protocol Date: 12 Apr 2017

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

ACE	angiotensin-converting enzyme
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BBs	beta-blockers
BMI	body mass index
BUN	blood urea nitrogen
CKD	chronic kidney disease
CRO	contract research organization
CT	computed tomography
CCB	calcium channel blocker
CV	coefficient of variation
DRI	direct renin inhibitor
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HPLC/MS/MS	high-performance liquid chromatography with tandem mass spectrometry
Ht	height
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
JCS 2012	Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases by the Japanese Circulation Society
JSH 2014	Guidelines for the Management of Hypertension 2014
LDH	lactate dehydrogenase
LFT	Liver Function Test
LLN	lower limit of normal
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NSAIDs	non-steroidal anti-inflammatory drugs

OTC	over-the-counter
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
PTE	pretreatment event
PTP	press through package
QOL	quality of life
RAS	renin-angiotensin-system
RBC	red blood cell
SAE	serious AE
SAP	statistical analysis plan
SDTM	study data tabulation model
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
SV	subject visits
TEAE	treatment emergent AE
TPC	Takeda Pharmaceutical Company Limited
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WHO Drug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

To evaluate the safety of administration of TAK-536 in pediatric patients aged 6 to less than 16 years with hypertension

4.2 Secondary Objectives

To evaluate the efficacy and pharmacokinetics of administration of TAK-536 in pediatric patients aged 6 to less than 16 years with hypertension

4.3 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 aged 6 to less than 16 years with hypertension.

The study consists of a 2-week Run-in Period, a 52-week Treatment Period (Treatment Period I, 12 weeks; Treatment Period II, 40 weeks), and a 2-week Follow-up Period (56 weeks in total).

(1) Screening and Run-in Period

Subjects eligible at screening will initiate 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. The subjects whose blood pressures meet the inclusion criteria 1 week (at earliest) after receiving placebo in the Run-in Period can enter the Treatment Period. For subjects who have been treated with any antihypertensive drugs as a prior treatment, the Run-in Period can be extended up to 4 weeks if their blood pressures do not meet the inclusion criteria.

Subjects who have been treated with renin-angiotensin-system (RAS) inhibitors (ACE inhibitors, ARB, and DRI) until the start of the Run-in Period should discontinue them at the start of the Run-in Period. Subjects who have been 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 investigator or subinvestigator considers that the subjects need additional treatment for hypertension in Treatment Period I; the antihypertensive drug should be administered under the same dosage at the time of the start of the Run-in Period. If subjects have difficulty in discontinuing antihypertensive drugs completely at the start of the Run-in Period, the antihypertensive drugs can be down-titrated concurrently with the administration of placebo. In the case of down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of Treatment Period I. Specifically, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBs may cause withdrawal syndrome.

(2) Treatment Period I

In Treatment Period I (Week 0 to 12), the initial dose of TAK-536 will be 2.5 mg for subjects weighing < 50 kg or 5 mg for subjects weighing ≥ 50 kg. After the initial dose, TAK-536 will be titrated to 5 mg, 10 mg, and 20 mg for subjects weighing < 50 kg or to 10 mg, 20 mg, and 40 mg for subjects weighing ≥ 50 kg at the investigator's or subinvestigator's discretion when the subjects do not achieve the target blood pressure* and no concerns are found in tolerability. TAK-536 will be titrated at any scheduled visit for Week 2, 4, or 8 in Treatment Period I, as a general rule. Between the visits for Week 4 and 8 during Treatment Period I, an additional unscheduled visit during 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 a further decrease in blood pressure is needed. TAK-536 can be reduced at the investigator's or subinvestigator's discretion if there are any concerns about tolerability with titration of TAK-536 (i.e., in case of the occurrence of any adverse events [AEs] caused by titration of TAK-536). During Treatment Period I, change in the dosage of the antihypertensive drug is prohibited in subjects who are being treated with a single antihypertensive drug other than RAS inhibitors at the start of Treatment Period I.

*target blood pressure:

< 95th percentile shown in Table 5.a Reference Blood Pressure Values of Children by Gender and Age for essential hypertension, < 90th percentile shown in Table 5.a Reference Blood Pressure Values of Children by Gender and Age for secondary hypertension

(3) Treatment Period II

During Treatment Period II (Week 12 to 52), the treatments at the End of Treatment Period I will be continued. TAK-536 can be titrated to the highest dose (20 mg for subjects weighing < 50 kg or 40 mg for subjects weighing ≥ 50 kg, the same hereinafter) at the investigator's or subinvestigator's discretion when the subjects do not achieve the target blood pressure and no concerns are found in tolerability. When the subjects do not achieve the target blood pressure with the highest dose 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.

When the antihypertensive drugs require dose reduction or interruption because of concerns in tolerability with titration in Treatment Period II (i.e., excessive reduction in blood pressure, other AEs, etc.), the antihypertensive drugs other than TAK-536 (in case of concomitant use) should be reduced or interrupted first. Thereafter, dose reduction or interruption of TAK-536 should be considered.

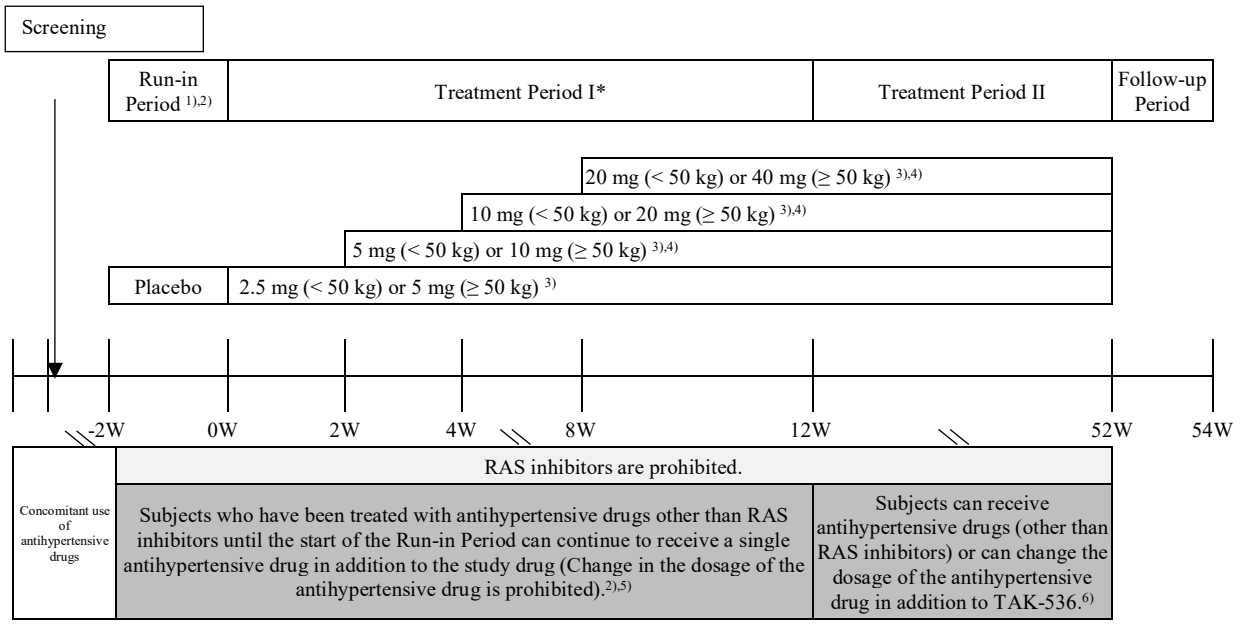
(4) Follow-up Period

The Follow-up Period will be 2 weeks from the day after the final dose of TAK-536. Safety will be evaluated at Week 54 after the start of the Treatment Period.

At the time when the data from approximately 25 subjects are collected, the data until Week 12 in the Treatment Period will be analyzed. In addition, 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 separately after being locked. These analyses will not intend to continue or discontinue this study.

A schematic of the study design is included as Figure 4.a.



1) The subjects whose blood pressures meet the inclusion criteria 1 week (at the earliest) after receiving placebo in the Run-in Period can enter the Treatment Period. For subjects who have been treated with any antihypertensive drugs as a prior treatment, the Run-in Period can be extended up to 4 weeks if their blood pressures do not meet the inclusion criteria.
2) If subjects have difficulty in discontinuing antihypertensive drugs completely at the start of the Run-in Period, the antihypertensive drugs can be down-titrated concurrently with the administration of placebo. In the case of down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of Treatment Period I. Specifically, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBs may cause withdrawal syndrome.
3) In Treatment Period I, TAK-536 can be titrated biweekly when the subjects do not achieve the target blood pressure while evaluating safety and tolerability. TAK-536 can be reduced at the investigator's or subinvestigator's discretion if there are any concerns about tolerability with titration of TAK-536 (i.e., in case of the occurrence of any adverse events [AEs] caused by titration of TAK-536).
4) When the antihypertensive drugs require dose reduction or interruption because of concerns in tolerability with titration in Treatment Period II (i.e., excessive reduction in blood pressure, other AEs, etc.), the antihypertensive drugs other than TAK-536 (in case of concomitant use) should be reduced or interrupted first. Thereafter, dose reduction or interruption of TAK-536 should be considered.
5) Subjects who have been 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 investigator or subinvestigator considers that the subjects need additional treatments for hypertension in Treatment Period I. Change in the dosage of the antihypertensive drug at the start of the Run-in Period I is prohibited until the End of Treatment Period I.
6) In Treatment Period II, when the subjects do not achieve the target blood pressure with the highest dose of TAK-536, the subjects can receive antihypertensive drugs (other than RAS inhibitors) or can change in dosage of the antihypertensive drug in addition to TAK-536 at the investigator's or subinvestigator's discretion.

* Between the visits for Week 4 and 8, an additional unscheduled visit during 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 a further decrease in blood pressure is needed.

Figure 4.a Schematic of Study Design

5.0 ANALYSIS ENDPOINTS

Primary Efficacy Endpoint

<Safety>

AEs, anthropometric (weight, height, and body mass index [BMI]) measurements, laboratory tests, resting 12-lead electrocardiogram (ECG), and vital signs (office standing blood pressure, office sitting pulse rate, office standing pulse rate, and home sitting blood pressure)

Secondary Efficacy Endpoints

<Efficacy>

Office trough* sitting diastolic and systolic blood pressures

* Trough: The time point immediately before the next dosing, when the blood drug concentration is assumed to be lowest

Proportion of subjects who achieve the target blood pressure**

** Target blood pressure: < 95th percentile shown in Table 5.a Reference Blood Pressure Values of Children by Gender and Age for essential hypertension, < 90th percentile shown in Table 5.a Reference Blood Pressure Values of Children by Gender and Age for secondary hypertension

Table 5.a Reference Blood Pressure Values of Children by Gender and Age

	Boy			Girl		
	90th	**95th**	**99th**	**90th**	**95th**	**99th**
6 years old	110/70	114/74	121/82	108/70	111/74	119/81
7 years old	111/72	115/76	122/84	109/71	113/75	120/82
8 years old	112/73	116/78	123/86	111/72	115/76	122/83
9 years old	114/75	118/79	125/87	113/73	117/77	124/84
10 years old	115/75	119/80	127/88	115/74	119/78	126/86
11 years old	117/76	121/80	129/88	117/75	121/79	128/87
12 years old	120/76	123/81	131/89	119/76	123/80	130/88
13 years old	122/77	126/81	133/89	121/77	124/81	132/89
14 years old	125/78	128/82	136/90	122/78	126/82	133/90
15 years old	127/79	131/83	138/91	123/79	127/83	134/91
16 years old	130/80	134/84	141/92	124/80	128/84	135/91

Systolic/diastolic blood pressures (mmHg, JCS2012)
The 90th, 95th, and 99th indicate 90th, 95th, and 99th percentiles, respectively.

<Pharmacokinetics>

Plasma concentrations of TAK-536 and its metabolites (M-I and M-II)

6.0 DETERMINATION OF SAMPLE SIZE

Total of 50 subjects (who enter the Treatment Period).

[Sample Size Justification]

A total of 50 subjects to enter the Treatment Period was set in consideration of feasibility.

Assuming a mean change of trough sitting diastolic blood pressure from the end of the Run-in Period (Week 0) to the end of Treatment Period I of −6.5 mmHg and an SD of 10.5 mmHg, and a mean change of trough sitting systolic blood pressure from the end of the Run-in Period (Week 0) to the end of Treatment Period I of −9.5 mmHg and an SD of 15.5 mmHg, the planned 50 subjects will provide at least 90% power by a 1-sample t-test at a 0.05 significance level (2-sided).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

- 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 first study drug administration for the Treatment Period
- 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
- Summary statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- 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
- Compliance rate with the study drug for the 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 (rounded to 1 decimal place)
- Office trough sitting diastolic and systolic blood pressures on each measuring day: The mean of 3 values on a given measuring day (rounded to integers) is used as the representative value of that measuring day.
- Achievement of target blood pressure on each measuring day: Subjects are determined to have achieved their target blood pressures if their blood pressures are the < 95th percentile (both diastolic and systolic) shown in Table 5.a Reference Blood Pressure Values of Children by Gender and Age for essential hypertension or < 90th percentile (both diastolic and systolic) shown in Table 5.a Reference Blood Pressure Values of Children by Gender and Age 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] − Time of onset [or diagnosis] of underlying disease [year and month]) / 12 (rounded to 1 decimal place)
  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$^{0.33}$])
- CV (%): Standard deviation / mean × 100

7.1.2 Definition of Study Days

- Study Day: The day before the first study drug administration for the Treatment Period will be defined as Day −1 and the day of the first study drug administration for the Treatment Period will be defined as Day 1.
- Follow-up Day: The day after the last study drug administration for the Treatment Period will be defined as Follow-up Day 1.

7.1.3 Definition of Study Visit Windows

For each test, observation, and endpoint except for home blood pressure, all evaluable data (i.e., non-missing data) will be handled according to the following rules.

For each visit other than the End of Treatment Period I and the End of Treatment Period, the evaluable data within the acceptable time window will be used. If more than one evaluable datum lies within the same acceptable time window, the data whose test/observation/evaluation time point is closest to the scheduled time point will be used. If there are two data equidistant to the scheduled time point, the data obtained later will be used. The temporal distance from the scheduled time point will be determined based on the Study Day and the time interval between the latest study drug administration and the blood sample collection.

For the End of Treatment Period I and the End of the Treatment Period, the evaluable data within the acceptable time window with the largest Study Day will be used.

Table 7.a Visit Window of Office Sitting Blood Pressure and Pulse Rate

Visit	Scheduled Study Day	Acceptable Time Window	
		Study Day	Follow-up Day
At the End of Run-in Period (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 71	< 4
Week 12	Study Day: 85	72 to 99	< 4
Week 16 (postdose)	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 372	< 4
Week 54 (Follow-up Period)	Study Day: 379	373 to 386	> 0
At the End of Treatment Period I[*1]		2 to 99	< 4
At the End of Treatment Period[*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. Not applicable for office sitting pulse rate.
*2 The condition of *1 will not apply to this handling. Not applicable for office sitting pulse rate.

Table 7.b Visit Window of Clinical Laboratory Test Items

Visit	Scheduled Study Day	Acceptable Time Window	
		Study Day	Follow-up Day
At the End of Run-in Period (Week 0)	Study Day: 1	−28 to 1	
Week 2	Study Day: 15	2 to 22	< 15
Week 4	Study Day: 29	23 to 43	< 15
Week 8	Study Day: 57	44 to 71	< 15
Week 12	Study Day: 85	72 to 99	< 15
Week 16 (postdose)	Study Day: 113	100 to 141	< 15
Week 24	Study Day: 169	142 to 225	< 15
Week 40	Study Day: 281	226 to 323	< 15
Week 52	Study Day: 365	324 to 379	< 15

Table 7.c Visit Window of Office Standing Blood Pressure and Pulse Rate

Visit	Scheduled Study Day	Acceptable Time Window	
		Study Day	Follow-up Day
At the End of Run-in Period (Week 0)	Study Day: 1	−28 to 1	
Week 12	Study Day: 85	2 to 127	< 4
Week 24	Study Day: 169	128 to 267	< 4
Week 52	Study Day: 365	268 to 379	< 4

Table 7.d Visit Window of Height and Weight

Visit	Scheduled Study Day	Acceptable Time Window	
		Study Day	Follow-up Day
At the End of Run-in Period (Week 0)	Study Day: 1	−28 to 1	
Week 12	Study Day: 85	2 to 127	< 15
Week 24	Study Day: 169	128 to 225	< 15
Week 40	Study Day: 281	226 to 323	< 15
Week 52	Study Day: 365	324 to 379	< 15

Table 7.e Visit Window of Resting 12-lead ECG

Visit	Scheduled Study Day	Acceptable Time Window	
		Study Day	Follow-up Day
At the End of Run-in Period (Week 0)	Study Day: 1	−42 to 1	
Week 12	Study Day: 85	2 to 127	< 15
Week 24	Study Day: 169	128 to 267	< 15
Week 52	Study Day: 365	268 to 379	< 15

Table 7.f Visit Window of Plasma Drug Concentration (day of blood sample collection)

Visit	Scheduled Study Day	Acceptable Time Window
		Study Day
Week 2 (predose, postdose)	Study Day: 15	2 to 22
Week 4 (predose, postdose)	Study Day: 29	23 to 43
Week 8 (predose, postdose)	Study Day: 57	44 to 71
Week 12 (predose, postdose)	Study Day: 85	72 to 99
Week 16 (postdose)	Study Day: 113	100 to 127

Table 7.g Visit Window of Plasma Drug Concentration (time of blood sample collection)

Time Point	Time Interval between the Latest Study Drug Administration and the Blood Sample Collection	
	Scheduled Time	Acceptable Time Window
Predose	24 hours	21 to 27 hours
Postdose	2 hours	1 to 3 hours

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 (do not round off). If only one measurement is performed on a given measuring day, that value will be used as the representative value. Next, based on Table 7.h, the mean of the representative values on each measuring day within each acceptable time window (rounded to integers) 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. At the End of Treatment Period I, among the values from Week 0 (postdose) to Week 12 included based on Table 7.h, the value at the last visit excluding missing data will be used. If the acceptable time window overlaps at different visits, the value will be included in the earlier visit and excluded from the later visit.

Table 7.h Visit Window of Home Blood Pressure

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

7.1.4 Significance Level and Confidence Coefficient

- Significance level: 5% (2-sided test)
- Confidence coefficient: 95% (2-sided estimates)

No statistical testing and calculation of confidence interval will be performed if there are less than 2 subjects to be analyzed.

7.1.5 Conventions for Missing Adverse Event Dates

Not applicable in this study.

7.1.6 Conventions for Missing Concomitant Medication Dates

Not applicable in this study.

7.2 Analysis Sets

- Full analysis set (FAS): All subjects who received at least 1 dose of the study drug for the Treatment Period
- Safety analysis set: All subjects who received at least 1 dose of the study drug for the Treatment Period

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis set:

All subjects who signed the informed consent form

Analysis variable(s):

Date the first subject signed the informed consent form

Date of last observation/test or contact, whichever comes later

MedDRA version

WHO Drug version

SAS version used for creating the data sets

Analytical method(s):

The following analysis will be performed for the above analysis variables.

(1) Display of analysis variables

7.3.2 Screen Failures

Analysis set:

All subjects who did not enter the Treatment Period

Analysis variable(s):

Categories in parenthesis [ ] (hereinafter, the same)

Age (years) [6, 7, 8, 9, 10, 11, 12, 13, 14, 15]

Gender [Male, Female]

Analytical method(s):

The following analysis will be performed for the above analysis variables.

(1) Frequency distributions for categorical variables and summary statistics for continuous variables

7.3.3 Subject Eligibility

Analysis set:

All subjects who signed the informed consent form

Analysis variable(s):

Entrance into the Treatment Period [Yes, No]

Primary reason for subject not entering the Treatment Period [Death, Adverse event, Screening failure, Protocol deviation, Lost to follow-up, Withdrawal by subject, Withdrawal by parent/guardian, Study terminated by sponsor, Pregnancy, Other]

Analytical method(s):

The following analysis will be performed for the above analysis variables.

When calculating the percentages for the primary reasons for subjects not entering the Treatment Period, the total number of subjects who did not enter the Treatment Period will be used as the denominator.

(1) Frequency distributions

7.3.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis set:

All subjects who entered the Treatment Period

Analysis variable(s):

Entrance into the Treatment Period [Yes]

Stratum:

Study Site [Study site number is used for site classification]

Analytical method(s):

The following analysis will be performed for the above analysis variables by each stratum.

(1) Frequency distributions

7.3.5 Disposition of Subjects

Analysis set:

All subjects who entered the Treatment Period

Analysis variable(s):

Completed study drug for the Treatment Period [Completed, Prematurely discontinued]

Reason for discontinuation [Death, Adverse event, Protocol deviation, Lost to follow-up, Withdrawal by subject, Withdrawal by parent/guardian, Study terminated by Sponsor, Pregnancy, Lack of efficacy, Other]

Completed Follow-up Period [Completed, Prematurely discontinued]

Reason for discontinuation [Death, Adverse event, Protocol deviation, Lost to follow-up, Withdrawal by subject, Withdrawal by parent/guardian, Study terminated by Sponsor, Pregnancy, Lack of efficacy, Other]

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups. When calculating the percentages for the reasons for subjects not receiving the study drug, the total number of subjects who did not receive the study drug for the Treatment Period will be used as the denominator and when calculating the percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

(1) Frequency distributions

7.3.6 **Study Drug Completion Status**

Analysis set:

All subjects who entered the Treatment Period

Analysis variable(s):

Completed study drug for the Treatment Period [Completed, Prematurely discontinued]

Reason for discontinuation [Death, Adverse event, Protocol deviation, Lost to follow-up, Withdrawal by subject, Withdrawal by parent/guardian, Study terminated by Sponsor, Pregnancy, Lack of efficacy, Other]

Categories:

Duration of exposure to study drug for the Treatment Period (days) [0, 1≤ - ≤84, 85≤ - ≤168, 169≤ - ≤252, 253≤ - ≤336, 337≤ - ≤420, 421≤ - ≤Max]

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

(1) Frequency distributions by duration of exposure to study drug for the Treatment Period

7.3.7 **Protocol Deviations and Analysis Sets**

7.3.7.1 Protocol Deviations

Analysis set:

All subjects who entered the Treatment Period

Analysis variable(s):

Protocol deviations [Deviations of protocol entry criteria, Deviations concerning excluded medication or therapy, Noncompliance with protocol, Deviations related to the treatment procedure or dose, Deviations of discontinuation criteria, Major GCP violations]

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

Frequency distribution of subjects with protocol deviations will be provided for above each deviation category. A subject who has several deviations that can be classified into the same category will be counted once in each appropriate category (overlapped counting).

(1) Frequency distributions

7.3.7.2 Analysis Sets

Analysis set:

All subjects who entered the Treatment Period

Analysis variable(s):

Handling of subjects in analysis sets [Categories are based on the specifications in Subject Evaluability List]

Inclusion/exclusion of analysis set

Full analysis set [Included]

Safety analysis set [Included]

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

For (1), a subject who falls into several categories will be counted once in each appropriate category (overlapped counting).

(1) Frequency distributions concerning handling of subjects in each analysis set

(2) Frequency distributions concerning number of subjects included in each analysis set

7.4 Demographic and Other Baseline Characteristics

Analysis set:

Safety analysis set

Analysis variable(s):

Age (years) [6, 7, 8, 9, 10, 11, 12, 13, 14, 15]

Gender [Male, Female]

Height (cm) at Week 0 [Min≤ - ≤99, 100≤ - ≤109, 110≤ - ≤119, 120≤ - ≤129, 130≤ - ≤139, 140≤ - ≤149, 150≤ - ≤159, 160≤ - ≤169, 170≤ - ≤179, 180≤ - ≤Max]

Weight (kg) at Week 0 [Min≤ - ≤19.9, 20.0≤ - ≤29.9, 30.0≤ - ≤39.9, 40.0≤ - ≤49.9, 50.0≤ - ≤59.9, 60.0≤ - ≤69.9, 70.0≤ - ≤79.9, 80.0≤ - ≤Max]
[Min≤ - ≤49.9, 50.0≤ - ≤Max]

BMI (kg/m^2) at Week 0 [Min≤ - ≤14.9, 15.0≤ - ≤17.9, 18.0≤ - ≤20.9, 21.0≤ - ≤23.9, 24.0≤ - ≤26.9, 27.0≤ - ≤Max]

Disease duration (years) [Min≤ - ≤0.9, 1.0≤ - ≤1.9, 2.0≤ - ≤2.9, 3.0≤ - ≤3.9, 4.0≤ - ≤Max]

Type of hypertension [Essential hypertension, Secondary hypertension]

- Drug induced hypertension [Yes, No]
- Disease 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 I [Yes, No]

- CCB [Yes, No]
- Diuretics [Yes, No]

Alpha-blockers [Yes, No]

Beta-blockers [Yes, No]

Other [Yes, No]

Office sitting blood pressure (systolic) (mmHg) at Week 0 [Min≤ - ≤109, 110≤ - ≤119, 120≤ - ≤129, 130≤ - ≤139, 140≤ - ≤Max]

Office sitting blood pressure (diastolic) (mmHg) at Week 0 [Min≤ - ≤69, 70≤ - ≤79, 80≤ - ≤89, 90≤ - ≤99, 100≤ - ≤Max]

eGFR (mL/min/1.73 m^2) [Min≤ - ≤29, 30≤ - ≤59, 60≤ - ≤89, 90≤ - ≤Max]

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

(1) Frequency distributions for categorical variables and summary statistics for continuous variables

7.5 Medical History and Concurrent Medical Conditions

Analysis set:

Safety analysis set

Analysis variable(s):

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 method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

Analysis variables will be coded using MedDRA and will be summarized based on SOCs and PTs. SOCs will be sorted alphabetically and PTs will be sorted in decreasing frequency.

(1) Frequency distributions for underlying diseases of secondary hypertension by SOC and PT

(2) Frequency distributions for medical history by SOC and PT

(3) Frequency distributions for concurrent medical conditions by SOC and PT

The frequency distributions will be provided according to the rules below:

[Number of subjects]

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.

7.6 Medication History and Concomitant Medications

Analysis set:

Safety analysis set

Analysis variable(s):

Medication history

Concomitant medications (antihypertensive drugs)

Concomitant medications (other than antihypertensive drugs)

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

Analysis variables will be coded using the WHO Drug and will be summarized based on Preferred Name, which will be sorted in decreasing frequency. A subject who has been administered several medications with the same Preferred Name will be counted only once for that Preferred Name.

(1) Frequency distributions for medication history

(2) Frequency distributions for concomitant medications (antihypertensive drugs) that stopped prior to the study drug administration for the Treatment Period

(3) Frequency distributions for concomitant medications (antihypertensive drugs) that started prior to the study drug administration for the Treatment Period and were ongoing during the Treatment Period

(4) Frequency distributions for concomitant medications (antihypertensive drugs) that started after the study drug administration for the Treatment Period

(5) Frequency distributions for concomitant medications that started prior to the study drug administration for the Treatment Period and were ongoing during the Treatment Period and concomitant medications (other than antihypertensive drugs) that started after the study drug administration for the Treatment Period

7.7 Study Drug Exposure and Compliance

7.7.1 Study Drug Exposure and Compliance

Analysis set:

Safety analysis set

Analysis variable(s):

Duration of exposure to study drug for the Treatment Period (days) [1≤ - ≤84, 85≤ - ≤168, 169≤ - ≤252, 253≤ - ≤336, 337≤ - ≤420, 421≤ - ≤Max]

Study drug compliance rate for the Treatment Period (%) [Min≤ - ≤69.9, 70.0≤ - ≤79.9, 80.0≤ - ≤89.9, 90.0≤ - ≤Max]

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

(1) Frequency distributions for categorical variables and summary statistics for continuous variables

7.7.2 Dose Escalation

Analysis set:

Safety analysis set

Analysis variable(s):

Dose dispensed at each visit [2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg]

Visit:

Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 32, 40, and at the End of Treatment Period

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

For the dose dispensed at each visit, the dose dispensed on the day of first study drug administration for the Treatment Period will be used for Week 0 and the dose dispensed on the day before the visit day will be used except for Week 0. If dose on the visit day is missing, the last dose dispensed by the scheduled study day (Days 1, 15, 29, 43, 57, 85, 113, 141, 169, 225, and 281 for Weeks 0, 2, 4, 6, 8, 12, 16, 20, 24, 32, and 40, respectively [the day of the first study drug administration for the Treatment Period to be defined as Day 1]) will be used until the day of study drug discontinuation. After the day of study drug discontinuation, the dose dispensed on that visit will be handled as missing and excluded from summaries.

The dose dispensed at the End of the Treatment Period will be the last dose dispensed for each subject.

(1) Frequency distributions

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

The safety endpoints are the primary endpoints in this study.

7.8.2 Secondary Efficacy Endpoint(s)

Analysis set:

Full analysis set

Analysis variable(s):

Office trough sitting diastolic blood pressure

Office trough sitting systolic blood pressure

Proportion of subjects who achieved the target blood pressure

Visit:

Weeks 0, 2, 4, 8, 12, 16 (postdose), 20, 24, 32, 40, 52, 54 (Follow-up Period), at the End of Treatment Period I, and at the End of Treatment Period

Analytical method(s):

The following analyses (1) and (2) will be performed for office trough sitting diastolic and systolic blood pressures by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

The following analysis (3) will be performed for the proportion of subjects who achieved the target blood pressure by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

The measurement at Week 16 (postdose) will be performed after the study drug administration, while the measurement at other visits than Week 16 (postdose) will be performed before the study drug administration.

(1) Summary statistics and 2-sided 95% confidence intervals of means at each visit will be calculated.

(2) Summary statistics and 2-sided 95% confidence intervals of means will be calculated for changes (each visit after Week 2 − Week 0) at each visit. For the population in the combined weight groups, a one-sample t-test will be applied for reference.

(3) Frequency distributions will be provided at each visit and the 2-sided 95% confidence interval of the proportion will be calculated.

7.8.3 Additional Efficacy Endpoint(s)

Analysis set:

Full analysis set

Analysis variable(s):

Home sitting diastolic blood pressure

Home sitting systolic blood pressure

Visit:

Weeks 0 (predose), 0 (postdose), 2, 4, 8, 12, and at the End of Treatment Period I

Analytical method(s):

The following analyses will be performed for home sitting diastolic and systolic blood pressures by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

(1) Summary statistics and 2-sided 95% confidence intervals of means at each visit will be calculated.

(2) Summary statistics and 2-sided 95% confidence intervals of means will be calculated for changes (each visit after Week 0 (postdose) − Week 0 (predose) at each visit. For the population in the combined weight groups, a one-sample t-test will be applied for reference.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable in this study.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results will be excluded from statistical analyses and estimations for that item. Plasma concentrations and clinical laboratory data below the lower limit of quantification will be handled as 0. Clinical laboratory data above the upper limit of quantification will be handled as the upper limit of quantification.

7.8.4.3 Multicenter Studies

This is a single arm study, and thus no arms-sites interaction will be analyzed.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable in this study.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable in this study.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

Not applicable in this study.

7.8.4.7 Examination of Subgroups

Analysis set:

Full analysis set

Analysis variable(s):

Office trough sitting diastolic blood pressure (change at the End of Treatment Period I)

Office trough sitting systolic blood pressure (change at the End of Treatment Period I)

Proportion of subjects who achieved the target blood pressure (at the End of Treatment Period I)

Stratum:

Gender [Male, Female]

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 I [Yes, No]

eGFR (mL/min/1.73 m^2) [Min≤ - ≤59, 60≤ - ≤89, 90≤ - ≤Max]

Analytical Method(s):

The following analysis (1) will be performed for office trough sitting diastolic and systolic blood pressures by each stratum. The following analysis (2) will be performed for the proportion of subjects who achieved the target blood pressure by each stratum.

(1) Summary statistics

(2) Frequency distributions

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Analysis set:

Subjects who underwent proper determination of plasma concentrations of TAK-536 in the "full analysis set"

Analysis variable(s):

Plasma concentrations of TAK-536 and its metabolites (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), and Week 16 (postdose)

Analytical method(s):

The following analysis (1) will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups. The dose immediately before the blood sample collection for plasma concentrations will be used. The following analysis (2) will be performed in the combined weight groups.

(1) Summary statistics and CV (%) by dose at each visit

(2) A scatter plot for TAK-536 plasma concentration at Week 2 (predose) and changes in office sitting blood pressure (diastolic and systolic) at the same visit will be presented.

7.9.2 Pharmacodynamic Analysis

Not applicable in this study.

7.10 Other Outcomes

Not applicable in this study.

7.11 Safety Analysis

The safety endpoints are the primary endpoints in this study.

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis set:

Safety analysis set

Analysis variable(s):

TEAE

Categories:

Relationship to study drug	[Related, Not related]
Intensity	[Mild, Moderate, Severe]

Analytical method(s):

The following summaries will be provided for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

(1) Overview of TEAE

1) All TEAEs (number of events, number and percentage of subjects)
2) Relationship of all TEAEs to study drug (number of events, number and percentage of subjects)
3) Intensity of all TEAEs (number of events, number and percentage of subjects)
4) TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious TEAEs (number of events, number and percentage of subjects)
6) Relationship of serious TEAEs to study drug (number of events, number and percentage of subjects)
7) Serious TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
8) TEAEs resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below:

[Number of subjects]

- In case of "summaries by relationship to study drug"

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

- In case of "summaries by intensity"

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

- In case of summaries other than the above

  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.

7.11.1.2 Displays of Treatment-Emergent Adverse events

Analysis set:

Safety analysis set

Analysis variable(s):

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 method(s):

The following summaries will be provided for the above analysis variables using frequency distributions by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

TEAEs will be coded using MedDRA and will be summarized based on SOCs and PTs. SOCs will be sorted alphabetically and PTs 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 SOC only or PT only.

See "9.0 APPENDIX" for definitions of the TEAEs related to hypotension and renal dysfunction.

(1) All TEAEs by SOC and PT

(2) All TEAEs by SOC

(3) All TEAEs by PT

(4) Drug-related TEAEs by SOC and PT

(5) Intensity of all TEAEs by SOC and PT

(6) Intensity of drug-related TEAEs by SOC and PT

(7) TEAEs leading to study drug discontinuation by SOC and PT

(8) Serious TEAEs by SOC and PT

(9) All TEAEs by SOC and PT over time

(10) TEAEs related to hypotension by SOC and PT

(11) TEAEs related to renal dysfunction by SOC and PT

(12) Non-serious TEAEs whose incidence summarized by PT is ≥ 2% by SOC and PT

The frequency distribution and incidence will be provided according to the rules below:

[Number of subjects]

- In case of “summaries by SOC and PT, by SOC only, or PT only”

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Also, when calculating the percentages for TEAEs, the number of subjects in the safety analysis set will be used as the denominator.

- In case of “summaries of intensity by SOC and PT”

  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. Also, when calculating the

percentages for TEAEs, the number of subjects in the safety analysis set will be used as the denominator.

- In case of "summaries by SOC and PT over time"

  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 the percentages of TEAEs for each time interval, the number of subjects at risk (i.e., "subjects who either have an exposure to study drug 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.

7.11.1.3 Displays of Pretreatment Events

Analysis set:

All subjects who signed the informed consent form

Analysis variable(s):

PTE

Analytical method(s):

The following analysis will be performed for the above analysis variables using frequency distributions.

PTEs will be coded using MedDRA and will be summarized based on SOCs and PTs. SOCs will be sorted alphabetically and PTs will be sorted in decreasing frequency.

(1) All PTEs by SOC and PT

(2) Serious PTEs by SOC and PT

The frequency distributions will be provided according to the rules below:

[Number of subjects]

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.11.1.4 Displays of Run-in Adverse Events

Analysis set:

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

Analysis variable(s):

AEs during the Run-in Period

Analytical method(s):

The following analysis will be performed for the above analysis variables using frequency distributions.

AEs during the Run-in Period will be coded using MedDRA and will be summarized based on SOCs and PTs. SOCs will be sorted alphabetically and PTs will be sorted in decreasing frequency.

(1) All AEs during the Run-in Period by SOC and PT

(2) Serious AEs during the Run-in Period by SOC and PT

The frequency distributions will be provided according to the rules below:

[Number of subjects]

A subject with multiple occurrences of AE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of AE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety analysis set

Analysis variable(s):

Hematology

Red blood cell count, White blood cell count with differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes), Hemoglobin, Hematocrit, Platelets

Serum Chemistry

ALT, Albumin, ALP, AST, Total bilirubin, BUN, Calcium, Chloride, Creatinine, Creatinine kinase, Cystatin C, eGFR, GGT, Glucose, Total cholesterol, Triglycerides, Phosphate, Potassium, Sodium, Total Protein, LDH

Categories:

Results of determination based on normal reference range [Below lower limit of normal range, Within normal range, Over upper limit of normal range]

Visit:

Weeks 0, 2, 4, 8, 12, 16 (postdose), 24, 40, and 52

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

When performing analyses on MAV, if a laboratory parameter has both lower and upper MAV criteria, an analysis will be performed for each. See "9.0 APPENDIX" for test items to be analyzed and definitions of MAV criteria.

The measurement at Week 16 will be performed after the study drug administration, while the measurement at other visits than Week 16 will be performed before the study drug administration.

(1) Summary statistics for observed values and changes (each visit after administration [Week 2 to Week 52] − Week 0) will be provided for each visit.

(2) Case Plots

(3) Shift tables showing results of determination based on normal reference range at Week 0 and each visit after administration

(4) Overall frequency distributions of MAV during the Treatment Period

7.11.2.2 Urinalysis

Analysis set:

Safety analysis set

Analysis variable(s):

Quantitative variable(s)

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

Qualitative variable(s)

Glucose, pH, Protein, Occult blood, Ketones

Categories:

Results of determination based on normal reference range [Below lower limit of normal range, Within normal range, Over upper limit of normal range]

Visit:

Weeks 0, 2, 4, 8, 12, 16 (postdose), 24, 40, and 52

Analytical method(s):

The following analyses (1), (2), and (4) will be performed for the quantitative variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

The following analyses (3) and (4) will be per formed for the qualitative variables, by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

The measurement at Week 16 will be performed after the study drug administration, while the measurement at other visits than Week 16 will be performed before the study drug administration.

(1) Summary statistics for observed values and changes (each visit after administration [Week 2 to Week 52] − Week 0) will be provided for each visit.

(2) Case Plots

(3) Shift tables at Week 0 and each visit after administration

(4) Shift tables showing results of determination based on normal reference range at Week 0 and each visit after administration (variables with normal reference range)

7.11.3 **Vital Signs and Weight**

Analysis set:

Safety analysis set

Analysis variable(s):

Office sitting pulse rate

Office standing systolic blood pressure, Office standing diastolic blood pressure, Office standing pulse rate

Home sitting systolic and diastolic blood pressures

Height, Weight

Visit

Office sitting pulse rate: Weeks 0, 2, 4, 8, 12, 16 (postdose), 20, 24, 32, 40, 52, 54 (Follow-up Period)

Office standing blood pressure and pulse rate: Weeks 0, 12, 24, and 52

Home blood pressure: Week 0 (predose), Week 0 (postdose), Weeks 2, 4, 8, and 12

Height and weight: Weeks 0, 12, 24, 40, and 52

Analytical method(s):

The following analysis will be performed for the above analysis variables by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

The measurement of office sitting pulse rate at Week 16 will be performed after the study drug administration, while the measurement at other visits than Week 16 will be performed before the study drug administration.

(1) Summary statistics for observed values and changes (each visit after administration [each visit other than Week 0] − Week 0) will be provided for each visit.

Home blood pressure will be provided for changes (each visit after administration [each visit other than Week 0 (predose)] − Week 0 [predose]).

(2) Case Plots

(3) Overall frequency distributions of home blood pressure during the Treatment Period. See "9.0 APPENDIX" for the criteria."

7.11.4 **12-Lead ECGs**

Analysis set:

Safety analysis set

Analysis variable(s):

Heart rate

RR interval

PR interval

QT interval

QTcF interval

QRS interval

Resting 12-lead ECG interpretation [Within normal limits, Abnormal but not clinically significant, Abnormal and clinically significant]

Visit:

Weeks 0, 12, 24, and 52

Analytical method(s):

The following analyses (1) and (2) will be performed for the above analysis variables excluding resting 12-lead ECG interpretation by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

The following analysis (3) will be performed for resting 12-lead ECG interpretation by weight group (< 50 kg, ≥ 50 kg) and in the combined weight groups.

(1) Summary statistics for observed values and changes (each visit after administration [Week 12 to Week 52] − Week 0) will be provided for each visit.

(2) Case Plots

(3) Shift tables at Week 0 and each visit after administration

7.11.5 Other Observations Related to Safety

7.11.5.1 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis set:

Safety analysis set

Analysis variable(s):

TEAE

Analytical method(s):

The similar summaries as Section 7.11.1.2 will be provided for the above analysis variables. All summaries will be presented in Japanese.

7.12 Interim Analysis

At the time when the data from approximately 25 subjects are collected, the data until Week 12 in the Treatment Period will be analyzed. In addition, 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 separately after being locked. These analyses will not intend to continue or discontinue this study.

The analyses at Week 12 will be performed only for items required to examine the study design for subjects aged less than 6 years in this statistical analysis plan. Specifically, they are 7.3.5, 7.3.6, 7.4, 7.5, 7.7.1, 7.7.2, 7.8.2, 7.8.4.7, 7.9.1 (1), 7.11.1, 7.11.1.2, (1), (4) to (11) (and the corresponding Japanese analysis [7.11.5.1]), and 7.11.2.1. The results of these analyses will be included in the consultation materials with regulatory authorities and not included in the clinical study report. Additional analyses may be performed in response to changes in the policy for preparing consultation materials or requests from regulatory authorities. In such cases, the statistical analysis plan will not be revised or the additional analysis plan will not be prepared.

7.13 Changes in the Statistical Analysis Plan

Although home blood pressure is defined as a safety endpoint in the protocol, it will be also evaluated as an efficacy endpoint as described in 7.8.3 in this statistical analysis plan.

8.0 REFERENCES

Not applicable.

9.0 APPENDIX

9.1 AEs of Special Interest

Table 9.a Hypotention-related AE

PT_NAME	PT_CODE
Bezold-Jarisch reflex	10076999
Blood pressure ambulatory decreased	10005731
Blood pressure decreased	10005734
Blood pressure diastolic decreased	10005737
Blood pressure immeasurable	10005748
Blood pressure orthostatic abnormal	10053354
Blood pressure orthostatic decreased	10053356
Blood pressure systolic decreased	10005758
Blood pressure systolic inspiratory decreased	10005761
Capillary leak syndrome	10007196
Cardiogenic shock	10007625
Cardiovascular insufficiency	10065929
Circulatory collapse	10009192
CT hypotension complex	10078280
Diastolic hypotension	10066077
Dizziness	10013573
Dizziness exertional	10013576
Dizziness postural	10013578
Hypoperfusion	10058558
Hypotension	10021097
Hypotensive transfusion reaction	10072264
Hypovolaemia	10021137
Hypovolaemic shock	10021138
Mean arterial pressure decreased	10026983
Mesenteric traction syndrome	10069699
Neonatal hypotension	10049223
Obstructive shock	10073708
Orthostatic hypotension	10031127
Orthostatic intolerance	10063927
Presyncope	10036653
Procedural hypotension	10062300
Shock	10040560
Shock haemorrhagic	10049771
Shock symptom	10040581
Syncope	10042772
Vascular resistance systemic decreased	10047106
Vasoplegia syndrome	10067080
Loss of consciousness	10024855
Vertigo	10047340

MedDRA Version 21.0

Table 9.b Renal Dysfunction-related AE

PT_CODE	PT_NAME
10069339	Acute kidney injury
10069688	Acute phosphate nephropathy
10002847	Anuria
10003885	Azotaemia
10066338	Continuous haemodiafiltration
10061105	Dialysis
10078987	Foetal renal impairment
10018875	Haemodialysis
10053090	Haemofiltration
10077515	Hyponatriuria
10049778	Neonatal anuria
10029155	Nephropathy toxic
10030302	Oliguria
10034660	Peritoneal dialysis
10072370	Prerenal failure
10038435	Renal failure
10038447	Renal failure neonatal
10062237	Renal impairment
10049776	Renal impairment neonatal

MedDRA Version 21.0

9.2 Criteria for Markedly Abnormal Values

For each test item, MAV will be determined according to the table below for evaluable data (i.e., non-missing data) obtained within 14 days after the last study drug administration for the Treatment Period (including Day 14 after the last study drug administration for the Treatment Period; the day after the last study drug administration for the Treatment Period to be defined as Day 1). The lower limit of the normal range and the upper limit of the normal range of each test item are abbreviated as LLN and ULN in the table below.

Table 9.c MAV Criteria for Serum Chemistry

Test Item	Gender	Age (years)	MAV Criteria	
			Lower	Upper
BUN (mg/dL)	-	-	-	> 30
Chloride (mEq/L)	-	-	< 75	> 126
Creatinine (mg/dL)	-	-	-	> 2.0
Potassium (mEq/L)			< 3.0	> 6.0
Sodium (mEq/L)			< 130	> 150
eGFR (mL/min/1.73 m^2)			< 30	
ALT (IU/L)	-	-	-	> 3 × ULN
AST (IU/L)	-	-	-	> 3 × ULN
GGT (IU/L)	-	-	-	> 3 × ULN
Total bilirubin (mg/dL)	-	-	-	> 2.0
Creatinine kinase (U/L)				> 5×ULN

Classifying Subjects for the Overall Treatment Period

For each test item and subject, MAV will be determined according to the conditions [1] to [3] provided below. If there are criteria for "Upper" and "Lower" in the MAV Criteria for the same test item, the determination will be made for each criterion.

[1] A subject will be classified as those "with MAV" if he/she has at least one data that "meets the MAV Criteria" among the evaluable data obtained after the study drug administration for the Treatment Period.

[2] A subject will be classified as those "without MAV" if he/she does not meet condition [1] and has at least one data that does "not meet the MAV Criteria" among the evaluable data obtained after the study drug administration for the Treatment Period.

[3] A subject who does not meet conditions [1] or [2] will be excluded from the analysis of MAV for that item.

9.3 Criteria for Home Blood Pressure

For each test item, home blood pressure will be determined according to the table below for evaluable data (i.e., non-missing data) obtained within 3 days after the last study drug administration for the Treatment Period (including Day 3 after the last study drug administration for the Treatment Period; the day after the last study drug administration for the Treatment Period to be defined as Day 1). The value before calculating the representative value on each measuring day (value described in the case report form) will be used for this determination.

Table 9.d Criteria for Home Blood Pressure

Test Item	Gender	Age (years)	Criteria	
			Lower	Upper
Home sitting systolic blood pressure (mmHg)	-	-	-	≥ 99th percentile of Table 5.a + 15 mmHg
Home sitting diastolic blood pressure (mmHg)	-	-	-	≥ 99th percentile of Table 5.a + 10 mmHg

Classifying Subjects for the Overall Treatment Period

For each test item and subject, home blood pressure will be determined according to the conditions [1] to [3] provided below.

[1] A subject will be classified as those "with markedly abnormal blood pressure" if he/she has at least one data that "meets the Criteria for Home Blood Pressure" among the evaluable data obtained after the study drug administration for the Treatment Period.

[2] A subject will be classified as those "without markedly abnormal blood pressure" if he/she does not meet condition [1] and has at least one data that does "not meet the Criteria for Home Blood Pressure" among the evaluable data obtained after the study drug administration for the Treatment Period.

[3] A subject who does not meet conditions [1] or [2] will be excluded from the analysis of home blood pressure for that item.