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

Protocol Approve Date: 12-APR-2017

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

PROTOCOL

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

A Phase 3 Long-term Study of TAK-536 in Pediatric Patients 6 to Less Than 16 Years with Hypertension

Sponsor: Takeda Pharmaceutical Company Limited
1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Study Number: TAK-536/OCT-101

IND Number: Not Applicable **EudraCT Number:** Not Applicable

Compound: TAK-536

Date: 12 Apr 2017 **Amendment Number:** 02

Amendment History:

Date	Amendment Number	Region
16 March 2016	First version	All sites
12 May 2016	01	All sites
12 April 2017	02	All sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the attachments.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

1.3 Protocol Amendment 02 Summary of Changes

Reporting items are added to collect the information accurately about the action taken with the study drug when AEs occurred. Detailed description of amendments are given in Appendix C.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

CCI [redacted]

2.0 STUDY SUMMARY

<table>
<tr><td>Clinical Study Sponsor:
Takeda Pharmaceutical Company Limited</td><td colspan="2">Compound:
TAK-536</td></tr>
<tr><td>Study 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</td><td>IND No.:
Not Applicable</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td>Study Identifier: TAK-536/OCT-101</td><td colspan="2">Phase: 3</td></tr>
<tr><td colspan="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-week; Treatment Period II, 40-week), and a 2-week Follow-up Period (56 weeks in total).
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 the subjects only who treated with any antihypertensive drugs as a prior treatment, the Run-in Period could be extended up to 4 weeks if blood pressures do not meet the inclusion criteria. Subjects who 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 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 treatments for hypertension in the Treatment Period I by the investigator or subinvestigator; 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 administration of placebo. In the case of the down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period I. Especially, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBS may cause withdrawal syndrome.
In the Treatment Period I (Week 0 to 12), initial dose of TAK-536 will be 2.5 mg for the subjects weighing < 50 kg or 5 mg for the subjects weighing ≥ 50 kg. After the initial dose, TAK-536 will be titrated to 5 mg, 10 mg, and 20 mg for the subjects weighing < 50 kg or to 10 mg, 20 mg, and 40 mg for the subjects weighing ≥ 50 kg when the subjects do not achieve the target blood pressure and there are no concerns in tolerability. TAK-536 will be titrated at any scheduled visit of Week 2, 4, or 8 in the Treatment Period I. Between the visits of Week 4 and 8 during the Treatment Period I, an additional unscheduled visit of Week 6 may be requested at the investigator's discretion in order to titrate the dose of the study drug in the subjects when the 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 in tolerability with titration of TAK-536 (i.e., in case of occurring any AEs caused by titration of TAK-536). During the Treatment Period I, change in the dosage of the antihypertensive drug is prohibited in the subjects who treated with a single antihypertensive drug other than RAS inhibitors at the start of the Treatment Period I.
During the Treatment Period II (Week 12 to 52), the treatments at the end of the Treatment Period I will be continued. TAK-536 can be titrated to the highest dose (20 mg for the subjects weighing < 50 kg or 40 mg for the 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. When the antihypertensive drugs are required dose reduction or interruption because of the concerns in tolerability with titration (i.e., excessive reduction in blood pressure, other AE, etc.) in the Treatment Period II, the antihypertensive drugs other than TAK-536 (in case of concomitant use) should be reduced or interrupted first. Thereafter, dose reduction or</td></tr>
</table>

<table>
<tr><td colspan="2">interruption of TAK-536 should be considered.
Follow-up Period will be 2 weeks from the next day of 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.</td></tr>
<tr><td colspan="2">Primary Objectives:
To evaluate the safety of administration of TAK-536 in pediatric patients aged 6 to less than 16 years with hypertension</td></tr>
<tr><td colspan="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</td></tr>
<tr><td colspan="2">Subject Population: Pediatric patients aged 6 to less than 16 years, with essential or secondary hypertension.</td></tr>
<tr><td>Planned Number of Subjects:
Total of 50 subjects (who enter the Treatment Period).</td><td>Planned Number of Sites:
Approximately 25 sites</td></tr>
<tr><td>Dose Level(s):
Regimen: Subjects will orally receive the study drug once daily before or after breakfast.
Dose: Placebo during the Run-in Period. Any of TAK-536 2.5 mg, 5 mg, 10 mg, 20 mg tablet for the subjects weighing < 50 kg, or any of TAK-536 5 mg, 10 mg, 20 mg, 40 mg tablet for those weighing ≥ 50 kg during the Treatment Period.</td><td>Route of Administration:
Oral</td></tr>
<tr><td>Duration of Treatment:
52 weeks</td><td>Study Length:
2 weeks of the Run-in Period (acceptable range, 1 to 4 weeks), 52 weeks of the Treatment Period (12 weeks of the Treatment Period I and 40 weeks of the Treatment Period II), 2 weeks of the Follow-up Period</td></tr>
</table>

Main Criteria for Inclusion:

- The Japanese subject who has a diagnosis of hypertension. A subject is eligible if he/she is deemed hypertensive according to the reference blood pressure values of children by gender and age; office sitting diastolic or systolic blood pressure ≥ 95 percentile for essential hypertension without concomitant hypertensive organ damage, and ≥ 90 percentile for secondary hypertension with concomitant chronic kidney disease (CKD), diabetes mellitus, heart failure or any hypertensive organ damage.
  In addition, subjects need to meet the following criteria:
  (1) If currently treated with any antihypertensive drugs at the start of the Run-in Period: Subject has a documented historical diagnosis of hypertension and an office sitting diastolic or systolic blood pressure meeting the above criteria at the end of the Run-in Period (Week 0).
  (2) If currently untreated with any antihypertensive drugs at the start of the Run-in Period: Subject who meets the above criteria on 3 separate time points including screening and the end of the Run-in Period (Week 0). In addition, subject with essential hypertension without concomitant hypertensive organ damage still maintains hypertension with non-pharmacotherapy including foods or exercises for at least 3 months within 1 year prior to the start of screening.
- The subject is male or female and aged 6 to less than 16 years at the time of informed consent.
- The subject weighs at least 20 kg at screening.
- A subject who has undergone kidney transplantation is eligible if he/she underwent the transplantation at least 6 months earlier at screening, and the graft has been functionally stable (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2) for at least 6 months with evidence (e.g., Doppler echography, CT scan [computed tomography] or MRI [magnetic resonance imaging]) excluding grafted kidney arterial stenosis. A subject on immunosuppressive therapy with a stable dose at least 30 days prior to screening is eligible.

Main Criteria for Exclusion:

- The subject has poorly controlled hypertension indicated by an office sitting systolic blood pressure higher by at least 15 mmHg and/or an office sitting diastolic blood pressure higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age.
- The subject has a diagnosis of malignant or accelerated hypertension.
- The subject was noncompliant (< 70% or > 130%) with the study drug during the Run-in Period.
- The subject has severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), is receiving dialysis, has a renovascular disease affecting one or both kidneys, severe nephrotic syndrome not in remission, or a serum albumin level < 2.5 g/dL.
- The subject has a history of, or the signs/symptoms of serious cardiovascular, hepatobiliary, gastrointestinal, endocrine (eg, hyperthyroidism, Cushing's syndrome), hematological, immunological, urinogenital, psychiatric disease, cancer, or any other disease that adversely affects subject's health, or, in the opinion of the investigator or subinvestigator, potentially confounds the study results.
- The subject has hemodynamically significant left ventricular outflow obstruction due to aortic stenosis or aortic valvular disease, or is scheduled to undergo a medical procedure affecting blood pressure during the study (eg, correction of arterial anomaly).
- The subject has a history of or concurrent clinically significant abnormality of 12-lead electrocardiogram (ECG) that, in the opinion of the investigator or subinvestigator, disqualifies the subject for participation in the study.
- The subject has poorly controlled diabetes mellitus indicated by HbA1c > 9.0% at screening.
- The subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 2.5 × the upper limit of normal (ULN), or a total bilirubin level ≥ 1.5 × ULN at screening, severely impaired hepatic function, any active liver disease, or jaundice.
- The subject has hyperkalemia exceeding ULN at screening.

Main Criteria for Evaluation and Analyses:

(1) Primary Endpoint

<Safety>

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

(2) Secondary endpoints

<Efficacy>

- Office trough sitting systolic and diastolic blood pressure
- Proportion of subjects who achieve the target blood pressure*

*: < 95 percentile shown in a table of the reference blood pressure values of children by gender and age for essential hypertension, < 90 percentile shown in the same table for secondary hypertension

<Pharmacokinetic endpoints>

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

Statistical Considerations:

<Primary endpoints and analytical methods>

[Primary endpoints]

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

[Analytical methods]

The following analyses will be conducted with the safety analysis set.

(1) AEs (Treatment-emergent AEs)

A treatment-emergent AE (TEAE) is defined as any AE occurring after the start of TAK-536 administration of the Treatment Period.

The incidence of TEAEs listed below will be analyzed. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The frequency distribution will be provided using the system organ class (SOC) and preferred term (PT) using MedDRA as follows:

- TEAEs
- Drug-related TEAEs
- Severity of TEAEs
- Severity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs overt time

(2) Anthropometric (weight, height and BMI) measurements, laboratory tests, resting 12-lead ECG, and vital signs (office standing blood pressure, office sitting pulse rate, office standing pulse rate, and home sitting blood pressure)

For continuous variables, the observed values, and the changes from the end of the Run-in Period (Week 0) will be summarized for each time point. In addition, individual figures of the observed values will be provided.

For categorical values, shift tables of the data before and after administration will be provided.

Sample Size Justification:

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

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

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
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
eGFR	estimated glomerular filtration rate
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
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
PTP	press through package

QOL	quality of life
RAS	renin-angiotensin-system
RBC	red blood cell
SAE	serious AE
SAP	statistical analysis plan
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment emergent AE
TPC	Takeda Pharmaceutical Company Limited
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Hypertension develops in not only in adults but also in children and adolescents. While there are few epidemiological reports about the number of pediatric patients with hypertension in Japan, it is reported that hypertension is detected in 0.1% to 1% among elementary-school and junior-high-school students and in approximately 3% among high-school students in health checkups for Japanese children [1, 2]. According to the 2013 Population Projection, the number of pediatric patients with hypertension is estimated to be approximately 11 million in elementary-school and junior-high-school students (6 to 15 years) and approximately 3.6 million in high-school students (16 to 18 years). Therefore, on the basis of the morbidity rate of hypertension in health checkups above, the number of pediatric patients with hypertension is estimated to be 100 to 200 thousand (10 to 110 thousand in elementary-school and junior-high-school students and 110 thousand in high-school students).

Pediatric hypertension is classified into essential hypertension and secondary hypertension as described for adults. Although essential hypertension in children is generally mild, such patients are at a high risk of cardiovascular disease including left ventricular hypertrophy and carotid intima-media wall thickening as well as organ damage, eg, renal dysfunction [3, 4]. Furthermore, essential hypertension in children can track into adult essential hypertension with patients' growth [5]. The possibility of secondary hypertension, in contrast, increases with a younger age and the majority cases are severe. Hypertension caused by renal diseases (renal hypertension) accounts for 60% to 80% of children with secondary hypertension, and chronic renal failure requires particular attention. Therefore, it is necessary to prevent deterioration of renal function and progression of organ damage.

Moreover, hypertension persisting from childhood is likely to cause cardiovascular diseases and organ damage including renal dysfunction, thereby markedly affecting the patient's quality of life (QOL) and prognosis not only in childhood but also in future. Therefore, it is highly important to manage blood pressure in the early stage.

The Japanese Society of Hypertension Guidelines for the Management of Hypertension 2014 (JSH 2014) [6] recommends that drug therapy should be considered after non-pharmacological interventions (dietary and exercise therapy) are primarily performed since essential hypertension in children is often mild. For patients with secondary hypertension and patients with target organ damage, diabetes mellitus, or chronic kidney disease (CKD), drug therapy is highly recommended to prevent the development and progression of organ damage.

JSH 2014 [6] and the Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases by the Japanese Circulation Society (JCS 2012) [7] recommend angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers as the first-choice drugs for pediatric patients. In particular, more strict blood pressure management is recommended for hypertension with CKD or diabetes mellitus than that for hypertension without complications. Hypertension with such complications is recommended to be treated with ARBs having antiproteinuric effects and inhibitory effects of CKD progression in addition to ACE inhibitors.

While a number of antihypertensive drugs for adults are available in Japan, only 4 drugs are indicated for hypertension in children, valsartan being the only ARB among them. Therefore, the treatment options for pediatric patients with hypertension are not sufficient.

TAK-536 (azilsartan) is a novel ARB produced by Takeda Pharmaceutical Company Limited (TPC) and was approved for the treatment of adult hypertension under the product name of Azilva tablets 20 mg and 40 mg in January 2012. A supplementary new drug application was filed for the additional registration of Azilva tablet 10 mg, which was approved in March 2014. TAK-536 is superior to the existing ARBs (candesartan) in the antihypertensive effect as well as its persistence , while being safe and well tolerated. It is now widely used by adult patients with hypertension.

Thus, to resolve the unmet needs in the present treatment of pediatric hypertension, it is important to provide TAK-536 for pediatric patients with hypertension, whose clinical usefulness for adult patients is established.

Findings from a Clinical Study of TAK-536

Upon the development of TAK-536 as an antihypertensive drug for pediatric patients with hypertension, single-dose study (TAK-536/CPH-103) was conducted to evaluate the pharmacokinetics and safety of TAK-536 in 6 pediatric patients aged 6 to less than 16 years with hypertension. The dose of TAK-536 was 5 mg for subjects weighing less than 50 kg, and 10 mg for those weighing at least 50 kg.

TAK-536 was rapidly absorbed after a single oral administration of a TAK-536 5 mg tablet or 10 mg tablet and was detectable in the plasma of all subjects at 1 hour after administration. The mean Cmax of TAK-536 was 888.3 ng/mL in the 5 mg group and 831.3 ng/mL in the 10 mg group, and the mean AUC(0-inf) of TAK-536 was 6635.7 ng·hr/mL and 7433.3 ng·hr/mL, respectively.

Only 1 subject who received a TAK-536 5 mg tablet experienced a TEAE (gastroenteritis), which was mild in intensity and considered to be unrelated to the study drug. The outcome of gastroenteritis was “recovered/resolved.” No safety concerns were found in the study, and TAK-536 was well tolerated.

4.2 Rationale for the Proposed Study

TAK-536 is developed to be approved for the pediatric patients aged 1 to less than 16 years with hypertension. In the field of the pediatrics, the efficacy and safety should be evaluated in schoolchildren (6 to 16 years) first, and thereafter, the efficacy and safety should be evaluated in the lower aged pediatric patients [8]. Since no clinical studies have been conducted to evaluate safety and efficacy of TAK-536 in pediatric patients with hypertension, this study is planned to evaluate the safety, efficacy, and pharmacokinetics of long-term administration of TAK-536 in pediatric patients with hypertension aged 6 to less than 16 years before evaluating those in pediatric patients with hypertension aged 1 to less than 6 years.

CCI [redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 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

5.2 Endpoints

5.2.1 Primary Endpoints

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)

5.2.2 Secondary Endpoints

Efficacy:

- Office trough* sitting diastolic and systolic blood pressure

  *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**

  ** < 95 percentile shown in Table 5.a for essential hypertension

  < 90 percentile shown in Table 5.a for secondary hypertension

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

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

Systolic/diastolic blood pressures (mmHg, JCS2012 [7])
The 90th, 95th, and 99th indicate 90, 95, and 99 percentile, respectively.

Pharmacokinetics:

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

6.0 STUDY DESIGN AND DESCRIPTION

6.1 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-week; Treatment Period II, 40-week), 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 the subjects only who treated with any antihypertensive drugs as a prior treatment, the Run-in Period could be extended up to 4 weeks if blood pressures do not meet the inclusion criteria.

Subjects who 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 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 I by the investigator or subinvestigator; 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 administration of placebo. In the case of the down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period I. Especially, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBs may cause withdrawal syndrome.

(2) Treatment Period I

In the Treatment Period I (Week 0 to 12), initial dose of TAK-536 will be 2.5 mg for the subjects weighing < 50 kg or 5 mg for the subjects weighing ≥ 50 kg. After the initial dose, TAK-536 will be titrated to 5 mg, 10 mg, and 20 mg for the subjects weighing < 50 kg or to 10 mg, 20 mg, and 40 mg for the subjects weighing ≥ 50 kg 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 of Week 2, 4, or 8 in the Treatment Period I. Between the visits of Week 4 and 8 during the Treatment Period I, 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. TAK-536 can be reduced at the investigator's or subinvestigator's discretion if there are any concerns in tolerability with titration of TAK-536 (i.e., in case of occurring any AEs caused by titration of TAK-536). During the

Treatment Period I, change in the dosage of the antihypertensive drug is prohibited in the subjects who treated with a single antihypertensive drug other than RAS inhibitors at the start of the Treatment Period I.

* target blood pressure:

< 95 percentile shown in Table 5.a for essential hypertension, < 90 percentile shown in Table 5.a for secondary hypertension

(3) Treatment Period II

During the Treatment Period II (Week 12 to 52), the treatments at the end of the Treatment Period I will be continued. TAK-536 can be titrated to the highest dose (20 mg for the subjects weighing < 50 kg or 40 mg for the 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 are required dose reduction or interruption because of the concerns in tolerability with titration (i.e., excessive reduction in blood pressure, other AE, etc.) in the Treatment Period II, 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.

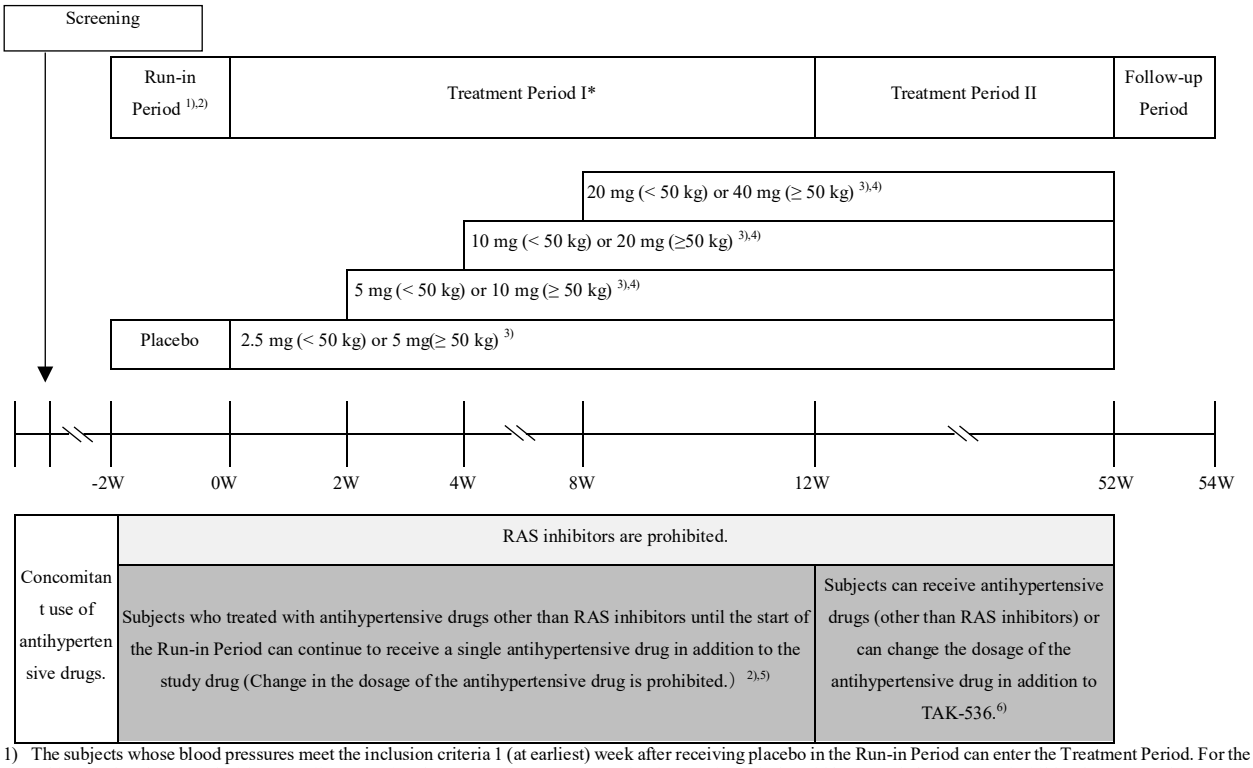
(4) Follow-up Period

Follow-up Period will be 2 weeks from the next day of 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 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



1) The subjects whose blood pressures meet the inclusion criteria 1 (at earliest) week after receiving placebo in the Run-in Period can enter the Treatment Period. For the subjects only who treated with any antihypertensive drugs as a prior treatment only, the Run-in Period could be extended up to 4 weeks if 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 administration of placebo. In the case of the down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period I. Especially, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBs may cause withdrawal syndrome.
3) In the Treatment Period I, TAK-536 can be titrated biweekly when the subjects do not achieve the target blood pressure while evaluation of safety and tolerability. TAK-536 can be reduced at the investigator's or subinvestigator's discretion if there are any concerns in tolerability with titration of TAK-536 (i.e., in case of occurring any AEs caused by titration of TAK-536).
4) When the antihypertensive drugs are required dose reduction or interruption because of the concerns in tolerability with titration (i.e., excessive reduction in blood pressure, other AE, etc.) in the Treatment Period II, 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 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 treatments for hypertension in the Treatment Period I by the investigator or subinvestigator. Change in the dosage of the antihypertensive drug at the start of the Run-in Period I is prohibited until the end of the Treatment Period I.
6) 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 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.

6.2 Justification for Study Design, Dose, Regimen, and Endpoints

[Justification for the Study Design]

Many pediatric patients with renal dysfunction are assumed to be entered this study since the proportion of pediatric patients with secondary hypertension caused by renal disease is high in pediatric patients with hypertension. Evidence-based Clinical Practice Guideline for CKD 2013 (JSN2013) [9] indicates that treatment with ARB should be start at a low dose in patients with renal dysfunction and the dose should be increased with caution by confirming the hypotensive effect of ARB and renal function. On the basis of above indication, an open-label, optional titration

design was selected in this study, in which TAK-536 can be titrated with monitoring subject condition.

Co-administration of RAS inhibitors, which is similar to TAK-536, is prohibited in order to evaluate appropriately the efficacy of TAK-536 in the pediatric patients throughout the Run-in Period and the Treatment Period I. In consideration of the safety for vulnerable pediatric population, subjects can continue to receive a single antihypertensive drug other than RAS inhibitors in the same dosage after the start of the Run-in Period, if the subjects are considered to need the additional treatment for hypertension by the investigator or subinvestigator. In the Treatment Period II, the subjects whose blood pressure is not reduced sufficiently by TAK-536 can receive additional antihypertensive drugs other than RAS inhibitors concomitantly in order to evaluate the efficacy and safety of the long-term administration of TAK-536 in pediatric patients under the condition of being closer to the routine medical care.

The Run-in Period with placebo was selected to wash out the placebo effect of the study drug and the influence of antihypertensive drugs as a prior treatment in subjects who were treated with any prior antihypertensive drugs. In addition, the Run-in Period allows the opportunity to assess subject compliance with the study drug (i.e., placebo) and subjects who are not sufficiently compliant with placebo will be excluded.

The Follow-up Period was selected to evaluate the subject safety after the study drug administration.

[Justification for the Doses]

The population pharmacokinetic model was developed based on data from a total of 58 subjects (6 for pediatric patients and 52 for healthy adult subjects). Also a population of subjects whose weights were uniformly distributed within the specified weight range between 20-80 kg by 1 kg (100 subjects for each body weight range and 6100 subjects in total) were generated and equally allocated to fixed TAK-536 doses of 2.5, 5, 10, 20, and 40 mg. Then, the population pharmacokinetic model was used to simulate the Cmax and AUC of TAK-536 following a single oral dose of each dose for each body weight category for virtual pediatric population, and distributions of simulated Cmax and AUC (median and 90% CI) of TAK-536 in pediatric patients weighing ≥ 20 kg and < 50 kg and those weighing ≥ 50 kg and < 80 kg were compared with actual parameters of Cmax and AUC (minimum and maximum) following TAK-536 10, 20, 40 and 80 mg in healthy adults.

Based on the simulation, estimated exposures to TAK-536 in pediatric patients weighing ≥ 50 kg and < 80 kg and those weighing ≥ 20 kg and < 50 kg after receiving TAK-536 2.5, 5, 10, 20, or 40 mg are similar to and a little below double of that in healthy adults receiving the same fixed dose, respectively. These findings indicate that exposures to TAK-536 in pediatric patients with doses up to 20 mg do not exceed the exposure in adults with the approved maximum dose of 40 mg.

Therefore, the initial dose was set at 5 mg, a half the typical adult half dose of 10 mg, for the subjects weighing ≥ 50 kg and at 2.5 mg for those weighing < 50 kg by further reducing the dose by half in consideration of subject safety.

On the basis of the results of the population pharmacokinetic model, 40 mg or 20 mg was selected as the highest dose of TAK-536 by weight for the subjects weighing ≥ 50 kg or < 50 kg, respectively. In the population pharmacokinetic model, estimated exposures to TAK-536 in pediatric patients weighing ≥ 50 kg after receiving TAK-536 40 mg as the highest clinical dose in adults or those in the patients weighing < 50 kg after receiving TAK-536 20 mg does not exceed the exposure to TAK-536 in adults after receiving TAK-536 40 mg as the approved maximum dose in adults. In addition, titrating from the lower dose while evaluation of safety and tolerability sufficiently were selected in consideration of subject safety.

TAK-536 has not been administered to the pediatric patients with hypertension with renal dysfunction. In addition, TAK-536 should be administered initially in lower dose to the adult patients with serious renal dysfunction and gradual titration is required for them in careful with monitoring subject condition in case of titration. The design of this study fulfills the above requirements.

[Justification for the Regimen]

Since meals do not affect the pharmacokinetics of TAK-536 in adults, the subjects receive the study drug before or after breakfast in the study.

[Justification of Endpoints]

Variables commonly used to evaluate the safety were selected as the primary endpoints because the primary objective of this study is to evaluate the long-term safety of TAK-536.

Office trough sitting diastolic and systolic blood pressure were selected as secondary endpoints to evaluate the efficacy and persistence of effect in reference to Principles for Clinical Evaluation of New Antihypertensive Drugs [10] and JSH2014 [6].

Plasma concentrations of TAK-536 and its metabolites (M-I and M-II) will be measured in order to evaluate the pharmacokinetics of TAK-536 in pediatric patients with hypertension.

[Justification for Study Duration]

(1) Run-in Period

Two weeks were set as the Run-in Period with placebo to wash out the placebo effect of the study drug or the influence of the antihypertensive drugs as a prior treatment. The subjects whose blood pressures meet the inclusion criteria 1 week (at earliest) after receiving placebo during the Run-in Period can enter the Treatment Period in consideration of subject safety. For the subjects only who treated with any antihypertensive drugs as a prior treatment, the Run-in Period could be extended up to 4 weeks while considering of subject safety if the blood pressures do not meet the inclusion criteria.

(2) Treatment Period

JSH2014 [6] recommends that low-dose therapy with a single antihypertensive drug should be initiated first for the treatment of the hypertensive patients, and the dose should be increased to a standard dose in 4 to 8 weeks while evaluating the effects. On the basis of above recommendation, 8 weeks were set as a titration period with 3 titration point and 2 weeks for each titration point for evaluating the tolerability. In addition, a phase 3 confirmatory study (TAK-536/CCT-005)

demonstrated that maximum decline of blood pressure was observed 4 weeks after the titration of TAK-536 in Japanese adult patients with hypertension. On the basis of the results, 4 weeks were set as the duration of administration with the highest dose in case of the titration of TAK-536 to the highest dose (20 mg or 40 mg). Therefore, 12 weeks in total were set as the Treatment Period I in this study.

Forty weeks was set as the Treatment Period II in reference to the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions [11], so that duration of administration would be 52 weeks in total with the Treatment Period I.

(3) Follow-up Period

The elimination half-life was 12.8 hours following the single administration of TAK-536 40 mg in healthy adult subjects. In reference to the amendment of the Guideline for Bioequivalence Studies of Generic Products [12], 2 weeks were set as Follow-up Period of 5 times or more the elimination half-life.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator or subinvestigator, the subject's parent or the subject's legal guardian is capable of understanding and complying with protocol requirements.
2. The subject's parent or the subject's legal guardian is capable of signing and dating a written, informed consent form on behalf of the subject prior to the initiation of any study procedures. Written informed assent is also obtained from the subject as much as possible.
3. The Japanese subject who has a diagnosis of hypertension. A subject is eligible if he/she is deemed hypertensive according to the reference blood pressure values of children by gender and age (Table 5.a); office sitting diastolic or systolic blood pressure ≥ 95 percentile for essential hypertension without concomitant hypertensive organ damage, and ≥ 90 percentile for secondary hypertension with concomitant CKD, diabetes mellitus, heart failure or any hypertensive organ damage.
   In addition, subjects need to meet the following criteria:
   (1) If currently treated with any antihypertensive drugs at the start of the Run-in Period: Subject has a documented historical diagnosis of hypertension and an office sitting diastolic or systolic blood pressure meeting the above criteria at the end of the Run-in Period (Week 0).
   (2) If currently untreated with any antihypertensive drugs at the start of the Run-in Period: Subject who meets the above criteria on 3 separate time points including screening and the end of the Run-in Period (Week 0). In addition, subject with essential hypertension without concomitant hypertensive organ damage still maintains hypertension with non-pharmacotherapy including foods or exercises for at least 3 months within 1 year prior to the start of screening.
4. The subject is male or female and aged 6 to less than 16 years at the time of informed consent.
5. The subject weighs at least 20 kg at screening.
6. The subject is capable of taking the tablets or granules supplied as the study drug.
7. A subject who has undergone kidney transplantation is eligible if he/she underwent the transplantation at least 6 months earlier at screening, and the graft has been functionally stable (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2) for at least 6 months with evidence (eg, Doppler echography, CT scan [computed tomography] or MRI [magnetic resonance imaging]) excluding grafted kidney arterial stenosis. A subject on immunosuppressive therapy with a stable dose at least 30 days prior to screening is eligible.
8. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent through 1 month after the completion of the study, and proves negative in the pregnancy test at screening.

*Definitions and acceptable methods of contraception are defined in Section 9.1.10 and reporting responsibilities are defined in Section 9.1.11.

9. The subjects judged by the investigator or subinvestigator that he/she can discontinue the therapy with RAS inhibitors for 2 weeks (acceptable range, 1 to 4 weeks) in safe prior to the Treatment Period.

[Justification of Inclusion Criteria]

1.2.6. These were set as the standard requirements for clinical studies in pediatric patients.

3. The patients with hypertension who can be candidates for pharmacotherapy was set in reference to JCS2012 [7]. Reference blood pressure value of hypertension in the US guideline's criteria for children of 50 percentile height categorized by age and gender was selected since which was also the diagnosing criteria for hypertension adopted by JCS2012 [7]. For patients untreated with any antihypertensive drugs at the start of the Run-in Period, blood pressure values of 3 separate time points were adopted since hypertension would be diagnosed with above criteria 3 times or more in separate day or week.
4. The subject can be male or female, since evaluation in boys and girls is needed. The subjects of this study will be school children. Since children aged 6 to 16 years are categorized as school children in the final report on the Guidelines for Clinical Evaluation of Antihypertensive Drugs in Children [8], 6 to 16 years will be an acceptable age range in this study.
5. According to the physical status survey (Part 2 of the National Health and Nutrition Survey 2011 [13]), the average weight of 6-year-old children was 20.2 kg for girls and 20.9 kg for boys. This study will therefore enroll children weighing at least 20 kg.
7. In consideration of possible effects on the evaluation of TAK-536 and the subject safety, the subject who has undergone kidney transplantation will be eligible only if his/her clinical course has been stable.
8. RAS inhibitors are contraindicated in pregnant women based on the disorders and deaths in fetuses and new-born children reported for women using them during pregnancy.
9. These were set in consideration of subject safety.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days prior to screening or is participating in another clinical study or a post-marketing clinical study.
   Note: This does not apply to subjects participating in observational studies without interventional or invasive therapy.
2. The subject previously received therapy with azilsartan.
   Note: This does not apply to subjects participating in single dose pharmacokinetic studies of TAK-536.

3. The subject has poorly controlled hypertension indicated by an office sitting systolic blood pressure higher by at least 15 mmHg and/or an office sitting diastolic blood pressure higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age (Table 5.a).
4. The subject has a diagnosis of malignant or accelerated hypertension.
5. The subject was noncompliant (< 70% or > 130%)* with the study drug during the Run-in Period.
   *: The proportion of the number of the received the study drug to the number of the study drug which the subjects should receive.
6. The subject has severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2), is receiving dialysis, has a renovascular disease affecting one or both kidneys, severe nephrotic syndrome not in remission, or a serum albumin level < 2.5 g/dL.
7. The subject has a history of, or the signs/symptoms of serious cardiovascular, hepatobiliary, gastrointestinal, endocrine (eg, hyperthyroidism, Cushing's syndrome), hematological, immunological, urinogenital, psychiatric disease, cancer, or any other disease that adversely affects subject's health, or, in the opinion of the investigator or subinvestigator, potentially confounds the study results.
8. The subject has hemodynamically significant left ventricular outflow obstruction due to aortic stenosis or aortic valvular disease, or is scheduled to undergo a medical procedure affecting blood pressure during the study (eg, correction of arterial anomaly).
9. The subject has a history of or concurrent clinically significant abnormality of 12-lead ECG that, in the opinion of the investigator or subinvestigator, disqualifies the subject for participation in the study.
10. The subject has poorly controlled diabetes mellitus indicated by HbA1c > 9.0% at screening.
11. The subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 2.5 × the upper limit of normal (ULN), or a total bilirubin level ≥ 1.5 × ULN at screening, severely impaired hepatic function, any active liver disease (regardless of the cause), or jaundice.
12. The subject has hyperkalemia exceeding ULN at screening.
13. The subject has a history of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection at screening.
14. The subject has a known hypersensitivity or allergy to any ARBs.
15. The subject needs treatment with any of the excluded medication.
16. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after the completion of this study.

[Justification of Exclusion Criteria]

1, 15. These were set as the standard exclusion criteria used for clinical studies.

2. This was set because of the potential for bias in evaluation of the safety and the efficacy.

3,4, 6-11, 13,14. These were set in consideration of the subject safety.

5. This was set to assure the appropriateness of the evaluation in this study.

12. This was set in consideration of the subject safety; hyperkalemia may develop after the administration of RAS inhibitors.

16. This was set as a standard requirement used for clinical studies. It was also due to a contraindication for pregnant females, because RAS inhibitors have caused fetal and neonatal disorders and death when used during pregnancy, and were transferred in the milk and affected nursing neonates when administered to lactating animals in nonclinical studies.

7.3 Excluded Medications and Treatments

7.3.1 Excluded Medications

The following medications including over-the-counter (OTC) drugs will be prohibited at the specified period during the study (Run-in Period and Treatment Period).

Subjects and subjects' parent or the subjects' legal guardian must be instructed not to take any medications including OTC products, without first consulting with the investigator or subinvestigator.

Other medications that are listed in the precautions for co-administration section of the package inserts of TAK-536 must be administered with caution.

<Run-in Period and Treatment Period I>

The following medications will be prohibited during the Run-in Period and Treatment Period I. A subject can continue the conventional therapy for the concurrent medical conditions without changing daily dosage except the excluded medications.

(1) RAS inhibitors (ACE inhibitors, ARB, and DRI)

(2) Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) excluding acetaminophen (4 days or more per week)

(3) Lithium

(4) Monoamine oxidase inhibitors

(5) Tricyclic antidepressants

(6) Amphetamine or it-derived materials (exception for the materials shown in the section of Medications Permitted with Conditions)

(7) Dopamine agonist

(8) Atypical antipsychotics

(9) Anticonvulsants

(10) Trazodone

(11) Nitrates

(12) Estrogen preparations

<Treatment Period II>

The following medications will be prohibited during the Treatment Period II.

(1) RAS inhibitors (ACE inhibitors, ARB, and DRI)

(2) Chronic use of NSAIDs excluding acetaminophen (4 days or more per week)

(3) Lithium

(4) Monoamine oxidase inhibitors

(5) Nitrates

(6) Estrogen preparations

[Justification for Excluded Medications]

<Run-in Period and Treatment Period I>

(1) These similar drugs are excluded because they could influence the evaluation of TAK-536 efficacy.

(2), (4)-(12) These drugs are excluded because they could increase or decrease blood pressure and influence the evaluation of TAK-536 efficacy.

(3) This drug is prohibited because their concomitant use with ARBs could cause poisoning.

<Treatment Period II>

(1) These similar drugs are excluded because they could influence the evaluation of TAK-536 efficacy.

(2), (4)-(6) These drugs will be supposed to be used chronically and are excluded because they could increase or decrease blood pressure and influence the evaluation of TAK-536 efficacy when these are used chronically.

(3) This drug is prohibited because their concomitant use with ARBs could cause poisoning.

7.3.2 Medications Permitted with Conditions

Following medications will be permitted with conditions in consideration of subject safety during the Run-in Period and Treatment Period I.

(1) Antihypertensive drugs other than RAS inhibitors: Subjects who 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 I by the investigator or subinvestigator; 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 administration of placebo. In the case of the down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period I. Especially, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBs may cause withdrawal syndrome.

(2) Steroids: Systemic steroid is permitted as an alternative therapy on a stable low dose/ maintenance dose in subjects with adrenal insufficiency. The highest dose per day is 12 mg/m^2 for hydrocortisone or equivalent dose to hydrocortisone for other steroids. Prednisolone or other steroids can be administered up to 15 mg/m^2 per day or equivalent dose to prednisolone for other steroids as an immunosuppressive therapy in subjects after renal transplantation or with glomerular disease. The steroids are permitted on a stable dose from 30 days or more prior to the screening to the end of the Treatment Period I (alternate-day administration is also permitted). Topical or inhaled steroid is permitted but the dose cannot be changed unless there are no medical needs.

(3) Central nervous system stimulants, non-central nervous system stimulants: Use for treatment of attention deficit/hyperactivity disorder is permitted on a stable dose from 30 days prior or more to the screening to the end of the Treatment Period I.

7.4 Diet, Fluid, and Activity Control

The investigator, the subinvestigator, and the study collaborator should instruct the subject, the subject's parent or the subject's legal guardian to adhere the following study requirements.

1. Subjects will be instructed to ask the investigator, the subinvestigator, or the study collaborator by telephone for their instructions or visit the study site, as soon as they experience vomiting or diarrhea frequently throughout the study.
2. Subjects will be fully explained about the possibility of excessive reduction in the blood pressure associated with TAK-536 treatment. Subjects will be instructed to rest in a supine position, as soon as they experience any symptoms suggesting decreased blood pressure (eg, dizziness, lightheadedness, etc.) outside the study site on days other than the scheduled visit. Subjects were instructed to ask the investigator, subinvestigator, or the study collaborator by telephone for further instructions, or to visit the study site, if the symptoms did not subside.
3. Subjects will be instructed to ask the investigator, subinvestigator, or the study collaborator by telephone for their instructions, or to visit the study site, as soon as they experience any symptoms associated with increased blood pressure (eg, headache, palpitations, hot flushes, perspiration, etc.) outside the study site on days other than the scheduled visit.
4. Subjects will be instructed to take the study drugs as directed (1 tablet or 1 sachet once daily) without fail and continue receiving the study drug at the same timing (before or after breakfast) throughout the study. Subjects will be instructed to take the study drug at the same time every day except for scheduled visit day. Subjects will be instructed to take the study drug by AM 9:00 at the latest, setting ±3-hours for acceptable range. Subjects will be instructed that they will be allowed to take the study drug when they realize it in case of failing to take the study

drug, but will not be allowed to take the study drugs for 2 days at once. On the day before scheduled visit, subjects must take the study drug 24 hours (acceptable range, 21 to 27 hours) before office blood pressure measurement on the following day. TAK-536 2.5 mg granules should be administered immediately after the sachet (aluminum strip) is torn off. TAK-536 2.5 mg granules sachet should not be administered if the sachet is torn off at least 1 hour before the administration.

5. Subjects will be fully explained about how to adequately measure home blood pressure. Subjects will be instructed to measure the home blood pressure, preferably consecutive 2 times daily immediately before the study drug administration for 1 week each before and after the visit at the start of the Treatment Period I, for 1 week after the following day of a visit of each time point between Week 2 and Week 8 of the Treatment Period I, and for 1 week from the day before the visit at Week 12 of the Treatment Period I. Subjects will be instructed to inform the study site if a home sitting systolic blood pressure which is higher by at least 15 mmHg and/or a home sitting diastolic blood pressure which is higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age in Table 5.a (See Section 9.1.6).
6. Subjects will be instructed not to eat or bathe within 1 hour before office blood pressure measurement, not to intake any caffeine containing product within 30 minutes before the measurement.
7. Subjects will be instructed to comply with and not to change a fixed diet (eg, caloric and salt intake) and/or exercise therapies, if performed, throughout the study.
8. Subjects will be instructed to avoid food with a high salt and to take adequate hydration and to maintain a routine sleep, behavior and caffeine intake. In addition, subjects will be instructed to avoid excessive drinking/eating, significant change of diet (eg, excessively high-fat diet), excessive exercise, and staying up late. Especially, subjects will be instructed to maintain a regular lifestyle on the day before visit days.
9. Subjects will be instructed to inform the investigator, subinvestigator before receiving treatment from another doctor, or to provide details of treatment the subject received in case of reporting afterwards. Subjects receiving treatment by another doctor will be instructed to inform another doctor of their participation in this study before the participation, as far as possible.
10. Subjects will be instructed to consult the investigator or subinvestigator before using or changing the dosage of any drug not prescribed by the investigator or subinvestigator (including vitamins supplements, OTC drugs, and herbal preparations). Subjects will be instructed to promptly provide the details when they use any such drug.
11. Subjects will be instructed to visit the study site at the scheduled times to undergo examinations and tests by the investigator or subinvestigator. Subjects will be instructed to promptly inform the investigator or subinvestigator when they are unable to visit the study site as scheduled.

12. Female subjects of childbearing potential (eg, a female subject of childbearing potential is defined by the investigator's or subinvestigator's positive opinion about the subject's reproductive potential) will be instructed to use appropriate contraception from signing of informed consent to 1 month after completing the study (see Section 9.1.10).

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (eCRF) using the following categories. For subject failure, refer to Section 9.1.14.

1. Death. The subject died on study.
   Note: If the subject dies on study, the event will be considered as SAE. See Section 10.2.2 for the reporting procedures.
2. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

   • Acute deterioration of renal function

   Acute deterioration of renal function or increase in potassium value should be monitored carefully. If 50% reduction in estimated glomerular filtration rate [eGFR] or less than 30 mL/min/1.73 m^2, or serum potassium value over 5.5 mEq/L is seen at consecutive 2 time points, discontinuation should be considered. Appropriate follow-up should be performed for all subjects who discontinue the study until the subjects have been recovered or stabilized (see Section 9.1.9).

   • Liver Function Test (LFT) Abnormalities

   Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.9), if the following circumstances occur at any time during study drug treatment:

   – ALT or AST > 8 ×ULN, or
   – ALT or AST > 5 × ULN and persists for more than 2 weeks, or
   – ALT or AST > 3 × ULN in conjunction with elevated total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5, or
   – ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).
3. Protocol deviation. The discovery after the start of the Treatment Period that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject, the subject's parent or the subject's legal guardian were unsuccessful. Attempts to contact the

subject, the subject's parent or the subject's legal guardian must be documented in the subject's source documents.

5. Withdrawal by subject. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).

6. Withdrawal by parent or guardian. The subject's parent or the subject's legal guardian wishes to withdraw the subject from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).

7. Study terminated by sponsor. The sponsor terminates the study.

8. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

9. Lack of efficacy. The investigator or subinvestigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject. For example, discontinuation should be considered in the following case; on consecutive visits, an office sitting systolic blood pressure is persistently higher by at least 15 mmHg and/or an office sitting diastolic blood pressure is persistently higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age in Table 5.a, or, subjective symptoms or findings deemed associated with poorly controlled blood pressure do not improve with titration of TAK-536 during the Treatment Period I or with the addition of any other antihypertensive drugs other than RAS inhibitors during the Treatment Period II.

10. Other.

    Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or subinvestigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or subinvestigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

(1) Dosage form and manufacturing

Code name: TAK-536

Chemical name: 2-Ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1*H*-benzo[*d*]imidazole-7-carboxylic acid

Generic name: Azilsartan (JAN)

Formulation and Strength:

Study drug	Formulation	Strength
TAK-536 2.5 mg granules (placebo for the Run-in Period)	White to nearly white granules	Contains no TAK-536 in 250 mg
TAK-536 2.5 mg granules (active drug for the Treatment Period)	White to nearly white granules	Contains 2.5 mg of TAK-536 in 250 mg
TAK-536 5 mg tablet (placebo for the Run-in Period)	Pale pink film-coated tablet	Contains no TAK-536 in 1 tablet
TAK-536 5 mg tablet (active drug for the Treatment Period)	Pale pink film-coated tablet	Contains 5 mg of TAK-536 in 1 tablet
TAK-536 10 mg tablet	Pale yellow to red film-coated tablet	Contains 10 mg of TAK-536 in 1 tablet
TAK-536 20 mg tablet	Pale-red film-coated tablet	Contains 20 mg of TAK-536 in 1 tablet
TAK-536 40 mg tablet	Yellow film-coated tablet	Contains 40 mg of TAK-536 in 1 tablet

Manufacturing: TPC

(2) Package and labeling

1) Package

– TAK-536 2.5 mg granules (placebo for the Run-in Period, active drug for the Treatment Period): For placebo for the Run-in Period, each aluminum strip sachet contains 250 mg of

TAK-536 granules containing no TAK-536. Forty two sachets are packaged in a box. For active drug for the Treatment Period, each aluminum strip sachet contains 250 mg of TAK-536 granules containing 2.5 mg of TAK-536. Seventy sachets are packaged in a box.

- TAK-536 5 mg tablet (placebo for the Run-in Period, active drug for the Treatment Period): For placebo for the Run-in Period, each press through package (PTP) sheet contains 14 tablets of TAK-536. Three sheets are packaged in a box. For active drug for the Treatment Period, each PTP sheet contains 14 tablets of TAK-536. Ten sheets are packaged in a box.
- TAK-536 10 mg, 20 mg, and 40 mg tablets: Each PTP sheet contains 14 tablets of TAK-536. Ten sheets are packaged in a box.

2) Labeling

Each outer box indicates the following information: the drug is for the study use only, study drug name, amount, the sponsor's name and address, batch number, and storage condition.

8.1.2 Storage

The study drugs are to be stored at room temperature (1 to 30°C).

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

During the Run-in Period, subjects will orally receive TAK-536 2.5 mg granules (placebo for the Run-in Period) if subjects weighing < 50 kg, or TAK-536 5 mg tablet (placebo for the Run-in Period) if subjects weighing ≥ 50 kg, once daily, before or after breakfast. During the Treatment Period, the same dose of the selected placebo during the Run-in Period will be the initial dose. After the initial dose, subjects will orally receive any of TAK-536 2.5 mg granules, TAK-536 5 mg, 10 mg, 20 mg tablet, once daily, before or after breakfast, if subjects weighing < 50 kg, or any of TAK-536 5 mg, 10 mg, 20 mg, 40 mg tablet, if subjects weighing ≥ 50 kg. For dose titration method, see Section 6.1 Study Design.

Because weight is likely to change during the study, the highest dose for the subjects is allowed to be changed if dose adjustment by changing of weight is required during the Treatment Period II.

The investigator or subinvestigator may select the timing of the study drug administration (i.e., before or after breakfast) in consideration of subject lifestyle but should not change this timing throughout the study. The investigator or its designee will record the guidance provided about the timing of the study drug administration (before or after breakfast) at the start of the Run-in Period (Week -2) in the eCRF.

At the start of the Run-in Period (Week -2), the study drug for the Run-in Period will be administered on the same day after completing all tests, observations, and evaluations. In case that

subjects take RAS inhibitors in the morning of the visit day, the administration of the study drug for the Run-in Period will be started from the next day.

Except for Week 16, subjects will visit the study site on each visit day without taking the study drugs, and receive them only after completing all tests, observations, and evaluations.

On the visit of Week 16, subjects, the subjects' parent or the subjects' legal guardian will be instructed to visit the study site after taking the study drug and the tests, observations, and evaluations 2 hour (acceptable time window, 1 to 3 hours) after taking the study drug will be performed.

Regular doses on days except for the visits will be administered no later than 9:00 AM, regardless of the specified dosing timing (i.e., before or after breakfast). The study drug should be administered at the almost same time every day throughout the study (acceptable range is ± 3 hours) except the visit day. The investigator or subinvestigator will confirm whether the subject has taken the study drug or not in the morning of each visit.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) about TAK-536 active drug for the Treatment Period, will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRFs according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Dispensing Procedures

The investigator or subinvestigator will dispense the study drug to subjects according to the study procedure.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage and management of study drugs created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent and assent are described in Section 15.2.

Informed assent of the subject, if deemed possible by the investigator or subinvestigator, and informed consent of the subject's parent or the subject's legal guardian must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

Assent and consent to participate in the study will be obtained from any subject before discontinuing the prior treatment (antihypertensive drugs).

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is explained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, race, diagnosis timing and type of hypertension, and underlying diseases in case of secondary hypertension at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the diseases under study that stopped within 1 year prior to informed consent. Any history of kidney transplantation should be documented regardless of the time elapsed. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes any medication stopped at or within 4 weeks prior to VISIT 2.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment performed before the study drug administration.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below: The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: BMI = weight (kg)/height $(m)^2$

Height in centimeters (cm) will be rounded to integers and weight in kilograms (kg) will be rounded to 1 decimal place. BMI will be rounded to 1 decimal place.

9.1.5 Vital Sign Procedure

Vital signs will include office sitting blood pressure (systolic and diastolic), office standing blood pressure (systolic and diastolic), office sitting pulse rate, and office standing pulse rate (pulse rate per 1 minute). All office blood pressure will be measured with a blood pressure meter specified by the sponsor.

Office blood pressure should be measured at the time of trough (approximately 21 to 27 hours after the latest dose, i.e., in the morning of that day) with the subject without taking the study drug in the morning of the scheduled visit except for Week 16. The subject, the subject's parent, or legal guardian will be instructed strongly not to take the study drug at home on the scheduled visit day except for Week 16. The subject, the subject's parent, or the subject's legal guardian will be instructed again if the subject receives the study drug before the measurements of vital signs on the scheduled visit day by mistake.

When vital signs are scheduled at the same time as blood draws, vital signs will be obtained before the scheduled blood draw.

Office sitting blood pressure after taking the study drug will be also measured only at Week 16 of the Treatment Period; the time point which the pharmacokinetics after receiving the study drug is evaluated.

Subjects will be instructed not to eat or bathe within 1 hour before office blood pressure measurement, not to intake any caffeine containing product 30 minutes before the measurement.

<Determining difference in blood pressure between right and left arm>

At screening, sitting blood pressure in the right and left arms will be measured once after sitting at rest for ≥ 5 minutes to determine the difference in blood pressure between the arms. The arm with a higher systolic blood pressure will be used to measure office blood pressure during the study. The right arm will be used if systolic blood pressure is the same on both sides. Change of the arm for measurement will not be allowed during the study.

<Measuring sitting blood pressure and sitting pulse rate>

Sitting blood pressure will be repeatedly measured 3 times at 1 to 2 minute intervals after the subject has been sitting at rest for at least 5 minutes and recorded in the subject source documents and eCRF. However, if 2 of the 3 systolic blood pressure measurements differ by more than 8 mmHg or diastolic blood pressure measurements differ by more than 5 mmHg, a second set of 3 sitting blood pressure measurements should be obtained and only the second set of readings should be recorded in the eCRF (even if these still differ by > 8 mmHg for systolic blood pressure or 5 mmHg for diastolic blood pressure). Original and repeat readings must all be recorded in the source documents with an explanation.

The arithmetic mean (rounded to integers) of 3 measurements of a session will be used for determination of the subject eligibility.

The pulse rate measured at the last measurement of the sitting blood pressure will be used as the sitting pulse rate value.

Sitting blood pressure must be measured after resting in a sitting position for at least 5 minutes. An appropriately sized cuff (40% of the arm's perimeter) should be used, and applied to an upper arm held at the heart level. All measurements must be made on the same arm using the same-sized cuff. Every effort should be made to standardize the condition of office blood pressure measurements as possible, such as measurement time, the same blood pressure device should be used, whenever possible, by the same investigator, subinvestigator, or the study collaborator.

<Measuring standing blood pressure and standing pulse rate>

Standing blood pressure will be measured to evaluate the orthostatic vital signs at the scheduled visit of Week 0, 12, 24 and 52. After measuring the sitting blood pressure, standing blood pressure will be measured once after the subject has been standing for 2 minutes. Standing systolic and diastolic blood pressure will be also measured with the same device which measures sitting blood pressure on the same arm. For standing blood pressure measurements, the arm should be supported and extended such that the cuff is at heart level. Standing pulse rate will be measured once during the subject maintains a standing position.

9.1.6 Measuring Home Blood Pressure

Each subject, the subject's parent, or the subject's legal guardian will be provided a home blood pressure meter and adequately informed of the measurement procedures at the start of the Run-in Period (Week -2) by the sponsor through the study site.

The subject, the subject's parent, or the subject's legal guardian will be instructed to measure home blood pressure (systolic and diastolic), preferably consecutive 2 times daily immediately before the study drug administration for 1 week each before and after the visit at the start of the Treatment Period I, and for 1 week after the following day of a visit of each time point between Week 2 and Week 8 of the Treatment Period I (including visit at Week 6, when performed), and for 1 week from the day before the visit at Week 12 of the Treatment Period I.

The subject should measure blood pressure 2 times in a row after having been sitting for at least 5 minutes with the blood pressure cuff applied to the same arm as used to measure blood pressure at the visits. The blood pressure measurements should be recorded in patient diary and reviewed by the investigator or subinvestigator at each visit. The blood pressure measured twice immediately before the study drug administration should be recorded in CRFs. The subject, the subject's parent, or the subject's legal guardian will be instructed to inform the study site if a home sitting systolic blood pressure which is higher by at least 15 mmHg and/or a home sitting diastolic blood pressure which is higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age in Table 5.a. The subject, the subject's parent, or the subject's legal guardian will be instructed by the investigators to visit the study site to measure blood pressure again if needed. If the elevated blood pressure is confirmed by repeat measurements at the study site, the subject is to be considered to discontinue the study.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from the start of the Run-in Period [Week 2] through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF.

If the concomitant medications are antihypertensive drugs, the daily dosage and unit of concomitant medications must be recorded in the eCRF as well.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the first test after signing of informed consent. The condition (i.e., diagnosis) should be described.

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 8 mL.

Table 9.a Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Red blood cell count White blood cell count with differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes) Hemoglobin Hematocrit Platelets	Hemoglobin A1C/Hemoglobin (a) ALT Albumin Alkaline phosphatase (ALP) AST Bilirubin (Total bilirubin) Blood urea nitrogen (BUN) (b) Calcium Chloride (b) Creatinine (b) Creatine kinase Cystatin C Glomerular Filtration Rate (b) Gamma-glutamyl transferase (GGT) Glucose Cholesterol (Total cholesterol) Triglyceride Phosphate Potassium (b) Sodium (b) Protein (Total protein) Lactate dehydrogenase (LDH)	Qualitative tests for glucose, pH, protein, occult blood, Ketones Quantitative tests for protein, creatinine, Albumin Protein/creatinine ratio, albumin/creatinine ratio, specific gravity
Other		
Urine qualitative human chorionic gonadotropin (hCG) pregnancy test (only female subjects of childbearing potential)		

(a) Only patients with diabetes mellitus
(b) Only the laboratory tests associated with renal function. The local laboratory will perform the laboratory tests associated with renal function in addition to measuring at the central laboratory to confirm the tolerability when TAK-536 is titrating (including unscheduled visit), if needed at the investigator's discretion.

The central laboratory will perform laboratory tests for hematology, chemistries, and urinalysis (acceptable under the fed condition).

The local laboratory will perform the laboratory tests associated with renal function (BUN, chloride, creatinine, eGFR, potassium, and sodium) in addition to measuring at the central laboratory to confirm the tolerability when TAK-536 is titrating (including unscheduled visit), if needed at the investigator's discretion. The results of the local measurements will not be required recording in the eCRF.

The following formula proposed by the Committee for Pediatric Chronic Kidney Disease will be used to deduce eGFR in Japanese children.

eGFR in children (mL/min/1.73 m^2)
=110.2 × standard serum Cr (mg/dL)/serum Cr (mg/dL) + 2.93,

where, the standard serum Cr (mg/dL) is calculated from the height (Ht, in meter; Ht measured most recently will be used) as follows:

For a boy, $-1.259\ Ht^5 + 7.815\ Ht^4 - 18.57\ Ht^3 + 21.39\ Ht^2 - 11.71\ Ht + 2.628$
For a girl, $-4.536\ Ht^5 + 27.16\ Ht^4 - 63.47\ Ht^3 + 72.43\ Ht^2 - 40.06\ Ht + 8.778$

Uemura O, et al. Clin Exp Nephrol. 2014 [14]

Follow-up laboratory tests should be performed to determine whether the subject continue the study or not, in case of acute deterioration of renal function (eg, ≥50% reduction in eGFR or less than 30 mL/min/1.73 m^2 or serum potassium value over 5.5 mEq/L) (See Section 7.5).

If subjects experience ALT or AST > 3 ×ULN after the start of the Run-in Period (Week -2), follow-up laboratory tests (at a minimum, ALP [serum], ALT, AST, bilirubin [total bilirubin], GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted (Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.).

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

Only female subjects of childbearing potential, defined by the investigator's or subinvestigator's positive opinion about the subject's reproductive potential, will undergo a qualitative hCG pregnancy test. The local laboratory will perform the test.

The investigator or subinvestigator is reviewing and filing the laboratory results. The investigator will maintain a copy of the normal reference ranges including the archival records for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 1 month after the end of the study, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to preserve or donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation), who are postmenopausal (defined as at least 5 years since last regular menses, confirmed before any study drug is implemented), or who have no possibility of childbearing in the opinion of investigator or subinvestigator.

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, female subjects of childbearing potential must use copper intrauterine devices (IUDs) combined with male condom or female condom. Medications and devices containing hormones are excluded.

The subject and the subject's parent, or the subject's legal guardian will be provided with information on acceptable methods of contraception as part of the subject informed consent/assent process and will be asked to sign a consent/assent form stating that they understand the requirements for avoidance of pregnancy, preservation or donation of ova from providing the consent/assent until 1 month has passed from the end of the study.

During the course of the study, regular urine hCG pregnancy tests will be performed only for female subjects of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A).

This protocol does not condone or endorse under-age sexual activity.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study drug, or within 1 month of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in attachment 1.

If the female subject and her parent, or the subject's legal guardian agree to the primary care physician being informed, the investigator or subinvestigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 ECG Procedure

A resting 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: normal or abnormal. The investigator (or a qualified observer at the study site) will judge if it is clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, and QRS interval.

QTc will be calculated by the sponsor using the Fredericia's formula ($QT/RR^{0.33}$).

9.1.13 Pharmacokinetic Sample Collection

According to the study schedule (Appendix A), all pharmacokinetic samples should be collected on each visit except for Week 16, at the same time of blood sample collection for laboratory tests

to evaluate the trough values (approximately 21 to 27 hours after the latest dose) without taking the study drugs.

In addition to collection of the pharmacokinetic samples at trough, pharmacokinetic samples will be also collected once (total twice before and after the administration of the study drug) 2 hour (acceptable time window, 1 to 3 hours) after taking the study drug from the available subjects to evaluate the pharmacokinetics after taking the study drug at each visit by Week 12 of the Treatment Period.

On the visit of Week 16, subjects should visit the study site after taking the study drug to collect pharmacokinetic samples 2 hour (acceptable time window, 1 to 3 hours) after taking the study drug at the same time as the blood sample collection for laboratory tests.

9.1.13.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (one 2-mL sample per scheduled time) for pharmacokinetic analysis of TAK-536 and its metabolites (M-I and M-II) will be collected into vacutainers containing ethylenediaminetetraacetic acid dipotassium salt dihydrate (EDTA-2K). After mixing the vacutainers 5 to 6 times by inversion immediately, vacutainers will be centrifuged at 4°C and 3000 rpm for 10 minutes. The plasma will be dispensed from the vacutainers to polypropylene tube and be stored frozen below -20°C in a freezer until being shipped to the analytical institute.

For each sample, the date and time of the latest study drug administration and the actual time of blood sample collection will be recorded in the eCRF.

9.1.13.2 Bioanalytical Method

Plasma concentrations of TAK-536 and its metabolites (M-I and M-II) will be measured by HPLC/MS/MS (high-performance liquid chromatography with tandem mass spectrometry) at PPD

9.1.14 Documentation of Subjects Failure

An eCRF must be created for all subjects giving informed consent who withdrawn before the start of the Treatment Period.

The primary reason for subject failure is recorded in the eCRF using the following categories:

- Death
- Adverse Event
- Screen Failure (failed inclusion criteria or did meet exclusion criteria)
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject <specify reason>.
- Withdrawal by parent or guardian <specify reason>.

- Study terminated by sponsor.
- Pregnancy
- Other <specify reason>.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.15 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the Treatment Period.

If the subject is found to be not eligible for the Treatment Period, the investigator or subinvestigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Compliance with study drug (amount of dispense and return) between the visits, timing of the study dose (before or after breakfast) and the latest dosing date and time before collecting sample for pharmacokinetic evaluation will be confirmed and recorded in the eCRF.

Subjects, the subjects' parent, or the subjects' legal guardian will be instructed to be compliant with the study drug throughout the study. If a subject is noncompliant (< 70% or > 130%) with the study medication (TAK-536 placebo) during the Run-in Period, the subject will be excluded before the start of the Treatment Period, as indicated in the exclusion criteria No. 5. If a subject is noncompliant with the study medication (TAK-536) (eg, failure to take < 50% of the scheduled dosed after the last visit) after the start of the Treatment Period, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

9.3.1 Screening

Subjects will be screened within 14 days prior to the start of the Run-in Period. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

9.3.2 Start of the Run-in Period (Week -2)

The study drug (TAK-536 placebo) for the Run-in Period will be administered on the same day after the tests, observations and evaluations specified for each visit are performed. In case that subjects take RAS inhibitors in the morning of the visit day, the administration of the study drug (TAK-536 placebo) for the Run-in Period will be started from the next day.

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

9.3.3 End of the Run-in Period (Week 0)

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be entered after performing the tests and observations specified for each visit and will be initiated to receive the study drug for the Treatment Period on the same day.

The first and the last date of the study drugs administration for the Run-in Period will be recorded in the eCRF for those receiving the study drugs for the Run-in Period and subsequently received the study drug for the Treatment Period.

See Section 9.1.14 for procedures for documenting subjects withdrawn before the start of the Treatment Period.

9.3.4 Treatment Period (Weeks 2, 4, 8, 12, 16, 20, 24, 32, and 40)

The tests and observations specified for each visit will be performed.

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

On the visit of Week 16, subjects should visit the study site after taking the study drug and the tests and observations specified will be performed.

9.3.5 Final Visit or Early Termination

The Final Visit will be performed on Week 52 or at the Early Termination Visit.

The tests and observations specified for each visit will be performed.

For subjects early terminate the study after the start of the Treatment Period, if possible, the same tests, observations, and evaluations as those scheduled at Week 52 should be performed. Whenever possible, office sitting blood pressure should be determined within 3 days after early termination and the other tests, observations, and evaluations should be performed within 14 days after early termination (the next day of the final dose should be calculated as the first day).

For all subjects who entered the Treatment Period, the investigator or subinvestigator must complete the Subject Status on eCRF page with the first day when the subjects received the study drug for the Treatment Period and study completion or early termination status until Week 24 and study completion status at Week 52 for subjects who continuingly received the study drug beyond Week 24.

9.3.6 Follow-up Period: Week 54

Follow-up Period will begin the first day after the final administration of TAK-536 for the Treatment Period and will continue until 2 weeks. The tests and observations specified for each visit will be performed. If subjects terminate the study drug in the Run-in Period or at an early stage of the Treatment Period, no tests, observations, and evaluations will be required but care should be taken for subject safety.

9.3.7 Post Study Care

The study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study participation whether or not it is considered related to the drug or study procedures.

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator or subinvestigator for any reason.
- AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator or subinvestigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition after informed consent is signed, the worsening or complication should be recorded appropriately as an AE. The investigator or subnvestigator should ensure that the event term recorded captures the change in the condition (eg, "worsening of …").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious or severe in nature, that is, the investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, the investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of …").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the study drug, or if a sign or a symptom appears secondarily due to an AE, the worsening or complication should be recorded appropriately as a new AE. The investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in the study drug, or if a sign or a symptom appears secondarily due to an AE, the worsening or complication should be recorded as a new AE. The investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE that are not related to starting the study drug or changing in the dose or regimen, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator or subinvestigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

10.1.4 AEs of Special Interest

An AEs of Special Interest (treatment-emergent only, serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator or subinvestigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for the investigator or subinvestigator as to how and when they should be reported to Takeda.

10.1.5 Severity of AEs

The different categories of severity are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs to Study Drugs

The causality of each AE to study drugs will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

The causality should be assessed as Related if the investigator or subinvestigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the causality should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or the investigator or subinvestigator.

10.1.9 End Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Pattern of Adverse Event

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Taken with Study Treatment

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE, the AE that occurred before the study drug administration.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Drug Interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed

study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".

- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time the subject signs the informed consent. Routine collection of AEs will continue until the end of the Follow-up Period (or the tests performed at early termination).

10.2.1.2 AE Reporting

At each study visit, the investigator or subinvestigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious AE that occurs prior to the first exposure to study drug must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious AEs that occur prior to the first exposure to study drug, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs after the first exposure to study drug, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator or subinvestigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and end date.
3. Pattern.
4. Severity.
5. Investigator's opinion of the causality between the event and administration of study drug(s).

6. Investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure.
7. Action taken with study treatment (not applicable for the AE that occurred before the study drug administration).
8. Outcome of event.
9. Seriousness.
10. After administration of study drug.
11. Treatment emergent.

10.2.1.3 AEs of Special Interest Reporting

Pediatric subjects, the subject population of this study, are vulnerable, and as such need special attention with regard to the risk of the over decrease in blood pressure accompanying the use of antihypertensive drugs. Furthermore, kidney function is often impaired in pediatric subjects with secondary hypertension. Administration of RAS inhibitors to such patients may reduce GFR, deteriorating the kidney function. Hence, the following adverse events related to hypotension or renal impairment will be investigated as special interest AEs in this study.

[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.

If this AE of special interest occurs during the Run-in Period, the Treatment Period or the Follow-up Period, it should be reported to the sponsor (described in the separate contact information list) immediately or within 1 business day of first onset or subject's notification of the event. Hypotension-related AE or renal dysfunction-related AE Form or an SAE Form should be completed, signed and/or sealed by the principal investigator, and reported to appropriate personnel in the separate contact information list within 10 business days.

The AE of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be reported to the sponsor (described in the separate contact information list) within 1 business day of first onset or subject's, the subject's parent's, or the subject's legal guardian's notification of the event. The principal investigator should submit the completed SAE

form within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's or subinvestigator's name.
- Name of the study drugs
- Causality assessment.

Any SAE spontaneously reported to the investigator or subinvestigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST > 3 ×ULN and total bilirubin > 2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator or subinvestigator must contact the sponsor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.9 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator or subinvestigator should complete a follow-up SAE form or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs, and the head of the study site, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee , SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs and medical history including concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs:

- Results of clinical laboratory tests conducted at the central laboratory
- Results of pharmacokinetics conducted at the analytical institute

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator or subinvestigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the

identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, the investigator and the head of the site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

At the time when the data of 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 or 52 in the Treatment Period, the data until Week 24 or 52 in the Treatment Period will be analyzed separately after being locked.

13.1.1 Analysis Sets

In this study, 2 kinds of analysis sets are defined: a full analysis set (FAS) and a safety analysis set. The safety analysis set used for safety analysis will be defined as "all subjects who received at least 1 dose of the study drug for the Treatment Period." The definition of each analysis set will be described in the Handling Rule for Analysis.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. The Handling Rule for Analysis must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics will be summarized using the safety analysis set.

13.1.3 Efficacy Analysis

(1) Secondary endpoints and analytical methods

[Secondary endpoints]

Office trough sitting systolic and diastolic blood pressure, proportion of subjects who achieve the target blood pressure

[Analytical methods]

The analyses discussed below will be conducted with the FAS.

Summary statistics (number of subjects, mean, standard deviation, maximum, minimum, and quartiles; hereinafter the same) and 2-sided 95% confidence intervals for mean values will be calculated for the office trough sitting systolic and diastolic blood pressure at each time point (including the end of the Treatment Period I and the end of the Treatment Period II; hereinafter the same).

Summary statistics and 2-sided 95% confidence intervals for mean values will be calculated referring to a 1-sample t-test for the change of office trough sitting systolic and diastolic blood pressure from the end of the Run-in Period (Week 0) to each time point during the Treatment Period.

The proportion of subjects who achieve the target blood pressure at each time point during the Treatment Period will be summarized.

(2) Data conversion methods and handling of missing data

Details of data conversion methods and handling of missing data will be defined in the Handling Rule for Analysis and SAP.

(3) Significant level and confidence coefficient

Significant level: 5% (2-sided test)

Confidence coefficient: 95% (2-sided estimates)

13.1.4 Pharmacokinetic Analysis

Pharmacokinetic endpoints and analytical methods

[Secondary endpoints]

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

[Analytical methods]

The following analyses will be conducted with the subjects who have adequately measured plasma concentration of TAK-536 in the FAS.

Concentration of TAK-536 and its metabolites (M-I and M-II) in plasma will be summarized at each time point.

A population pharmacokinetic analysis will be conducted with the subjects who have adequately measured plasma concentration of TAK-536 in the FAS. Population pharmacokinetic parameters in pediatric patients with hypertension will be estimated and the effect of weight on the pharmacokinetics of TAK-536 will be assessed quantitatively. In addition, other factors which affect the pharmacokinetics of TAK-536 will be explored. When the above analyses are conducted, an integrated analysis will be also performed with the data of the prior pharmacological study in pediatric patients with hypertension (TAK-536/CPH-103) as needed, and a SAP and an analysis results will be provided separately from those of this study.

13.1.5 Safety Analysis

[Primary endpoints]

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

[Analytical methods]

The following analyses will be conducted with the safety analysis set.

1) AEs (Treatment-emergent AEs)

A treatment-emergent AE (TEAE) is defined as any AE occurring after the start of TAK-536 administration of the Treatment Period.

The incidence of TEAEs listed below will be analyzed. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The frequency distribution will be provided using the system organ class (SOC) and preferred term (PT) using MedDRA as follows:

- TEAEs
- Drug-related TEAEs
- Severity of TEAEs
- Severity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

2) Anthropometric (weight, height and BMI) measurements, laboratory tests, resting 12-lead ECG, and vital signs (office standing blood pressure, office sitting pulse rate, office standing pulse rate, and home sitting blood pressure)

For continuous variables, the observed values and the changes from the end of the Run-in Period (Week 0) will be summarized for each time point. In addition, individual figures of the observed values will be provided.

For categorical values, shift tables of the data before and after administration will be provided.

13.2 Interim Analysis and Criteria for Early Termination

At the time when the data of 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.

13.3 Determination of Sample Size

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

[Justification for Determination of Sample Size]

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

Assuming the mean change of trough sitting diastolic blood pressure from the end of the Run-in Period (Week 0) to the end of the Treatment Period I of -6.5 mmHg and an SD of 10.5 mmHg, and

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

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, subinvestigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator or subinvestigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator or subinvestigator should document all protocol deviations. Significant protocol deviations will be entered into the eCRF, which is reviewed by the study sponsor or designee. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], PMDA). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent/assent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent/assent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent/assent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent/assent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject/parent/legal guardian incentives should not exert undue influence for participation. Payments to subjects, the subjects' parent, or the subjects' legal guardian must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent/Assent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. An assent document describes the study, using a language appropriate to the subject's age and development, to potential subjects with enough mental capacity to understand what it means to participate in a clinical study, and is used to obtain the

subject's assent (a pediatric subject's consent, which is not a regulatory requirement) separately from the subject's parent's, or the subject's legal guardian's consent. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent and assent forms. The informed consent and assent forms must be approved by both of the IRB and sponsor prior to use.

The subject assent form must be written in a language appropriate to the subject's age and development to the prospective subject. The informed consent form must be written in a language fully comprehensible to a subject's parent or the subjects' legal guardian. It is the responsibility of the investigator or subinvestigator to explain the subject assent form to the subject using a language and terms comprehensible and to explain the detailed elements of the informed consent form to a subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject and the subject's parent, or the subject's legal guardian must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject's parent or the subject's legal guardian determines the subject will participate in the study, then the informed consent form must be signed and dated by the subject's parent or the subject's legal guardian at the time of consent and prior to the subject entering into the study.

Whenever possible, the subject's own assent should be obtained in addition to the subject's parent's or the subject's legal guardian's consent. The subject's assent will be preferably obtained in writing, if he/she is a junior high school student or of a higher age. Whenever a written assent is not provided, though preferable also for subjects aged below junior high school students, the subject's oral assent must be documented in the informed consent form signed by the subject's parent or the subject's legal guardian. The subject's parent or the subject's legal guardian should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink.

Once signed, the original informed consent form, and the subject assent form (if applicable, the same hereinafter) will be stored in the investigator's site file. The investigator or subinvestigator must document and the dates the subject's parent or the subject's legal guardian signs the informed consent form and the date the subject signs the informed assent form in the subject's medical record. Copies of the signed informed consent form and the signed subject assent form shall be given to the subject, the subject's parent, or the subject's legal guardian.

All revised informed consent/assent forms must be reviewed and signed by relevant subjects, the relevant subject's parent or the subject's legal guardian in the same manner as the original informed consent/assent. The date the revised consent/assent was obtained should be recorded in

the subject's medical record, and the subject, the subject's parent, or legal guardian should receive a copy of the revised informed consent/assent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject and the subject's parent, or the subject's legal guardian as part of the informed consent/assent (if deemed appropriate by the investigator or subinvestigator) process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator and subinvestigator need to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register

interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator and subinvestigator have questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix C Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Amendment 02.

Page 51, Section 10.1.11 Action Taken with Study Treatment

Existing Text:

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE, the AE that occurred before the study drug administration.
- Drug Interrupted – the dose was interrupted due to the particular AE.

Revised Text:

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE, the AE that occurred before the study drug administration.
- **Dose Reduced – the dose was reduced due to the particular AE.**
- **Dose Increased – the dose was increased due to the particular AE.**
- Drug Interrupted – the dose was interrupted due to the particular AE.

Rationale for Amendment:

It was revised to collect the information accurately about the action taken with the study drug when AEs occurred.

Page 71, Appendix A Schedule of Study Procedures<Acceptable Time Windows for Study Procedures>

Existing Text:

Open Label Treatment				Follow-up
Week 32 (Day 225)	Week 40 (Day 281)	Week 52 (Day 365)	Early termination	Week 54 (*Day 379*)
212 to 239	268 to 295	*359* to 372	(b)	*373 to 386*

Note: The first day of the study drug administration for the Treatment Period is counted as Day 1. (Day X) indicates the reference day of each time point.

(a) Within 3 days after early termination for office sitting blood pressure, within 14 days after early termination for the other tests, observations, and evaluations (The day after the last study drug administration day is accounted as 1.).

Revised Text:

Open Label Treatment				Follow-up
Week 32 (Day 225)	Week 40 (Day 281)	Week 52 (Day 365)	Early termination	Week 54 (**Week 52+14**)
212 to 239	268 to 295	**352** to 372	(b)	**±7**

Note: The first day of the study drug administration for the Treatment Period is counted as Day 1. (Day X) indicates the reference day of each time point.

(b) Within 3 days after early termination for office sitting blood pressure, within 14 days after early termination for the other tests, observations, and evaluations (The day after the last study drug administration day is accounted as 1.).

Rationale for Amendment:

Correction of misdescription.

PROTOCOL

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

A Phase 3 Long-term Study of TAK-536 in Pediatric Patients 6 to Less Than 16 Years with Hypertension

Sponsor: Takeda Pharmaceutical Company Limited
1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan

Study Number: TAK-536/OCT-101

IND Number: Not Applicable **EudraCT Number:** Not Applicable

Compound: TAK-536

Date: 12 May 2016 **Amendment Number:** 01

Amendment History:

Date	Amendment Number	Region
16 March 2016	First version	All sites
12 May 2016	01	All sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the attachments.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

1.3 Protocol Amendment 01 Summary of Changes

The primary purpose of this amendment is to clarify examples of contraceptive methods. Some part are modified to clarify the contents. Detailed description of amendments are given in Appendix C.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

CCI [redacted]

2.0 STUDY SUMMARY

Clinical Study Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-536	
Study 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	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Identifier: TAK-536/OCT-101	**Phase:** 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-week; Treatment Period II, 40-week), and a 2-week Follow-up Period (56 weeks in total).

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 the subjects only who treated with any antihypertensive drugs as a prior treatment, the Run-in Period could be extended up to 4 weeks if blood pressures do not meet the inclusion criteria. Subjects who 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 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 treatments for hypertension in the Treatment Period I by the investigator or subinvestigator; 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 administration of placebo. In the case of the down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period I. Especially, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBS may cause withdrawal syndrome.

In the Treatment Period I (Week 0 to 12), initial dose of TAK-536 will be 2.5 mg for the subjects weighing < 50 kg or 5 mg for the subjects weighing ≥ 50 kg. After the initial dose, TAK-536 will be titrated to 5 mg, 10 mg, and 20 mg for the subjects weighing < 50 kg or to 10 mg, 20 mg, and 40 mg for the subjects weighing ≥ 50 kg when the subjects do not achieve the target blood pressure and there are no concerns in tolerability. TAK-536 will be titrated at any scheduled visit of Week 2, 4, or 8 in the Treatment Period I. Between the visits of Week 4 and 8 during the Treatment Period I, an additional unscheduled visit of Week 6 may be requested at the investigator's discretion in order to titrate the dose of the study drug in the subjects when the 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 in tolerability with titration of TAK-536 (i.e., in case of occurring any AEs caused by titration of TAK-536). During the Treatment Period I, change in the dosage of the antihypertensive drug is prohibited in the subjects who treated with a single antihypertensive drug other than RAS inhibitors at the start of the Treatment Period I.

During the Treatment Period II (Week 12 to 52), the treatments at the end of the Treatment Period I will be continued. TAK-536 can be titrated to the highest dose (20 mg for the subjects weighing < 50 kg or 40 mg for the 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. When the antihypertensive drugs are required dose reduction or interruption because of the concerns in tolerability with titration (i.e., excessive reduction in blood pressure, other AE, etc.) in the Treatment Period II, the antihypertensive drugs other than TAK-536 (in case of concomitant use) should be reduced or interrupted first. Thereafter, dose reduction or

<table>
<tr><td colspan="2">interruption of TAK-536 should be considered.
Follow-up Period will be 2 weeks from the next day of 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.</td></tr>
<tr><td colspan="2">Primary Objectives:
To evaluate the safety of administration of TAK-536 in pediatric patients aged 6 to less than 16 years with hypertension</td></tr>
<tr><td colspan="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</td></tr>
<tr><td colspan="2">Subject Population: Pediatric patients aged 6 to less than 16 years, with essential or secondary hypertension.</td></tr>
<tr><td>Planned Number of Subjects:
Total of 50 subjects (who enter the Treatment Period).</td><td>Planned Number of Sites:
Approximately 25 sites</td></tr>
<tr><td>Dose Level(s):
Regimen: Subjects will orally receive the study drug once daily before or after breakfast.
Dose: Placebo during the Run-in Period. Any of TAK-536 2.5 mg, 5 mg, 10 mg, 20 mg tablet for the subjects weighing < 50 kg, or any of TAK-536 5 mg, 10 mg, 20 mg, 40 mg tablet for those weighing ≥ 50 kg during the Treatment Period.</td><td>Route of Administration:
Oral</td></tr>
<tr><td>Duration of Treatment:
52 weeks</td><td>Study Length:
2 weeks of the Run-in Period (acceptable range, 1 to 4 weeks), 52 weeks of the Treatment Period (12 weeks of the Treatment Period I and 40 weeks of the Treatment Period II), 2 weeks of the Follow-up Period</td></tr>
</table>

Main Criteria for Inclusion:

- The Japanese subject who has a diagnosis of hypertension. A subject is eligible if he/she is deemed hypertensive according to the reference blood pressure values of children by gender and age; office sitting diastolic or systolic blood pressure ≥ 95 percentile for essential hypertension without concomitant hypertensive organ damage, and ≥ 90 percentile for secondary hypertension with concomitant chronic kidney disease (CKD), diabetes mellitus, heart failure or any hypertensive organ damage.
  In addition, subjects need to meet the following criteria:
  (1) If currently treated with any antihypertensive drugs at the start of the Run-in Period: Subject has a documented historical diagnosis of hypertension and an office sitting diastolic or systolic blood pressure meeting the above criteria at the end of the Run-in Period (Week 0).
  (2) If currently untreated with any antihypertensive drugs at the start of the Run-in Period: Subject who meets the above criteria on 3 separate time points including screening and the end of the Run-in Period (Week 0). In addition, subject with essential hypertension without concomitant hypertensive organ damage still maintains hypertension with non-pharmacotherapy including foods or exercises for at least 3 months within 1 year prior to the start of screening.
- The subject is male or female and aged 6 to less than 16 years at the time of informed consent.
- The subject weighs at least 20 kg at screening.
- A subject who has undergone kidney transplantation is eligible if he/she underwent the transplantation at least 6 months earlier at screening, and the graft has been functionally stable (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2) for at least 6 months with evidence (e.g., Doppler echography, CT scan [computed tomography] or MRI [magnetic resonance imaging]) excluding grafted kidney arterial stenosis. A subject on immunosuppressive therapy with a stable dose at least 30 days prior to screening is eligible.

Main Criteria for Exclusion:

- The subject has poorly controlled hypertension indicated by an office sitting systolic blood pressure higher by at least 15 mmHg and/or an office sitting diastolic blood pressure higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age.
- The subject has a diagnosis of malignant or accelerated hypertension.
- The subject was noncompliant (< 70% or > 130%) with the study drug during the Run-in Period.
- The subject has severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), is receiving dialysis, has a renovascular disease affecting one or both kidneys, severe nephrotic syndrome not in remission, or a serum albumin level < 2.5 g/dL.
- The subject has a history of, or the signs/symptoms of serious cardiovascular, hepatobiliary, gastrointestinal, endocrine (eg, hyperthyroidism, Cushing's syndrome), hematological, immunological, urinogenital, psychiatric disease, cancer, or any other disease that adversely affects subject's health, or, in the opinion of the investigator or subinvestigator, potentially confounds the study results.
- The subject has hemodynamically significant left ventricular outflow obstruction due to aortic stenosis or aortic valvular disease, or is scheduled to undergo a medical procedure affecting blood pressure during the study (eg, correction of arterial anomaly).
- The subject has a history of or concurrent clinically significant abnormality of 12-lead electrocardiogram (ECG) that, in the opinion of the investigator or subinvestigator, disqualifies the subject for participation in the study.
- The subject has poorly controlled diabetes mellitus indicated by HbA1c > 9.0% at screening.
- The subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 2.5 × the upper limit of normal (ULN), or a total bilirubin level ≥ 1.5 × ULN at screening, severely impaired hepatic function, any active liver disease, or jaundice.
- The subject has hyperkalemia exceeding ULN at screening.

Main Criteria for Evaluation and Analyses:

(1) Primary Endpoint

<Safety>

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

(2) Secondary endpoints

<Efficacy>

- Office trough sitting systolic and diastolic blood pressure
- Proportion of subjects who achieve the target blood pressure*

*: < 95 percentile shown in a table of the reference blood pressure values of children by gender and age for essential hypertension, < 90 percentile shown in the same table for secondary hypertension

<Pharmacokinetic endpoints>

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

Statistical Considerations:

<Primary endpoints and analytical methods>

[Primary endpoints]

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

[Analytical methods]

The following analyses will be conducted with the safety analysis set.

(1) AEs (Treatment-emergent AEs)

A treatment-emergent AE (TEAE) is defined as any AE occurring after the start of TAK-536 administration of the Treatment Period.

The incidence of TEAEs listed below will be analyzed. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The frequency distribution will be provided using the system organ class (SOC) and preferred term (PT) using MedDRA as follows:

- TEAEs
- Drug-related TEAEs
- Severity of TEAEs
- Severity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs overt time

(2) Anthropometric (weight, height and BMI) measurements, laboratory tests, resting 12-lead ECG, and vital signs (office standing blood pressure, office sitting pulse rate, office standing pulse rate, and home sitting blood pressure)

For continuous variables, the observed values, and the changes from the end of the Run-in Period (Week 0) will be summarized for each time point. In addition, individual figures of the observed values will be provided.

For categorical values, shift tables of the data before and after administration will be provided.

Sample Size Justification:

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

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

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
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
eGFR	estimated glomerular filtration rate
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
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
PTP	press through package

QOL	quality of life
RAS	renin-angiotensin-system
RBC	red blood cell
SAE	serious AE
SAP	statistical analysis plan
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment emergent AE
TPC	Takeda Pharmaceutical Company Limited
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Hypertension develops in not only in adults but also in children and adolescents. While there are few epidemiological reports about the number of pediatric patients with hypertension in Japan, it is reported that hypertension is detected in 0.1% to 1% among elementary-school and junior-high-school students and in approximately 3% among high-school students in health checkups for Japanese children [1, 2]. According to the 2013 Population Projection, the number of pediatric patients with hypertension is estimated to be approximately 11 million in elementary-school and junior-high-school students (6 to 15 years) and approximately 3.6 million in high-school students (16 to 18 years). Therefore, on the basis of the morbidity rate of hypertension in health checkups above, the number of pediatric patients with hypertension is estimated to be 100 to 200 thousand (10 to 110 thousand in elementary-school and junior-high-school students and 110 thousand in high-school students).

Pediatric hypertension is classified into essential hypertension and secondary hypertension as described for adults. Although essential hypertension in children is generally mild, such patients are at a high risk of cardiovascular disease including left ventricular hypertrophy and carotid intima-media wall thickening as well as organ damage, eg, renal dysfunction [3, 4]. Furthermore, essential hypertension in children can track into adult essential hypertension with patients' growth [5]. The possibility of secondary hypertension, in contrast, increases with a younger age and the majority cases are severe. Hypertension caused by renal diseases (renal hypertension) accounts for 60% to 80% of children with secondary hypertension, and chronic renal failure requires particular attention. Therefore, it is necessary to prevent deterioration of renal function and progression of organ damage.

Moreover, hypertension persisting from childhood is likely to cause cardiovascular diseases and organ damage including renal dysfunction, thereby markedly affecting the patient's quality of life (QOL) and prognosis not only in childhood but also in future. Therefore, it is highly important to manage blood pressure in the early stage.

The Japanese Society of Hypertension Guidelines for the Management of Hypertension 2014 (JSH 2014) [6] recommends that drug therapy should be considered after non-pharmacological interventions (dietary and exercise therapy) are primarily performed since essential hypertension in children is often mild. For patients with secondary hypertension and patients with target organ damage, diabetes mellitus, or chronic kidney disease (CKD), drug therapy is highly recommended to prevent the development and progression of organ damage.

JSH 2014 [6] and the Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases by the Japanese Circulation Society (JCS 2012) [7] recommend angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers as the first-choice drugs for pediatric patients. In particular, more strict blood pressure management is recommended for hypertension with CKD or diabetes mellitus than that for hypertension without complications. Hypertension with such complications is recommended to be treated with ARBs having antiproteinuric effects and inhibitory effects of CKD progression in addition to ACE inhibitors.

While a number of antihypertensive drugs for adults are available in Japan, only 4 drugs are indicated for hypertension in children, valsartan being the only ARB among them. Therefore, the treatment options for pediatric patients with hypertension are not sufficient.

TAK-536 (azilsartan) is a novel ARB produced by Takeda Pharmaceutical Company Limited (TPC) and was approved for the treatment of adult hypertension under the product name of Azilva tablets 20 mg and 40 mg in January 2012. A supplementary new drug application was filed for the additional registration of Azilva tablet 10 mg, which was approved in March 2014. TAK-536 is superior to the existing ARBs (candesartan) in the antihypertensive effect as well as its persistence , while being safe and well tolerated. It is now widely used by adult patients with hypertension.

Thus, to resolve the unmet needs in the present treatment of pediatric hypertension, it is important to provide TAK-536 for pediatric patients with hypertension, whose clinical usefulness for adult patients is established.

Findings from a Clinical Study of TAK-536

Upon the development of TAK-536 as an antihypertensive drug for pediatric patients with hypertension, single-dose study (TAK-536/CPH-103) was conducted to evaluate the pharmacokinetics and safety of TAK-536 in 6 pediatric patients aged 6 to less than 16 years with hypertension. The dose of TAK-536 was 5 mg for subjects weighing less than 50 kg, and 10 mg for those weighing at least 50 kg.

TAK-536 was rapidly absorbed after a single oral administration of a TAK-536 5 mg tablet or 10 mg tablet and was detectable in the plasma of all subjects at 1 hour after administration. The mean Cmax of TAK-536 was 888.3 ng/mL in the 5 mg group and 831.3 ng/mL in the 10 mg group, and the mean AUC(0-inf) of TAK-536 was 6635.7 ng·hr/mL and 7433.3 ng·hr/mL, respectively.

Only 1 subject who received a TAK-536 5 mg tablet experienced a TEAE (gastroenteritis), which was mild in intensity and considered to be unrelated to the study drug. The outcome of gastroenteritis was “recovered/resolved.” No safety concerns were found in the study, and TAK-536 was well tolerated.

4.2 Rationale for the Proposed Study

TAK-536 is developed to be approved for the pediatric patients aged 1 to less than 16 years with hypertension. In the field of the pediatrics, the efficacy and safety should be evaluated in schoolchildren (6 to 16 years) first, and thereafter, the efficacy and safety should be evaluated in the lower aged pediatric patients [8]. Since no clinical studies have been conducted to evaluate safety and efficacy of TAK-536 in pediatric patients with hypertension, this study is planned to evaluate the safety, efficacy, and pharmacokinetics of long-term administration of TAK-536 in pediatric patients with hypertension aged 6 to less than 16 years before evaluating those in pediatric patients with hypertension aged 1 to less than 6 years.

CCI [redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 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

5.2 Endpoints

5.2.1 Primary Endpoints

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)

5.2.2 Secondary Endpoints

Efficacy:

- Office trough* sitting diastolic and systolic blood pressure

  *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**

  ** < 95 percentile shown in Table 5.a for essential hypertension

  < 90 percentile shown in Table 5.a for secondary hypertension

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

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

Systolic/diastolic blood pressures (mmHg, JCS2012 [7])
The 90th, 95th, and 99th indicate 90, 95, and 99 percentile, respectively.

Pharmacokinetics:

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

6.0 STUDY DESIGN AND DESCRIPTION

6.1 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-week; Treatment Period II, 40-week), 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 the subjects only who treated with any antihypertensive drugs as a prior treatment, the Run-in Period could be extended up to 4 weeks if blood pressures do not meet the inclusion criteria.

Subjects who 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 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 I by the investigator or subinvestigator; 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 administration of placebo. In the case of the down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period I. Especially, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBs may cause withdrawal syndrome.

(2) Treatment Period I

In the Treatment Period I (Week 0 to 12), initial dose of TAK-536 will be 2.5 mg for the subjects weighing < 50 kg or 5 mg for the subjects weighing ≥ 50 kg. After the initial dose, TAK-536 will be titrated to 5 mg, 10 mg, and 20 mg for the subjects weighing < 50 kg or to 10 mg, 20 mg, and 40 mg for the subjects weighing ≥ 50 kg 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 of Week 2, 4, or 8 in the Treatment Period I. Between the visits of Week 4 and 8 during the Treatment Period I, 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. TAK-536 can be reduced at the investigator's or subinvestigator's discretion if there are any concerns in tolerability with titration of TAK-536 (i.e., in case of occurring any AEs caused by titration of TAK-536). During the

Treatment Period I, change in the dosage of the antihypertensive drug is prohibited in the subjects who treated with a single antihypertensive drug other than RAS inhibitors at the start of the Treatment Period I.

* target blood pressure:

< 95 percentile shown in Table 5.a for essential hypertension, < 90 percentile shown in Table 5.a for secondary hypertension

(3) Treatment Period II

During the Treatment Period II (Week 12 to 52), the treatments at the end of the Treatment Period I will be continued. TAK-536 can be titrated to the highest dose (20 mg for the subjects weighing < 50 kg or 40 mg for the 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 are required dose reduction or interruption because of the concerns in tolerability with titration (i.e., excessive reduction in blood pressure, other AE, etc.) in the Treatment Period II, 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.

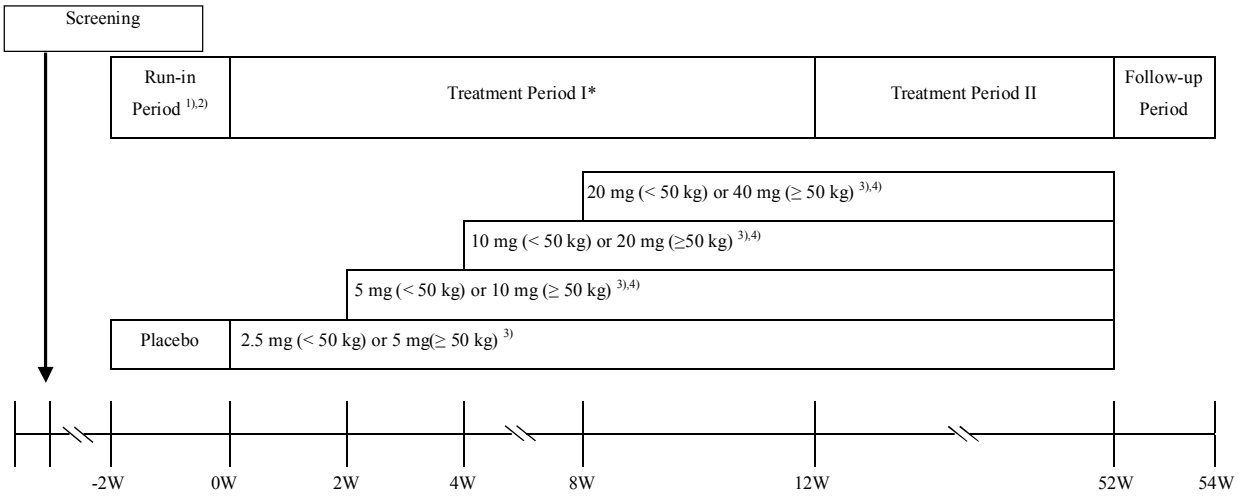
(4) Follow-up Period

Follow-up Period will be 2 weeks from the next day of 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 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



1) The subjects whose blood pressures meet the inclusion criteria 1 (at earliest) week after receiving placebo in the Run-in Period can enter the Treatment Period. For the subjects only who treated with any antihypertensive drugs as a prior treatment only, the Run-in Period could be extended up to 4 weeks if 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 administration of placebo. In the case of the down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period I. Especially, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBs may cause withdrawal syndrome.
3) In the Treatment Period I, TAK-536 can be titrated biweekly when the subjects do not achieve the target blood pressure while evaluation of safety and tolerability. TAK-536 can be reduced at the investigator's or subinvestigator's discretion if there are any concerns in tolerability with titration of TAK-536 (i.e., in case of occurring any AEs caused by titration of TAK-536).
4) When the antihypertensive drugs are required dose reduction or interruption because of the concerns in tolerability with titration (i.e., excessive reduction in blood pressure, other AE, etc.) in the Treatment Period II, 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 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 treatments for hypertension in the Treatment Period I by the investigator or subinvestigator. Change in the dosage of the antihypertensive drug at the start of the Run-in Period I is prohibited until the end of the Treatment Period I.
6) 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 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.

6.2 Justification for Study Design, Dose, Regimen, and Endpoints

[Justification for the Study Design]

Many pediatric patients with renal dysfunction are assumed to be entered this study since the proportion of pediatric patients with secondary hypertension caused by renal disease is high in pediatric patients with hypertension. Evidence-based Clinical Practice Guideline for CKD 2013 (JSN2013) [9] indicates that treatment with ARB should be start at a low dose in patients with renal dysfunction and the dose should be increased with caution by confirming the hypotensive effect of ARB and renal function. On the basis of above indication, an open-label, optional titration

design was selected in this study, in which TAK-536 can be titrated with monitoring subject condition.

Co-administration of RAS inhibitors, which is similar to TAK-536, is prohibited in order to evaluate appropriately the efficacy of TAK-536 in the pediatric patients throughout the Run-in Period and the Treatment Period I. In consideration of the safety for vulnerable pediatric population, subjects can continue to receive a single antihypertensive drug other than RAS inhibitors in the same dosage after the start of the Run-in Period, if the subjects are considered to need the additional treatment for hypertension by the investigator or subinvestigator. In the Treatment Period II, the subjects whose blood pressure is not reduced sufficiently by TAK-536 can receive additional antihypertensive drugs other than RAS inhibitors concomitantly in order to evaluate the efficacy and safety of the long-term administration of TAK-536 in pediatric patients under the condition of being closer to the routine medical care.

The Run-in Period with placebo was selected to wash out the placebo effect of the study drug and the influence of antihypertensive drugs as a prior treatment in subjects who were treated with any prior antihypertensive drugs. In addition, the Run-in Period allows the opportunity to assess subject compliance with the study drug (i.e., placebo) and subjects who are not sufficiently compliant with placebo will be excluded.

The Follow-up Period was selected to evaluate the subject safety after the study drug administration.

[Justification for the Doses]

The population pharmacokinetic model was developed based on data from a total of 58 subjects (6 for pediatric patients and 52 for healthy adult subjects). Also a population of subjects whose weights were uniformly distributed within the specified weight range between 20-80 kg by 1 kg (100 subjects for each body weight range and 6100 subjects in total) were generated and equally allocated to fixed TAK-536 doses of 2.5, 5, 10, 20, and 40 mg. Then, the population pharmacokinetic model was used to simulate the Cmax and AUC of TAK-536 following a single oral dose of each dose for each body weight category for virtual pediatric population, and distributions of simulated Cmax and AUC (median and 90% CI) of TAK-536 in pediatric patients weighing ≥ 20 kg and < 50 kg and those weighing ≥ 50 kg and < 80 kg were compared with actual parameters of Cmax and AUC (minimum and maximum) following TAK-536 10, 20, 40 and 80 mg in healthy adults.

Based on the simulation, estimated exposures to TAK-536 in pediatric patients weighing ≥ 50 kg and < 80 kg and those weighing ≥ 20 kg and < 50 kg after receiving TAK-536 2.5, 5, 10, 20, or 40 mg are similar to and a little below double of that in healthy adults receiving the same fixed dose, respectively. These findings indicate that exposures to TAK-536 in pediatric patients with doses up to 20 mg do not exceed the exposure in adults with the approved maximum dose of 40 mg.

Therefore, the initial dose was set at 5 mg, a half the typical adult half dose of 10 mg, for the subjects weighing ≥ 50 kg and at 2.5 mg for those weighing < 50 kg by further reducing the dose by half in consideration of subject safety.

On the basis of the results of the population pharmacokinetic model, 40 mg or 20 mg was selected as the highest dose of TAK-536 by weight for the subjects weighing ≥ 50 kg or < 50 kg, respectively. In the population pharmacokinetic model, estimated exposures to TAK-536 in pediatric patients weighing ≥ 50 kg after receiving TAK-536 40 mg as the highest clinical dose in adults or those in the patients weighing < 50 kg after receiving TAK-536 20 mg does not exceed the exposure to TAK-536 in adults after receiving TAK-536 40 mg as the approved maximum dose in adults. In addition, titrating from the lower dose while evaluation of safety and tolerability sufficiently were selected in consideration of subject safety.

TAK-536 has not been administered to the pediatric patients with hypertension with renal dysfunction. In addition, TAK-536 should be administered initially in lower dose to the adult patients with serious renal dysfunction and gradual titration is required for them in careful with monitoring subject condition in case of titration. The design of this study fulfills the above requirements.

[Justification for the Regimen]

Since meals do not affect the pharmacokinetics of TAK-536 in adults, the subjects receive the study drug before or after breakfast in the study.

[Justification of Endpoints]

Variables commonly used to evaluate the safety were selected as the primary endpoints because the primary objective of this study is to evaluate the long-term safety of TAK-536.

Office trough sitting diastolic and systolic blood pressure were selected as secondary endpoints to evaluate the efficacy and persistence of effect in reference to Principles for Clinical Evaluation of New Antihypertensive Drugs [10] and JSH2014 [6].

Plasma concentrations of TAK-536 and its metabolites (M-I and M-II) will be measured in order to evaluate the pharmacokinetics of TAK-536 in pediatric patients with hypertension.

[Justification for Study Duration]

(1) Run-in Period

Two weeks were set as the Run-in Period with placebo to wash out the placebo effect of the study drug or the influence of the antihypertensive drugs as a prior treatment. The subjects whose blood pressures meet the inclusion criteria 1 week (at earliest) after receiving placebo during the Run-in Period can enter the Treatment Period in consideration of subject safety. For the subjects only who treated with any antihypertensive drugs as a prior treatment, the Run-in Period could be extended up to 4 weeks while considering of subject safety if the blood pressures do not meet the inclusion criteria.

(2) Treatment Period

JSH2014 [6] recommends that low-dose therapy with a single antihypertensive drug should be initiated first for the treatment of the hypertensive patients, and the dose should be increased to a standard dose in 4 to 8 weeks while evaluating the effects. On the basis of above recommendation, 8 weeks were set as a titration period with 3 titration point and 2 weeks for each titration point for evaluating the tolerability. In addition, a phase 3 confirmatory study (TAK-536/CCT-005)

demonstrated that maximum decline of blood pressure was observed 4 weeks after the titration of TAK-536 in Japanese adult patients with hypertension. On the basis of the results, 4 weeks were set as the duration of administration with the highest dose in case of the titration of TAK-536 to the highest dose (20 mg or 40 mg). Therefore, 12 weeks in total were set as the Treatment Period I in this study.

Forty weeks was set as the Treatment Period II in reference to the Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions [11], so that duration of administration would be 52 weeks in total with the Treatment Period I.

(3) Follow-up Period

The elimination half-life was 12.8 hours following the single administration of TAK-536 40 mg in healthy adult subjects. In reference to the amendment of the Guideline for Bioequivalence Studies of Generic Products [12], 2 weeks were set as Follow-up Period of 5 times or more the elimination half-life.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator or subinvestigator, the subject's parent or the subject's legal guardian is capable of understanding and complying with protocol requirements.
2. The subject's parent or the subject's legal guardian is capable of signing and dating a written, informed consent form on behalf of the subject prior to the initiation of any study procedures. Written informed assent is also obtained from the subject as much as possible.
3. The Japanese subject who has a diagnosis of hypertension. A subject is eligible if he/she is deemed hypertensive according to the reference blood pressure values of children by gender and age (Table 5.a); office sitting diastolic or systolic blood pressure ≥ 95 percentile for essential hypertension without concomitant hypertensive organ damage, and ≥ 90 percentile for secondary hypertension with concomitant CKD, diabetes mellitus, heart failure or any hypertensive organ damage.
   In addition, subjects need to meet the following criteria:
   (1) If currently treated with any antihypertensive drugs at the start of the Run-in Period: Subject has a documented historical diagnosis of hypertension and an office sitting diastolic or systolic blood pressure meeting the above criteria at the end of the Run-in Period (Week 0).
   (2) If currently untreated with any antihypertensive drugs at the start of the Run-in Period: Subject who meets the above criteria on 3 separate time points including screening and the end of the Run-in Period (Week 0). In addition, subject with essential hypertension without concomitant hypertensive organ damage still maintains hypertension with non-pharmacotherapy including foods or exercises for at least 3 months within 1 year prior to the start of screening.
4. The subject is male or female and aged 6 to less than 16 years at the time of informed consent.
5. The subject weighs at least 20 kg at screening.
6. The subject is capable of taking the tablets or granules supplied as the study drug.
7. A subject who has undergone kidney transplantation is eligible if he/she underwent the transplantation at least 6 months earlier at screening, and the graft has been functionally stable (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2) for at least 6 months with evidence (eg, Doppler echography, CT scan [computed tomography] or MRI [magnetic resonance imaging]) excluding grafted kidney arterial stenosis. A subject on immunosuppressive therapy with a stable dose at least 30 days prior to screening is eligible.
8. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent through 1 month after the completion of the study, and proves negative in the pregnancy test at screening.

*Definitions and acceptable methods of contraception are defined in Section 9.1.10 and reporting responsibilities are defined in Section 9.1.11.

9. The subjects judged by the investigator or subinvestigator that he/she can discontinue the therapy with RAS inhibitors for 2 weeks (acceptable range, 1 to 4 weeks) in safe prior to the Treatment Period.

[Justification of Inclusion Criteria]

1.2.6. These were set as the standard requirements for clinical studies in pediatric patients.

3. The patients with hypertension who can be candidates for pharmacotherapy was set in reference to JCS2012 [7]. Reference blood pressure value of hypertension in the US guideline's criteria for children of 50 percentile height categorized by age and gender was selected since which was also the diagnosing criteria for hypertension adopted by JCS2012 [7]. For patients untreated with any antihypertensive drugs at the start of the Run-in Period, blood pressure values of 3 separate time points were adopted since hypertension would be diagnosed with above criteria 3 times or more in separate day or week.

4. The subject can be male or female, since evaluation in boys and girls is needed. The subjects of this study will be school children. Since children aged 6 to 16 years are categorized as school children in the final report on the Guidelines for Clinical Evaluation of Antihypertensive Drugs in Children [8], 6 to 16 years will be an acceptable age range in this study.

5. According to the physical status survey (Part 2 of the National Health and Nutrition Survey 2011 [13]), the average weight of 6-year-old children was 20.2 kg for girls and 20.9 kg for boys. This study will therefore enroll children weighing at least 20 kg.

7. In consideration of possible effects on the evaluation of TAK-536 and the subject safety, the subject who has undergone kidney transplantation will be eligible only if his/her clinical course has been stable.

8. RAS inhibitors are contraindicated in pregnant women based on the disorders and deaths in fetuses and new-born children reported for women using them during pregnancy.

9. These were set in consideration of subject safety.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 30 days prior to screening or is participating in another clinical study or a post-marketing clinical study.
   Note: This does not apply to subjects participating in observational studies without interventional or invasive therapy.

2. The subject previously received therapy with azilsartan.
   Note: This does not apply to subjects participating in single dose pharmacokinetic studies of TAK-536.

3. The subject has poorly controlled hypertension indicated by an office sitting systolic blood pressure higher by at least 15 mmHg and/or an office sitting diastolic blood pressure higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age (Table 5.a).
4. The subject has a diagnosis of malignant or accelerated hypertension.
5. The subject was noncompliant (< 70% or > 130%)* with the study drug during the Run-in Period.
   *: The proportion of the number of the received the study drug to the number of the study drug which the subjects should receive.
6. The subject has severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2), is receiving dialysis, has a renovascular disease affecting one or both kidneys, severe nephrotic syndrome not in remission, or a serum albumin level < 2.5 g/dL.
7. The subject has a history of, or the signs/symptoms of serious cardiovascular, hepatobiliary, gastrointestinal, endocrine (eg, hyperthyroidism, Cushing's syndrome), hematological, immunological, urinogenital, psychiatric disease, cancer, or any other disease that adversely affects subject's health, or, in the opinion of the investigator or subinvestigator, potentially confounds the study results.
8. The subject has hemodynamically significant left ventricular outflow obstruction due to aortic stenosis or aortic valvular disease, or is scheduled to undergo a medical procedure affecting blood pressure during the study (eg, correction of arterial anomaly).
9. The subject has a history of or concurrent clinically significant abnormality of 12-lead ECG that, in the opinion of the investigator or subinvestigator, disqualifies the subject for participation in the study.
10. The subject has poorly controlled diabetes mellitus indicated by HbA1c > 9.0% at screening.
11. The subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 2.5 × the upper limit of normal (ULN), or a total bilirubin level ≥ 1.5 × ULN at screening, severely impaired hepatic function, any active liver disease (regardless of the cause), or jaundice.
12. The subject has hyperkalemia exceeding ULN at screening.
13. The subject has a history of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection at screening.
14. The subject has a known hypersensitivity or allergy to any ARBs.
15. The subject needs treatment with any of the excluded medication.
16. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after the completion of this study.

[Justification of Exclusion Criteria]

1, 15. These were set as the standard exclusion criteria used for clinical studies.

2. This was set because of the potential for bias in evaluation of the safety and the efficacy.

3,4, 6-11, 13,14. These were set in consideration of the subject safety.

5. This was set to assure the appropriateness of the evaluation in this study.

12. This was set in consideration of the subject safety; hyperkalemia may develop after the administration of RAS inhibitors.

16. This was set as a standard requirement used for clinical studies. It was also due to a contraindication for pregnant females, because RAS inhibitors have caused fetal and neonatal disorders and death when used during pregnancy, and were transferred in the milk and affected nursing neonates when administered to lactating animals in nonclinical studies.

7.3 Excluded Medications and Treatments

7.3.1 Excluded Medications

The following medications including over-the-counter (OTC) drugs will be prohibited at the specified period during the study (Run-in Period and Treatment Period).

Subjects and subjects' parent or the subjects' legal guardian must be instructed not to take any medications including OTC products, without first consulting with the investigator or subinvestigator.

Other medications that are listed in the precautions for co-administration section of the package inserts of TAK-536 must be administered with caution.

<Run-in Period and Treatment Period I>

The following medications will be prohibited during the Run-in Period and Treatment Period I. A subject can continue the conventional therapy for the concurrent medical conditions without changing daily dosage except the excluded medications.

(1) RAS inhibitors (ACE inhibitors, ARB, and DRI)

(2) Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) excluding acetaminophen (4 days or more per week)

(3) Lithium

(4) Monoamine oxidase inhibitors

(5) Tricyclic antidepressants

(6) Amphetamine or it-derived materials (exception for the materials shown in the section of Medications Permitted with Conditions)

(7) Dopamine agonist

(8) Atypical antipsychotics

(9) Anticonvulsants

(10) Trazodone

(11) Nitrates

(12) Estrogen preparations

<Treatment Period II>

The following medications will be prohibited during the Treatment Period II.

(1) RAS inhibitors (ACE inhibitors, ARB, and DRI)

(2) Chronic use of NSAIDs excluding acetaminophen (4 days or more per week)

(3) Lithium

(4) Monoamine oxidase inhibitors

(5) Nitrates

(6) Estrogen preparations

[Justification for Excluded Medications]

<Run-in Period and Treatment Period I>

(1) These similar drugs are excluded because they could influence the evaluation of TAK-536 efficacy.

(2), (4)-(12) These drugs are excluded because they could increase or decrease blood pressure and influence the evaluation of TAK-536 efficacy.

(3) This drug is prohibited because their concomitant use with ARBs could cause poisoning.

<Treatment Period II>

(1) These similar drugs are excluded because they could influence the evaluation of TAK-536 efficacy.

(2), (4)-(6) These drugs will be supposed to be used chronically and are excluded because they could increase or decrease blood pressure and influence the evaluation of TAK-536 efficacy when these are used chronically.

(3) This drug is prohibited because their concomitant use with ARBs could cause poisoning.

7.3.2 Medications Permitted with Conditions

Following medications will be permitted with conditions in consideration of subject safety during the Run-in Period and Treatment Period I.

(1) Antihypertensive drugs other than RAS inhibitors: Subjects who 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 I by the investigator or subinvestigator; 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 administration of placebo. In the case of the down-titration, antihypertensive drugs should be discontinued at least 1 week (7 days) before the start of the Treatment Period I. Especially, beta-blockers (BBs) should be tapered off gradually since sudden discontinuation of BBs may cause withdrawal syndrome.

(2) Steroids: Systemic steroid is permitted as an alternative therapy on a stable low dose/ maintenance dose in subjects with adrenal insufficiency. The highest dose per day is 12 mg/m^2 for hydrocortisone or equivalent dose to hydrocortisone for other steroids. Prednisolone or other steroids can be administered up to 15 mg/m^2 per day or equivalent dose to prednisolone for other steroids as an immunosuppressive therapy in subjects after renal transplantation or with glomerular disease. The steroids are permitted on a stable dose from 30 days or more prior to the screening to the end of the Treatment Period I (alternate-day administration is also permitted). Topical or inhaled steroid is permitted but the dose cannot be changed unless there are no medical needs.

(3) Central nervous system stimulants, non-central nervous system stimulants: Use for treatment of attention deficit/hyperactivity disorder is permitted on a stable dose from 30 days prior or more to the screening to the end of the Treatment Period I.

7.4 Diet, Fluid, and Activity Control

The investigator, the subinvestigator, and the study collaborator should instruct the subject, the subject's parent or the subject's legal guardian to adhere the following study requirements.

1. Subjects will be instructed to ask the investigator, the subinvestigator, or the study collaborator by telephone for their instructions or visit the study site, as soon as they experience vomiting or diarrhea frequently throughout the study.
2. Subjects will be fully explained about the possibility of excessive reduction in the blood pressure associated with TAK-536 treatment. Subjects will be instructed to rest in a supine position, as soon as they experience any symptoms suggesting decreased blood pressure (eg, dizziness, lightheadedness, etc.) outside the study site on days other than the scheduled visit. Subjects were instructed to ask the investigator, subinvestigator, or the study collaborator by telephone for further instructions, or to visit the study site, if the symptoms did not subside.
3. Subjects will be instructed to ask the investigator, subinvestigator, or the study collaborator by telephone for their instructions, or to visit the study site, as soon as they experience any symptoms associated with increased blood pressure (eg, headache, palpitations, hot flushes, perspiration, etc.) outside the study site on days other than the scheduled visit.
4. Subjects will be instructed to take the study drugs as directed (1 tablet or 1 sachet once daily) without fail and continue receiving the study drug at the same timing (before or after breakfast) throughout the study. Subjects will be instructed to take the study drug at the same time every day except for scheduled visit day. Subjects will be instructed to take the study drug by AM 9:00 at the latest, setting ±3-hours for acceptable range. Subjects will be instructed that they will be allowed to take the study drug when they realize it in case of failing to take the study

drug, but will not be allowed to take the study drugs for 2 days at once. On the day before scheduled visit, subjects must take the study drug 24 hours (acceptable range, 21 to 27 hours) before office blood pressure measurement on the following day. TAK-536 2.5 mg granules should be administered immediately after the sachet (aluminum strip) is torn off. TAK-536 2.5 mg granules sachet should not be administered if the sachet is torn off at least 1 hour before the administration.

5. Subjects will be fully explained about how to adequately measure home blood pressure. Subjects will be instructed to measure the home blood pressure, preferably consecutive 2 times daily immediately before the study drug administration for 1 week each before and after the visit at the start of the Treatment Period I, for 1 week after the following day of a visit of each time point between Week 2 and Week 8 of the Treatment Period I, and for 1 week from the day before the visit at Week 12 of the Treatment Period I. Subjects will be instructed to inform the study site if a home sitting systolic blood pressure which is higher by at least 15 mmHg and/or a home sitting diastolic blood pressure which is higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age in Table 5.a (See Section 9.1.6).
6. Subjects will be instructed not to eat or bathe within 1 hour before office blood pressure measurement, not to intake any caffeine containing product within 30 minutes before the measurement.
7. Subjects will be instructed to comply with and not to change a fixed diet (eg, caloric and salt intake) and/or exercise therapies, if performed, throughout the study.
8. Subjects will be instructed to avoid food with a high salt and to take adequate hydration and to maintain a routine sleep, behavior and caffeine intake. In addition, subjects will be instructed to avoid excessive drinking/eating, significant change of diet (eg, excessively high-fat diet), excessive exercise, and staying up late. Especially, subjects will be instructed to maintain a regular lifestyle on the day before visit days.
9. Subjects will be instructed to inform the investigator, subinvestigator before receiving treatment from another doctor, or to provide details of treatment the subject received in case of reporting afterwards. Subjects receiving treatment by another doctor will be instructed to inform another doctor of their participation in this study before the participation, as far as possible.
10. Subjects will be instructed to consult the investigator or subinvestigator before using or changing the dosage of any drug not prescribed by the investigator or subinvestigator (including vitamins supplements, OTC drugs, and herbal preparations). Subjects will be instructed to promptly provide the details when they use any such drug.
11. Subjects will be instructed to visit the study site at the scheduled times to undergo examinations and tests by the investigator or subinvestigator. Subjects will be instructed to promptly inform the investigator or subinvestigator when they are unable to visit the study site as scheduled.

12. Female subjects of childbearing potential (eg, a female subject of childbearing potential is defined by the investigator's or subinvestigator's positive opinion about the subject's reproductive potential) will be instructed to use appropriate contraception from signing of informed consent to 1 month after completing the study (see Section 9.1.10).

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (eCRF) using the following categories. For subject failure, refer to Section 9.1.14.

1. Death. The subject died on study.
   Note: If the subject dies on study, the event will be considered as SAE. See Section 10.2.2 for the reporting procedures.
2. AE. The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
   - Acute deterioration of renal function

     Acute deterioration of renal function or increase in potassium value should be monitored carefully. If 50% reduction in estimated glomerular filtration rate [eGFR] or less than 30 mL/min/1.73 m^2, or serum potassium value over 5.5 mEq/L is seen at consecutive 2 time points, discontinuation should be considered. Appropriate follow-up should be performed for all subjects who discontinue the study until the subjects have been recovered or stabilized (see Section 9.1.9).
   - Liver Function Test (LFT) Abnormalities

     Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.9), if the following circumstances occur at any time during study drug treatment:

   – ALT or AST > 8 ×ULN, or
   – ALT or AST > 5 × ULN and persists for more than 2 weeks, or
   – ALT or AST > 3 × ULN in conjunction with elevated total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5, or
   – ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).
3. Protocol deviation. The discovery after the start of the Treatment Period that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject, the subject's parent or the subject's legal guardian were unsuccessful. Attempts to contact the

subject, the subject's parent or the subject's legal guardian must be documented in the subject's source documents.

5. Withdrawal by subject. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).

6. Withdrawal by parent or guardian. The subject's parent or the subject's legal guardian wishes to withdraw the subject from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).

7. Study terminated by sponsor. The sponsor terminates the study.

8. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

9. Lack of efficacy. The investigator or subinvestigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject. For example, discontinuation should be considered in the following case; on consecutive visits, an office sitting systolic blood pressure is persistently higher by at least 15 mmHg and/or an office sitting diastolic blood pressure is persistently higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age in Table 5.a, or, subjective symptoms or findings deemed associated with poorly controlled blood pressure do not improve with titration of TAK-536 during the Treatment Period I or with the addition of any other antihypertensive drugs other than RAS inhibitors during the Treatment Period II.

10. Other.

    Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or subinvestigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or subinvestigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

(1) Dosage form and manufacturing

Code name: TAK-536

Chemical name: 2-Ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl) biphenyl-4-yl]methyl}-1*H*-benzo[*d*]imidazole-7-carboxylic acid

Generic name: Azilsartan (JAN)

Formulation and Strength:

Study drug	Formulation	Strength
TAK-536 2.5 mg granules (placebo for the Run-in Period)	White to nearly white granules	Contains no TAK-536 in 250 mg
TAK-536 2.5 mg granules (active drug for the Treatment Period)	White to nearly white granules	Contains 2.5 mg of TAK-536 in 250 mg
TAK-536 5 mg tablet (placebo for the Run-in Period)	Pale pink film-coated tablet	Contains no TAK-536 in 1 tablet
TAK-536 5 mg tablet (active drug for the Treatment Period)	Pale pink film-coated tablet	Contains 5 mg of TAK-536 in 1 tablet
TAK-536 10 mg tablet	Pale yellow to red film-coated tablet	Contains 10 mg of TAK-536 in 1 tablet
TAK-536 20 mg tablet	Pale-red film-coated tablet	Contains 20 mg of TAK-536 in 1 tablet
TAK-536 40 mg tablet	Yellow film-coated tablet	Contains 40 mg of TAK-536 in 1 tablet

Manufacturing: TPC

(2) Package and labeling

1) Package

– TAK-536 2.5 mg granules (placebo for the Run-in Period, active drug for the Treatment Period): For placebo for the Run-in Period, each aluminum strip sachet contains 250 mg of

TAK-536 granules containing no TAK-536. Forty two sachets are packaged in a box. For active drug for the Treatment Period, each aluminum strip sachet contains 250 mg of TAK-536 granules containing 2.5 mg of TAK-536. Seventy sachets are packaged in a box.

- TAK-536 5 mg tablet (placebo for the Run-in Period, active drug for the Treatment Period): For placebo for the Run-in Period, each press through package (PTP) sheet contains 14 tablets of TAK-536. Three sheets are packaged in a box. For active drug for the Treatment Period, each PTP sheet contains 14 tablets of TAK-536. Ten sheets are packaged in a box.
- TAK-536 10 mg, 20 mg, and 40 mg tablets: Each PTP sheet contains 14 tablets of TAK-536. Ten sheets are packaged in a box.

2) Labeling

Each outer box indicates the following information: the drug is for the study use only, study drug name, amount, the sponsor's name and address, batch number, and storage condition.

8.1.2 Storage

The study drugs are to be stored at room temperature (1 to 30°C).

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

During the Run-in Period, subjects will orally receive TAK-536 2.5 mg granules (placebo for the Run-in Period) if subjects weighing < 50 kg, or TAK-536 5 mg tablet (placebo for the Run-in Period) if subjects weighing ≥ 50 kg, once daily, before or after breakfast. During the Treatment Period, the same dose of the selected placebo during the Run-in Period will be the initial dose. After the initial dose, subjects will orally receive any of TAK-536 2.5 mg granules, TAK-536 5 mg, 10 mg, 20 mg tablet, once daily, before or after breakfast, if subjects weighing < 50 kg, or any of TAK-536 5 mg, 10 mg, 20 mg, 40 mg tablet, if subjects weighing ≥ 50 kg. For dose titration method, see Section 6.1 Study Design.

Because weight is likely to change during the study, the highest dose for the subjects is allowed to be changed if dose adjustment by changing of weight is required during the Treatment Period II.

The investigator or subinvestigator may select the timing of the study drug administration (i.e., before or after breakfast) in consideration of subject lifestyle but should not change this timing throughout the study. The investigator or its designee will record the guidance provided about the timing of the study drug administration (before or after breakfast) at the start of the Run-in Period (Week -2) in the eCRF.

At the start of the Run-in Period (Week -2), the study drug for the Run-in Period will be administered on the same day after completing all tests, observations, and evaluations. In case that

subjects take RAS inhibitors in the morning of the visit day, the administration of the study drug for the Run-in Period will be started from the next day.

Except for Week 16, subjects will visit the study site on each visit day without taking the study drugs, and receive them only after completing all tests, observations, and evaluations.

On the visit of Week 16, subjects, the subjects' parent or the subjects' legal guardian will be instructed to visit the study site after taking the study drug and the tests, observations, and evaluations 2 hour (acceptable time window, 1 to 3 hours) after taking the study drug will be performed.

Regular doses on days except for the visits will be administered no later than 9:00 AM, regardless of the specified dosing timing (i.e., before or after breakfast). The study drug should be administered at the almost same time every day throughout the study (acceptable range is ± 3 hours) except the visit day. The investigator or subinvestigator will confirm whether the subject has taken the study drug or not in the morning of each visit.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) about TAK-536 active drug for the Treatment Period, will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRFs according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Dispensing Procedures

The investigator or subinvestigator will dispense the study drug to subjects according to the study procedure.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage and management of study drugs created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent and assent are described in Section 15.2.

Informed assent of the subject, if deemed possible by the investigator or subinvestigator, and informed consent of the subject's parent or the subject's legal guardian must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

Assent and consent to participate in the study will be obtained from any subject before discontinuing the prior treatment (antihypertensive drugs).

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is explained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, race, diagnosis timing and type of hypertension, and underlying diseases in case of secondary hypertension at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the diseases under study that stopped within 1 year prior to informed consent. Any history of kidney transplantation should be documented regardless of the time elapsed. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes any medication stopped at or within 4 weeks prior to VISIT 2.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment performed before the study drug administration.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below: The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: BMI = weight (kg)/height $(m)^2$

Height in centimeters (cm) will be rounded to integers and weight in kilograms (kg) will be rounded to 1 decimal place. BMI will be rounded to 1 decimal place.

9.1.5 Vital Sign Procedure

Vital signs will include office sitting blood pressure (systolic and diastolic), office standing blood pressure (systolic and diastolic), office sitting pulse rate, and office standing pulse rate (pulse rate per 1 minute). All office blood pressure will be measured with a blood pressure meter specified by the sponsor.

Office blood pressure should be measured at the time of trough (approximately 21 to 27 hours after the latest dose, i.e., in the morning of that day) with the subject without taking the study drug in the morning of the scheduled visit except for Week 16. The subject, the subject's parent, or legal guardian will be instructed strongly not to take the study drug at home on the scheduled visit day except for Week 16. The subject, the subject's parent, or the subject's legal guardian will be instructed again if the subject receives the study drug before the measurements of vital signs on the scheduled visit day by mistake.

When vital signs are scheduled at the same time as blood draws, vital signs will be obtained before the scheduled blood draw.

Office sitting blood pressure after taking the study drug will be also measured only at Week 16 of the Treatment Period; the time point which the pharmacokinetics after receiving the study drug is evaluated.

Subjects will be instructed not to eat or bathe within 1 hour before office blood pressure measurement, not to intake any caffeine containing product 30 minutes before the measurement.

<Determining difference in blood pressure between right and left arm>

At screening, sitting blood pressure in the right and left arms will be measured once after sitting at rest for ≥ 5 minutes to determine the difference in blood pressure between the arms. The arm with a higher systolic blood pressure will be used to measure office blood pressure during the study. The right arm will be used if systolic blood pressure is the same on both sides. Change of the arm for measurement will not be allowed during the study.

<Measuring sitting blood pressure and sitting pulse rate>

Sitting blood pressure will be repeatedly measured 3 times at 1 to 2 minute intervals after the subject has been sitting at rest for at least 5 minutes and recorded in the subject source documents and eCRF. However, if 2 of the 3 systolic blood pressure measurements differ by more than 8 mmHg or diastolic blood pressure measurements differ by more than 5 mmHg, a second set of 3 sitting blood pressure measurements should be obtained and only the second set of readings should be recorded in the eCRF (even if these still differ by > 8 mmHg for systolic blood pressure or 5 mmHg for diastolic blood pressure). Original and repeat readings must all be recorded in the source documents with an explanation.

The arithmetic mean (rounded to integers) of 3 measurements of a session will be used for determination of the subject eligibility.

The pulse rate measured at the last measurement of the sitting blood pressure will be used as the sitting pulse rate value.

Sitting blood pressure must be measured after resting in a sitting position for at least 5 minutes. An appropriately sized cuff (40% of the arm's perimeter) should be used, and applied to an upper arm held at the heart level. All measurements must be made on the same arm using the same-sized cuff. Every effort should be made to standardize the condition of office blood pressure measurements as possible, such as measurement time, the same blood pressure device should be used, whenever possible, by the same investigator, subinvestigator, or the study collaborator.

<Measuring standing blood pressure and standing pulse rate>

Standing blood pressure will be measured to evaluate the orthostatic vital signs at the scheduled visit of Week 0, 12, 24 and 52. After measuring the sitting blood pressure, standing blood pressure will be measured once after the subject has been standing for 2 minutes. Standing systolic and diastolic blood pressure will be also measured with the same device which measures sitting blood pressure on the same arm. For standing blood pressure measurements, the arm should be supported and extended such that the cuff is at heart level. Standing pulse rate will be measured once during the subject maintains a standing position.

9.1.6 Measuring Home Blood Pressure

Each subject, the subject's parent, or the subject's legal guardian will be provided a home blood pressure meter and adequately informed of the measurement procedures at the start of the Run-in Period (Week -2) by the sponsor through the study site.

The subject, the subject's parent, or the subject's legal guardian will be instructed to measure home blood pressure (systolic and diastolic), preferably consecutive 2 times daily immediately before the study drug administration for 1 week each before and after the visit at the start of the Treatment Period I, and for 1 week after the following day of a visit of each time point between Week 2 and Week 8 of the Treatment Period I (including visit at Week 6, when performed), and for 1 week from the day before the visit at Week 12 of the Treatment Period I.

The subject should measure blood pressure 2 times in a row after having been sitting for at least 5 minutes with the blood pressure cuff applied to the same arm as used to measure blood pressure at the visits. The blood pressure measurements should be recorded in patient diary and reviewed by the investigator or subinvestigator at each visit. The blood pressure measured twice immediately before the study drug administration should be recorded in CRFs. The subject, the subject's parent, or the subject's legal guardian will be instructed to inform the study site if a home sitting systolic blood pressure which is higher by at least 15 mmHg and/or a home sitting diastolic blood pressure which is higher by at least 10 mmHg than the 99 percentiles of the reference blood pressure values of children by gender and age in Table 5.a. The subject, the subject's parent, or the subject's legal guardian will be instructed by the investigators to visit the study site to measure blood pressure again if needed. If the elevated blood pressure is confirmed by repeat measurements at the study site, the subject is to be considered to discontinue the study.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from the start of the Run-in Period [Week 2] through the end of the study), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF.

If the concomitant medications are antihypertensive drugs, the daily dosage and unit of concomitant medications must be recorded in the eCRF as well.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the first test after signing of informed consent. The condition (i.e., diagnosis) should be described.

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 8 mL.

Table 9.a Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Red blood cell count White blood cell count with differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes) Hemoglobin Hematocrit Platelets	Hemoglobin A1C/Hemoglobin (a) ALT Albumin Alkaline phosphatase (ALP) AST Bilirubin (Total bilirubin) Blood urea nitrogen (BUN) (b) Calcium Chloride (b) Creatinine (b) Creatine kinase Cystatin C Glomerular Filtration Rate (b) Gamma-glutamyl transferase (GGT) Glucose Cholesterol (Total cholesterol) Triglyceride Phosphate Potassium (b) Sodium (b) Protein (Total protein) Lactate dehydrogenase (LDH)	Qualitative tests for glucose, pH, protein, occult blood, Ketones Quantitative tests for protein, creatinine, Albumin Protein/creatinine ratio, albumin/creatinine ratio, specific gravity
Other		
Urine qualitative human chorionic gonadotropin (hCG) pregnancy test (only female subjects of childbearing potential)		

(a) Only patients with diabetes mellitus
(b) Only the laboratory tests associated with renal function. The local laboratory will perform the laboratory tests associated with renal function in addition to measuring at the central laboratory to confirm the tolerability when TAK-536 is titrating (including unscheduled visit), if needed at the investigator's discretion.

The central laboratory will perform laboratory tests for hematology, chemistries, and urinalysis (acceptable under the fed condition).

The local laboratory will perform the laboratory tests associated with renal function (BUN, chloride, creatinine, eGFR, potassium, and sodium) in addition to measuring at the central laboratory to confirm the tolerability when TAK-536 is titrating (including unscheduled visit), if needed at the investigator's discretion. The results of the local measurements will not be required recording in the eCRF.

The following formula proposed by the Committee for Pediatric Chronic Kidney Disease will be used to deduce eGFR in Japanese children.

eGFR in children (mL/min/1.73 m^2)
=110.2 × standard serum Cr (mg/dL)/serum Cr (mg/dL) + 2.93,

where, the standard serum Cr (mg/dL) is calculated from the height (Ht, in meter; Ht measured most recently will be used) as follows:

For a boy, $-1.259\ Ht^5 + 7.815\ Ht^4 - 18.57\ Ht^3 + 21.39\ Ht^2 - 11.71\ Ht + 2.628$
For a girl, $-4.536\ Ht^5 + 27.16\ Ht^4 - 63.47\ Ht^3 + 72.43\ Ht^2 - 40.06\ Ht + 8.778$

Uemura O, et al. Clin Exp Nephrol. 2014 [14]

Follow-up laboratory tests should be performed to determine whether the subject continue the study or not, in case of acute deterioration of renal function (eg, ≥50% reduction in eGFR or less than 30 mL/min/1.73 m^2 or serum potassium value over 5.5 mEq/L) (See Section 7.5).

If subjects experience ALT or AST > 3 ×ULN after the start of the Run-in Period (Week -2), follow-up laboratory tests (at a minimum, ALP [serum], ALT, AST, bilirubin [total bilirubin], GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted (Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.).

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

Only female subjects of childbearing potential, defined by the investigator's or subinvestigator's positive opinion about the subject's reproductive potential, will undergo a qualitative hCG pregnancy test. The local laboratory will perform the test.

The investigator or subinvestigator is reviewing and filing the laboratory results. The investigator will maintain a copy of the normal reference ranges including the archival records for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 1 month after the end of the study, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to preserve or donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation), who are postmenopausal (defined as at least 5 years since last regular menses, confirmed before any study drug is implemented), or who have no possibility of childbearing in the opinion of investigator or subinvestigator.

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, female subjects of childbearing potential must use copper intrauterine devices (IUDs) combined with male condom or female condom. Medications and devices containing hormones are excluded.

The subject and the subject's parent, or the subject's legal guardian will be provided with information on acceptable methods of contraception as part of the subject informed consent/assent process and will be asked to sign a consent/assent form stating that they understand the requirements for avoidance of pregnancy, preservation or donation of ova from providing the consent/assent until 1 month has passed from the end of the study.

During the course of the study, regular urine hCG pregnancy tests will be performed only for female subjects of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A).

This protocol does not condone or endorse under-age sexual activity.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study drug, or within 1 month of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in attachment 1.

If the female subject and her parent, or the subject's legal guardian agree to the primary care physician being informed, the investigator or subinvestigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 ECG Procedure

A resting 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: normal or abnormal. The investigator (or a qualified observer at the study site) will judge if it is clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, and QRS interval.

QTc will be calculated by the sponsor using the Fredericia's formula ($QT/RR^{0.33}$).

9.1.13 Pharmacokinetic Sample Collection

According to the study schedule (Appendix A), all pharmacokinetic samples should be collected on each visit except for Week 16, at the same time of blood sample collection for laboratory tests

to evaluate the trough values (approximately 21 to 27 hours after the latest dose) without taking the study drugs.

In addition to collection of the pharmacokinetic samples at trough, pharmacokinetic samples will be also collected once (total twice before and after the administration of the study drug) 2 hour (acceptable time window, 1 to 3 hours) after taking the study drug from the available subjects to evaluate the pharmacokinetics after taking the study drug at each visit by Week 12 of the Treatment Period.

On the visit of Week 16, subjects should visit the study site after taking the study drug to collect pharmacokinetic samples 2 hour (acceptable time window, 1 to 3 hours) after taking the study drug at the same time as the blood sample collection for laboratory tests.

9.1.13.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (one 2-mL sample per scheduled time) for pharmacokinetic analysis of TAK-536 and its metabolites (M-I and M-II) will be collected into vacutainers containing ethylenediaminetetraacetic acid dipotassium salt dihydrate (EDTA-2K). After mixing the vacutainers 5 to 6 times by inversion immediately, vacutainers will be centrifuged at 4°C and 3000 rpm for 10 minutes. The plasma will be dispensed from the vacutainers to polypropylene tube and be stored frozen below -20°C in a freezer until being shipped to the analytical institute.

For each sample, the date and time of the latest study drug administration and the actual time of blood sample collection will be recorded in the eCRF.

9.1.13.2 Bioanalytical Method

Plasma concentrations of TAK-536 and its metabolites (M-I and M-II) will be measured by HPLC/MS/MS (high-performance liquid chromatography with tandem mass spectrometry) at PPD

9.1.14 Documentation of Subjects Failure

An eCRF must be created for all subjects giving informed consent who withdrawn before the start of the Treatment Period.

The primary reason for subject failure is recorded in the eCRF using the following categories:

- Death
- Adverse Event
- Screen Failure (failed inclusion criteria or did meet exclusion criteria)
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject <specify reason>.
- Withdrawal by parent or guardian <specify reason>.

- Study terminated by sponsor.
- Pregnancy
- Other <specify reason>.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.15 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the Treatment Period.

If the subject is found to be not eligible for the Treatment Period, the investigator or subinvestigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Compliance with study drug (amount of dispense and return) between the visits, timing of the study dose (before or after breakfast) and the latest dosing date and time before collecting sample for pharmacokinetic evaluation will be confirmed and recorded in the eCRF.

Subjects, the subjects' parent, or the subjects' legal guardian will be instructed to be compliant with the study drug throughout the study. If a subject is noncompliant (< 70% or > 130%) with the study medication (TAK-536 placebo) during the Run-in Period, the subject will be excluded before the start of the Treatment Period, as indicated in the exclusion criteria No. 5. If a subject is noncompliant with the study medication (TAK-536) (eg, failure to take < 50% of the scheduled dosed after the last visit) after the start of the Treatment Period, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

9.3.1 Screening

Subjects will be screened within 14 days prior to the start of the Run-in Period. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

9.3.2 Start of the Run-in Period (Week -2)

The study drug (TAK-536 placebo) for the Run-in Period will be administered on the same day after the tests, observations and evaluations specified for each visit are performed. In case that subjects take RAS inhibitors in the morning of the visit day, the administration of the study drug (TAK-536 placebo) for the Run-in Period will be started from the next day.

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

9.3.3 End of the Run-in Period (Week 0)

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be entered after performing the tests and observations specified for each visit and will be initiated to receive the study drug for the Treatment Period on the same day.

The first and the last date of the study drugs administration for the Run-in Period will be recorded in the eCRF for those receiving the study drugs for the Run-in Period and subsequently received the study drug for the Treatment Period.

See Section 9.1.14 for procedures for documenting subjects withdrawn before the start of the Treatment Period.

9.3.4 Treatment Period (Weeks 2, 4, 8, 12, 16, 20, 24, 32, and 40)

The tests and observations specified for each visit will be performed.

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

On the visit of Week 16, subjects should visit the study site after taking the study drug and the tests and observations specified will be performed.

9.3.5 Final Visit or Early Termination

The Final Visit will be performed on Week 52 or at the Early Termination Visit.

The tests and observations specified for each visit will be performed.

For subjects early terminate the study after the start of the Treatment Period, if possible, the same tests, observations, and evaluations as those scheduled at Week 52 should be performed. Whenever possible, office sitting blood pressure should be determined within 3 days after early termination and the other tests, observations, and evaluations should be performed within 14 days after early termination (the next day of the final dose should be calculated as the first day).

For all subjects who entered the Treatment Period, the investigator or subinvestigator must complete the Subject Status on eCRF page with the first day when the subjects received the study drug for the Treatment Period and study completion or early termination status until Week 24 and study completion status at Week 52 for subjects who continuingly received the study drug beyond Week 24.

9.3.6 Follow-up Period: Week 54

Follow-up Period will begin the first day after the final administration of TAK-536 for the Treatment Period and will continue until 2 weeks. The tests and observations specified for each visit will be performed. If subjects terminate the study drug in the Run-in Period or at an early stage of the Treatment Period, no tests, observations, and evaluations will be required but care should be taken for subject safety.

9.3.7 Post Study Care

The study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study participation whether or not it is considered related to the drug or study procedures.

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator or subinvestigator for any reason.
- AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator or subinvestigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition after informed consent is signed, the worsening or complication should be recorded appropriately as an AE. The investigator or subnvestigator should ensure that the event term recorded captures the change in the condition (eg, "worsening of …").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious or severe in nature, that is, the investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, the investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of …").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the study drug, or if a sign or a symptom appears secondarily due to an AE, the worsening or complication should be recorded appropriately as a new AE. The investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in the study drug, or if a sign or a symptom appears secondarily due to an AE, the worsening or complication should be recorded as a new AE. The investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE that are not related to starting the study drug or changing in the dose or regimen, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator or subinvestigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

10.1.4 AEs of Special Interest

An AEs of Special Interest (treatment-emergent only, serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator or subinvestigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for the investigator or subinvestigator as to how and when they should be reported to Takeda.

10.1.5 Severity of AEs

The different categories of severity are characterized as follows:

Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.

Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs to Study Drugs

The causality of each AE to study drugs will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

The causality should be assessed as Related if the investigator or subinvestigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the causality should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or the investigator or subinvestigator.

10.1.9 End Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Pattern of Adverse Event

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Taken with Study Treatment

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE, the AE that occurred before the study drug administration.
- Drug Interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining “Not recovered/not resolved”.

- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time the subject signs the informed consent. Routine collection of AEs will continue until the end of the Follow-up Period (or the tests performed at early termination).

10.2.1.2 AE Reporting

At each study visit, the investigator or subinvestigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious AE that occurs prior to the first exposure to study drug must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious AEs that occur prior to the first exposure to study drug, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs after the first exposure to study drug, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator or subinvestigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and end date.
3. Pattern.
4. Severity.
5. Investigator's opinion of the causality between the event and administration of study drug(s).
6. Investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure.

7. Action taken with study treatment (not applicable for the AE that occurred before the study drug administration).
8. Outcome of event.
9. Seriousness.
10. After administration of study drug.
11. Treatment emergent.

10.2.1.3 AEs of Special Interest Reporting

Pediatric subjects, the subject population of this study, are vulnerable, and as such need special attention with regard to the risk of the over decrease in blood pressure accompanying the use of antihypertensive drugs. Furthermore, kidney function is often impaired in pediatric subjects with secondary hypertension. Administration of RAS inhibitors to such patients may reduce GFR, deteriorating the kidney function. Hence, the following adverse events related to hypotension or renal impairment will be investigated as special interest AEs in this study.

[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.

If this AE of special interest occurs during the Run-in Period, the Treatment Period or the Follow-up Period, it should be reported to the sponsor (described in the separate contact information list) immediately or within 1 business day of first onset or subject's notification of the event. Hypotension-related AE or renal dysfunction-related AE Form or an SAE Form should be completed, signed and/or sealed by the principal investigator, and reported to appropriate personnel in the separate contact information list within 10 business days.

The AE of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be reported to the sponsor (described in the separate contact information list) within 1 business day of first onset or subject's, the subject's parent's, or the subject's legal guardian's notification of the event. The principal investigator should submit the completed SAE form within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's or subinvestigator's name.
- Name of the study drugs
- Causality assessment.

Any SAE spontaneously reported to the investigator or subinvestigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST > 3 ×ULN and total bilirubin > 2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator or subinvestigator must contact the sponsor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.9 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator or subinvestigator should complete a follow-up SAE form or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs, and the head of the study site, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee , SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs and medical history including concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs:

- Results of clinical laboratory tests conducted at the central laboratory
- Results of pharmacokinetics conducted at the analytical institute

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator or subinvestigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the

identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, the investigator and the head of the site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

At the time when the data of 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 or 52 in the Treatment Period, the data until Week 24 or 52 in the Treatment Period will be analyzed separately after being locked.

13.1.1 Analysis Sets

In this study, 2 kinds of analysis sets are defined: a full analysis set (FAS) and a safety analysis set. The safety analysis set used for safety analysis will be defined as "all subjects who received at least 1 dose of the study drug for the Treatment Period." The definition of each analysis set will be described in the Handling Rule for Analysis.

The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. The Handling Rule for Analysis must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics will be summarized using the safety analysis set.

13.1.3 Efficacy Analysis

(1) Secondary endpoints and analytical methods

[Secondary endpoints]

Office trough sitting systolic and diastolic blood pressure, proportion of subjects who achieve the target blood pressure

[Analytical methods]

The analyses discussed below will be conducted with the FAS.

Summary statistics (number of subjects, mean, standard deviation, maximum, minimum, and quartiles; hereinafter the same) and 2-sided 95% confidence intervals for mean values will be calculated for the office trough sitting systolic and diastolic blood pressure at each time point (including the end of the Treatment Period I and the end of the Treatment Period II; hereinafter the same).

Summary statistics and 2-sided 95% confidence intervals for mean values will be calculated referring to a 1-sample t-test for the change of office trough sitting systolic and diastolic blood pressure from the end of the Run-in Period (Week 0) to each time point during the Treatment Period.

The proportion of subjects who achieve the target blood pressure at each time point during the Treatment Period will be summarized.

(2) Data conversion methods and handling of missing data

Details of data conversion methods and handling of missing data will be defined in the Handling Rule for Analysis and SAP.

(3) Significant level and confidence coefficient

Significant level: 5% (2-sided test)

Confidence coefficient: 95% (2-sided estimates)

13.1.4 Pharmacokinetic Analysis

Pharmacokinetic endpoints and analytical methods

[Secondary endpoints]

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

[Analytical methods]

The following analyses will be conducted with the subjects who have adequately measured plasma concentration of TAK-536 in the FAS.

Concentration of TAK-536 and its metabolites (M-I and M-II) in plasma will be summarized at each time point.

A population pharmacokinetic analysis will be conducted with the subjects who have adequately measured plasma concentration of TAK-536 in the FAS. Population pharmacokinetic parameters in pediatric patients with hypertension will be estimated and the effect of weight on the pharmacokinetics of TAK-536 will be assessed quantitatively. In addition, other factors which affect the pharmacokinetics of TAK-536 will be explored. When the above analyses are conducted, an integrated analysis will be also performed with the data of the prior pharmacological study in pediatric patients with hypertension (TAK-536/CPH-103) as needed, and a SAP and an analysis results will be provided separately from those of this study.

13.1.5 Safety Analysis

[Primary endpoints]

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

[Analytical methods]

The following analyses will be conducted with the safety analysis set.

1) AEs (Treatment-emergent AEs)

A treatment-emergent AE (TEAE) is defined as any AE occurring after the start of TAK-536 administration of the Treatment Period.

The incidence of TEAEs listed below will be analyzed. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The frequency distribution will be provided using the system organ class (SOC) and preferred term (PT) using MedDRA as follows:

- TEAEs
- Drug-related TEAEs
- Severity of TEAEs
- Severity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs
- TEAEs over time

2) Anthropometric (weight, height and BMI) measurements, laboratory tests, resting 12-lead ECG, and vital signs (office standing blood pressure, office sitting pulse rate, office standing pulse rate, and home sitting blood pressure)

For continuous variables, the observed values and the changes from the end of the Run-in Period (Week 0) will be summarized for each time point. In addition, individual figures of the observed values will be provided.

For categorical values, shift tables of the data before and after administration will be provided.

13.2 Interim Analysis and Criteria for Early Termination

At the time when the data of 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.

13.3 Determination of Sample Size

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

[Justification for Determination of Sample Size]

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

Assuming the mean change of trough sitting diastolic blood pressure from the end of the Run-in Period (Week 0) to the end of the Treatment Period I of -6.5 mmHg and an SD of 10.5 mmHg, and the mean change of trough sitting systolic blood pressure from the end of the Run-in Period (Week 0) to the end of the Treatment Period I of -9.5 mmHg and an SD of 15.5 mmHg, planned 50

subjects will provide at least 90% power by a 1-sample t-test at the 0.05 significance level (2-sided).

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator, subinvestigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator or subinvestigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator or subinvestigator should document all protocol deviations. Significant protocol deviations will be entered into the eCRF, which is reviewed by the study sponsor or designee. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], PMDA). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent/assent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent/assent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent/assent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent/assent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject/parent/legal guardian incentives should not exert undue influence for participation. Payments to subjects, the subjects' parent, or the subjects' legal guardian must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent/Assent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. An assent document describes the study, using a language appropriate to the subject's age and development, to potential subjects with enough mental capacity to understand what it means to participate in a clinical study, and is used to obtain the

subject's assent (a pediatric subject's consent, which is not a regulatory requirement) separately from the subject's parent's, or the subject's legal guardian's consent. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent and assent forms. The informed consent and assent forms must be approved by both of the IRB and sponsor prior to use.

The subject assent form must be written in a language appropriate to the subject's age and development to the prospective subject. The informed consent form must be written in a language fully comprehensible to a subject's parent or the subjects' legal guardian. It is the responsibility of the investigator or subinvestigator to explain the subject assent form to the subject using a language and terms comprehensible and to explain the detailed elements of the informed consent form to a subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject and the subject's parent, or the subject's legal guardian must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject's parent or the subject's legal guardian determines the subject will participate in the study, then the informed consent form must be signed and dated by the subject's parent or the subject's legal guardian at the time of consent and prior to the subject entering into the study.

Whenever possible, the subject's own assent should be obtained in addition to the subject's parent's or the subject's legal guardian's consent. The subject's assent will be preferably obtained in writing, if he/she is a junior high school student or of a higher age. Whenever a written assent is not provided, though preferable also for subjects aged below junior high school students, the subject's oral assent must be documented in the informed consent form signed by the subject's parent or the subject's legal guardian. The subject's parent or the subject's legal guardian should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink.

Once signed, the original informed consent form, and the subject assent form (if applicable, the same hereinafter) will be stored in the investigator's site file. The investigator or subinvestigator must document and the dates the subject's parent or the subject's legal guardian signs the informed consent form and the date the subject signs the informed assent form in the subject's medical record. Copies of the signed informed consent form and the signed subject assent form shall be given to the subject, the subject's parent, or the subject's legal guardian.

All revised informed consent/assent forms must be reviewed and signed by relevant subjects, the relevant subject's parent or the subject's legal guardian in the same manner as the original informed consent/assent. The date the revised consent/assent was obtained should be recorded in

the subject's medical record, and the subject, the subject's parent, or legal guardian should receive a copy of the revised informed consent/assent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject and the subject's parent, or the subject's legal guardian as part of the informed consent/assent (if deemed appropriate by the investigator or subinvestigator) process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator and subinvestigator need to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register

interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator and subinvestigator have questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix C Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in amendment 01 are described. The corresponding text has been revised throughout the protocol.

The primary change: Section 7.3.1 Excluded Medications

Existing Text: RAS inhibitors

Revised Text: RAS inhibitors **(ACE inhibitors, ARB, and DRI)**

Rationale for Amendment: Clarify definition of RAS inhibitors.

The primary change: Section 8.1.3 Dose and Regimen

Added Text:

At the start of the Run-in Period (Week -2), the study drug for the Run-in Period will be administered on the same day after completing all tests, observations, and evaluations. In case that subjects take RAS inhibitors in the morning of the visit day, the administration of the study drug for the Run-in Period will be started from the next day.

Rationale for Amendment: Clarify dosage of the Run-in Period (Week -2).

The primary change: Section 9.1.10 Contraception and Pregnancy Avoidance Procedure

Existing Text:

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are excluded, *the only acceptable methods of contraception are:*

Barrier methods (each time the subject has intercourse):

- *Male condom PLUS spermicide.*

Intrauterine devices (IUDs):

- *Copper T PLUS condom.*

The subject and the subject's parent, or the subject's legal guardian will be provided with information on acceptable methods of contraception as part of the subject informed consent/assent process and will be asked to sign a consent/assent form stating that they understand the requirements for avoidance of pregnancy, *donation of ova* from providing the consent/assent until 1 month has passed from the end of the study.

Revised Text:

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, **female subjects of childbearing potential must use copper intrauterine devices (IUDs) combined with male condom or female condom**. Medications and devices containing hormones are excluded.

The subject and the subject's parent, or the subject's legal guardian will be provided with information on acceptable methods of contraception as part of the subject informed consent/assent

process and will be asked to sign a consent/assent form stating that they understand the requirements for avoidance of pregnancy, **preservation or donation of ova** from providing the consent/assent until 1 month has passed from the end of the study.

Rationale for Amendment: Clarify examples of contraceptive methods and add the description as to avoiding preservation of ova.