Clinical Study Protocol

NCT Number: NCT04668157

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

Study Number: Azilsartan-3004

Document Version and Date: Amendment 1 / 21-Feb-2023

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

TAKEDA PHARMACEUTICALS

PROTOCOL

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

A Phase 3 Long-term Study of TAK-536 in Pediatric Subjects from 2 to Less Than 6 Years of Age with Hypertension

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan		
Study Number:	Azilsartan-3004		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-536 (Azilsartan)		
Date:	21 February 2023	**Version/Amendment Number:**	Version 2.0/ Amendment 1

Amendment History:

Date	Amendment Number	Region
15 September 2020	Initial version	All sites
21 February 2023	Amendment 1 (Version 2.0)	All sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the annexes.

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 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 1 Summary of Changes

Protocol Amendment 1 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are to:

- Update the description of cuff size for blood pressure measurements.
- Add the supply method of study drug to subjects and the acceptable time window for scheduled visits in case subjects cannot visit the site due to the COVID-19 associated event/issue.
- Correct inconsistencies.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 7.3.2 Medications Permitted with Conditions	Deleted the terms “during this study” from the texts in the explanations of the highest dose of steroids.	Correction of inconsistencies with the study design.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
2	Section 8.1.3 Dose and Regimen	Removed the sentence for recording the guidance provided about the timing of the study drug administration in the eCRF.	Correction of an inconsistency with data collection in the eCRF.
3	Section 8.2 Study Drug Assignment and Dispensing Procedures	Added the description regarding the supply of the study drug to subjects.	Maintainance of subjects' access to the study drug in case subjects cannot visit the site due to the COVID-19 associated event/issue.
4	Section 9.1.5 Vital Sign Procedure	Deleted the terms "using the same-sized cuff" from the texts in the explanation of the blood pressure measurement procedure.	Pediatric subjects may grow and change in their body size during the study. Therefore, the cuff size was allowed to be selected based on the upper arm circumference.
5	Section 9.2 Monitoring Subject Treatment Compliance	Deleted the term "timing of the study dose (before or after breakfast)" from the items to be recorded in the eCRF.	Correction of an inconsistency with data collection in the eCRF.
6	Section 10.2.1.3 AEs of Special Interest Reporting	Deleted the term "the Run-in Period" from the text in the reporting of AEs of special interest.	Correction of an inconsistency with the definition of the AEs of special interest.
7	Section 14.2 Protocol Deviations	Deleted the description regarding eCRF of protocol deviations	Protocol deviation other than COVID-19 impact was not to be input to eCRF.
8	[redacted]	[redacted]	[redacted]

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

[redacted] Date [redacted] Date

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-536 (Azilsartan)	
Title of Protocol: A Phase 3, Open-label, Multicenter, Long-term Study to Evaluate the Safety, Efficacy and Pharmacokinetics of TAK-536 in Pediatric Subjects from 2 to Less Than 6 Years of Age with Hypertension	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: Azilsartan-3004	**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 subjects with hypertension aged 2 to less than 6 years. The study consists of a 2-week Run-in Period, a 52-week Treatment Period, and a 2-week Follow-up Period (56 weeks in total).

Screening and Run-in Period

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

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

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

Subjects who were treated with antihypertensive drugs other than RAS inhibitors until the start of the Run-in Period can continue to receive a single antihypertensive drug in addition to the study drug if the subjects are considered to need the additional treatment for hypertension in the Treatment Period by the investigator or subinvestigator; the dose of the antihypertensive drug used before the Run-in period should be the same once the Run-in period starts.

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

Treatment Period

Study drugs will be dosed according to the subject's body weight. In the Treatment Period, the initial dose of TAK-536 will be 0.1 mg/kg (not exceeding 2.5 mg/day). After the initial dose, TAK-536 will be titrated to 0.2 mg/kg (not exceeding 5 mg/day) , 0.4 mg/kg (not exceeding 10 mg/day), and 0.8 mg/kg (not exceeding 20 mg/day) if the subjects do not achieve the target blood pressure (Table 5.a) and no concerns are found in safety and tolerability. TAK-536 will be titrated at the visit in Weeks 2, 4, or 8. Between the visits of Week 4 and 8, an additional unscheduled visit of Week 6 may be requested at the investigator's or subinvestigator's discretion in order to titrate the dose of the study drug in the subjects when the further decrease in blood pressure is needed. Even if the dose is not titrated to the maximum dose (0.8 mg/kg) by Week 8, TAK-536 may be titrated to 0.2 mg/kg, 0.4 mg/kg, and 0.8 mg/kg in a stepwise order after Week 8 if the subjects do not achieve the target blood pressure and there are no concerns regarding safety and tolerability.

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

adverse events [AEs] associated with titration of TAK-536).

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

Follow-up Period

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

Primary Objectives:

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

Secondary Objectives:

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

Subject Population:

Pediatric subjects with essential or secondary hypertension aged 2 to less than 6 years

Number of Subjects:	**Number of Sites:**
Total of 10 subjects (who enter the Treatment Period).	Approximately 20 sites (Japan)
Dose Level(s): <Regimen> Subjects will receive the study drug orally once daily before or after breakfast. <Dose *> Placebo during the Run-in Period. Subjects will receive TAK-536 0.1 mg/kg (not exceeding 2.5 mg/day), or 0.2 mg/kg (not exceeding 5 mg/day), or 0.4 mg/kg (not exceeding 10 mg/day), or 0.8 mg/kg (not exceeded 20 mg/day) * Dose of the study drug for each subject will be decided based on each subject's body weight.	**Route of Administration:** Oral
Duration of Treatment: 52 weeks	**Period of Evaluation:** 2 weeks of the Run-in Period (acceptable range, 1 to 4 weeks) 52 weeks of the Treatment Period 2 weeks of the Follow-up Period

Main Criteria for Inclusion:

- A 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 ≥95th percentile for essential hypertension without concomitant hypertensive organ damage, and ≥90th percentile for secondary hypertension with concomitant chronic kidney disease (CKD), diabetes mellitus, heart failure or 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 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 meets the above criteria for hypertension on 3 separate time points including screening and the end of the Run-in Period (Week 0). In addition, for a subject with essential hypertension without hypertensive organ damage, the subject does not respond to non-pharmacologic therapy such as diet modification or exercises for at least 3 months within 1 year prior to the start of screening.

- The subject is male or female and aged 2 to less than 6 years at the time of informed consent.
- At screening, the subject has not less than minus 2 standard deviations from mean weight for age of reference population shown in the table of pediatric body weight by the Japanese Society for Pediatric Endocrinology.
- A subject who has undergone kidney transplantation is eligible if he/she underwent the transplantation, 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 [computed tomography] scan or MRI [magnetic resonance imaging]) excluding transplanted 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 22 mmHg and/or an office sitting diastolic blood pressure higher by at least 17 mmHg than the 95th 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 (compliance: <70% or >130%) with the study drug during the Run-in Period.
- 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.
- The subject has a history of, or the signs/symptoms of serious cardiovascular, hepatobiliary, gastrointestinal, endocrine (eg, hyperthyroidism, Cushing's syndrome), hematological, immunological, urogenital, 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 uncorrected 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 (regardless of the cause), or jaundice.
- The subject has hyperkalemia exceeding ULN at screening.

Main Criteria for Evaluation and Analyses:

(1) Primary Endpoints

Safety:

- AEs
- Resting 12-lead ECG parameters
- Anthropometric measurements (weight, height, and body mass index [BMI])
- Laboratory test values

- Vital sign measurements (office sitting pulse rate* and home sitting blood pressure*)

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

(2) Secondary Endpoints

Efficacy:

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

Note: The target blood pressure is <95th percentile for essential hypertension and <90th percentile for subjects with secondary hypertension.

Pharmacokinetics:

Plasma concentrations of TAK-536

Statistical Considerations:

<Primary endpoints and analytical methods>

[Primary endpoints]

AEs, resting 12-lead ECG parameters, anthropometric measurements (weight, height, and BMI), laboratory test values, and vital sign measurements (office sitting 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, and until the end of follow-up period (or the tests performed at early termination).

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) Resting 12-lead ECG parameters, anthropometric measurements (weight, height and BMI), laboratory test values, and vital sign measurements (office sitting 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. The number and percentage of Markedly Abnormal Values (MAV) for serum chemistry will be provided.

Sample Size Rationale:

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

Interim Analysis

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

3.0 LIST OF ABBREVIATIONS

ACE	angiotensin-converting enzyme
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
BBs	beta-blockers
BMI	body mass index
BUN	blood urea nitrogen
CKD	chronic kidney disease
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CT	computed tomography
DB	double-blind
DTP	Direct to Patient
DRI	direct renin inhibitor
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
HPLC/MS/MS	high-performance liquid chromatography with tandem mass spectrometry
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology system
JCS 2018	Guideline on the Clinical Examination for Decision Making of Diagnosis and Drug therapy in Pediatric Patients with Congenital Heart Disease and Cardiovascular Disorder
JSH2019	Guidelines for the Management of Hypertension 2019
LDH	lactate dehydrogenase
LFT	liver function tests
LOCF	last observation carried forward

MAV	markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NSAIDs	non-steroidal anti-inflammatory drugs
OL	open-label
OTC	over-the-counter
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
QOL	quality of life
RAS	renin-angiotensin-system
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WD	withdrawal
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

TAK-536 (azilsartan) is a novel angiotensin-receptor blocker (ARB) produced by Takeda Pharmaceutical Company Limited 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. As hypertension affects not only adults but children and adolescents as well, Takeda is further developing TAK-536 for pediatric use.

While there are few epidemiological reports about the number of Japanese pediatric patients with hypertension less than 6 years of age, it is reported that hypertension was detected in 0.1% to 4.4% of students in elementary-school and junior-high-school at general health checkups[1], and it is anticipated that the number of patients less than 6 years of age with hypertension is similar.

For pediatric hypertension, it is known that the prevalence of secondary hypertension is higher in younger children, especially in patients under 12 years of age [2]. The most common etiology for hypertension in children less than 6 years of age is renal parenchymal diseases, aortic stenosis and renal artery stenosis [3]. Although the prognosis of secondary hypertension depends on the underlying disease and its treatment [4], both essential hypertension and secondary hypertension set target blood pressures as part of their treatment goals, in order to prevent organ damage due to hypertension [5]. Hypertension persisting from childhood is likely to cause cardiovascular diseases and organ damage including renal dysfunction. This can markedly affect 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 at an early stage.

According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension 2019 (JSH 2019) [6], drug therapy is indicated for children with hypertension meeting the following criteria: persistent hypertension despite non-drug therapy involving lifestyle modifications, symptomatic hypertension, secondary hypertension requiring drug therapy, the concomitant development of target organ damage, the presence of chronic kidney disease (CKD), and the presence of diabetes mellitus.

While a number of antihypertensive drugs for adults are available in Japan, only 5 drugs are indicated for hypertension in children, ie, valsartan and candesartan as ARBs, enalapril and lisinopril as angiotensin-converting enzyme (ACE) inhibitors, and amlodipine as calcium channel blocker. Of these, only candesartan and enalapril have an indication for patients less than 6 years of age. Furthermore, currently marketed antihypertensive drugs have no formulation developed for pediatric patients even though this is strongly desired in medical settings. Therefore, the existing treatment options for pediatric patients with hypertension are not sufficient.

Thus, to resolve the unmet needs in the present treatment of pediatric hypertension, TAK-536 clincal studies are being conducted and a pediatric-specific granule formulation for this drug has been developed and will be the formulation used for this study.

Findings from Clinical Studies of TAK-536

For adult subjects with hypertension, 4 phase 3 studies to evaluate the efficacy and safety of TAK-536 were conducted. In the Phase 3 studies, doses of TAK-536 from 10 to 40 mg showed clinically significant and stable antihypertensive effects and were well-tolerated.

For pediatric subjects with hypertension, a phase 3 study for TAK-536 (TAK-536/OCT-101) and another phase 3 study (AR14.001) using TAK-491, a prodrug of TAK-536, were conducted.

TAK-536/OCT-101 study is a Phase 3, open-label, long-term study to evaluate the safety, efficacy and pharmacokinetics of administration of TAK-536 once daily for 52 weeks in Japanese pediatric patients aged 6 to less than 16 years with hypertension. The initial dose of TAK-536 was 2.5 mg for the subjects weighing <50 kg or 5 mg for the subjects weighing ≥50 kg. After the initial dose, TAK-536 was 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 if the subjects did not achieve the target blood pressure. A total of 27 subjects participated. A decrease of office trough sitting diastolic and systolic blood pressures started at Week 2 and significant reduction was shown at the End of the Treatment Period I (Week 12) and the End of the Treatment (Week 52). TAK-536 once daily for 52 weeks was well-tolerated.

AR14.001 study is a global, Phase 3, efficacy and safety study of TAK-491 in pediatric subjects aged 6 to less than 18 years with hypertension. This study included a 6 week, double-blind, randomized, treatment double-blind (DB) Phase, followed by a 2-week, double-blind, randomized placebo-controlled withdrawal (WD) Phase. In the DB Phase, 215 subjects were randomized (1:1:1:1) to the following groups: TAK-491-L, TAK-491-M, and TAK-491-H, or losartan. In the WD Phase, 203 subjects were randomized (1:1) to continue taking their previously assigned active treatment or were switched to placebo. This study also included a 44-week, open-label (OL) Phase in which all 197 subjects received TAK-491 and other antihypertensive medications (if needed) according to a titrate-to-target blood pressure algorithm. TAK-491 demonstrated statistically significant and clinically relevant improvements of efficacy endpoints. Treatment with TAK-491 in low, medium, and high doses was safe and well-tolerated during the DB Phase, WD Phase and OL Phase of the study.

In TAK-536/OCT-101 study and AR14.001 study, no safety signals were identified in subjects aged 6 years and older and it was assessed that the risks of TAK-536 administration in pediatric subjects were similar to that of adults.

4.2 Rationale for the Proposed Study

After completion of the clinical studies for TAK-536 in subjects 6 to less than 16 years of age in which blood pressure reduction effects of TAK-536 and no significant safety issues were observed, this current study is planned to evaluate the safety, efficacy, and pharmacokinetics of 52-week administration of TAK-536 in pediatric patients with hypertension aged 2 to less than 6 years.

Before conducting this study, the sponsor had the consultation with the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) in June 2020.

4.3 Benefit/Risk Profile

TAK-536 has been approved for adult patients with hypertension since 2014. It has also demonstrated long-term consistent antihypertensive effects in 2 Phase 3 studies for pediatric subjects with either primary or secondary hypertension aged 6 years and older (TAK-536/OCT-101 study and AR14.001 study of TAK-491, a prodrug of TAK-536). Therefore, TAK-536 is expected to show similar antihypertensive effects and to contribute to the appropriate management of hypertension in subjects 2 to less than 6 years of age in this study.

With respect to safety, hypotension, impairment in renal function and hyperkalemia are important risks identified in the adult population as class effect of ARBs. In TAK-536/OCT-101 study and AR14.001 study, no new safety signals were identified in subjects aged 6 years and older and it was assessed that the risks of TAK-536 administration in pediatric subjects were similar to that of adults.

This is the first study for TAK-536 in pediatric subjects less than 6 years of age, and appropriate considerations are included in this study to manage the risks for this drug. This study has an open-label, optional titration design in which TAK-536 is initially administrated at a low dose, and can be titrated while monitoring subject condition. Additionally, as the subjects of this study may have other comorbidities, certain medications are allowed to be used concomitantly.

Subjects with high risk of renal function impairment and of hyperkalemia will be excluded in this study. In addition, during the study, the investigator or subinvestigator will carefully monitor subjects' condition, especially hypotension, renal dysfunction and hyperkalemia.

Based on the benefits that can be conferred to pediatric subjects with hypertension, as well as the risks and the appropriate measures to mitigate them, it is assessed that the benefit-risk profile would be acceptable for this population.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 Secondary Objectives

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

5.2 Endpoints

5.2.1 Primary Endpoints

Safety:

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

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

5.2.2 Secondary Endpoints

Efficacy:

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

Note: The target blood pressure is <95th percentile for essential hypertension and <90th percentile for subjects with secondary hypertension [3]. The values are shown in Table 5.a.

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

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

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

Pharmacokinetics:

Plasma concentrations of TAK-536

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 with hypertension aged 2 to less than 6 years.

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

Screening and Run-in Period:

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

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

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

Subjects who were treated with antihypertensive drugs other than RAS inhibitors until the start of the Run-in Period can continue to receive a single antihypertensive drug in addition to the study drug if the subjects are considered to need the additional treatment for hypertension in the Treatment Period by the investigator or subinvestigator. The dose of the antihypertensive drug used before the Run-in period should be the same once the Run-in period starts.

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

Treatment Period:

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

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

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

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

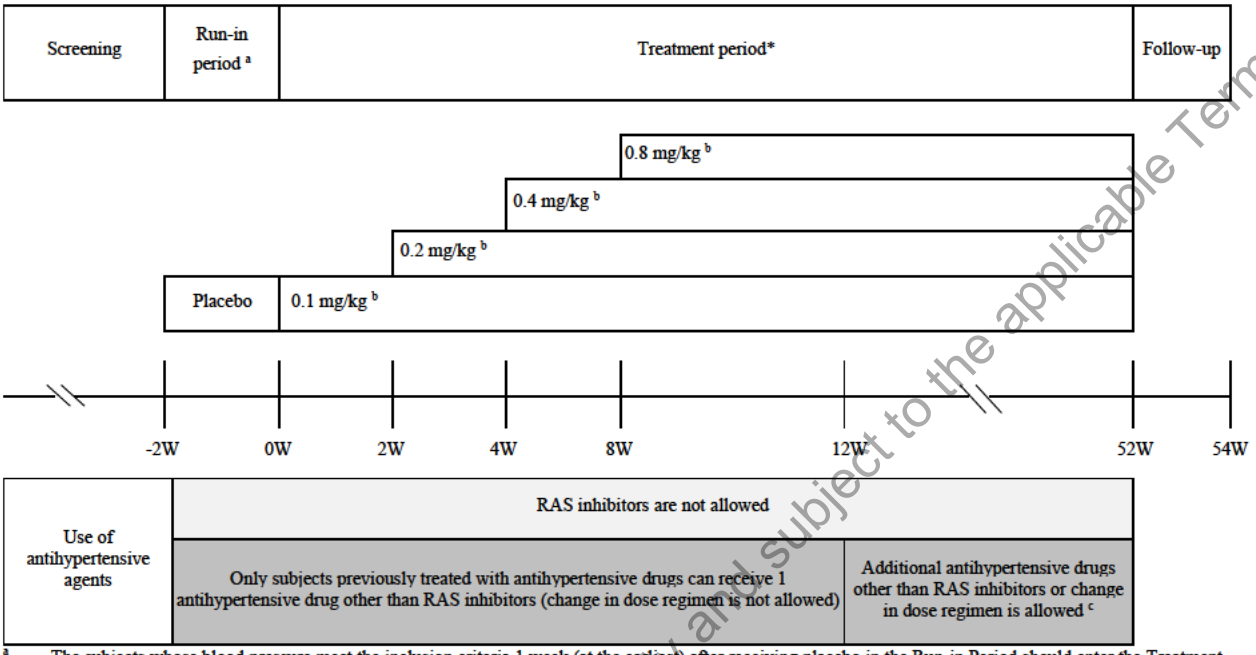
Follow-up Period:

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

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

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



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

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

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

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

6.2 Justification for Study Design, Dose, and Endpoints

[Justification for the Study Design]

Based on the disease epidemiology of hypertension in the pediatric population, renal disease is the most common underlying comorbidity for secondary hypertension. It is therefore foreseen that a number of subjects with renal dysfunction will be enrolled in this study. Evidence-based Clinical Practice Guideline for CKD 2013 (JSN2013) [7] indicates that treatment with ARB should be started 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 the subject's 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 while monitoring subject condition.

Co-administration of RAS inhibitors, which is similar to TAK-536, is not allowed in order to evaluate appropriately the efficacy of TAK-536 in the pediatric subjects throughout the Run-in Period and the Treatment Period. 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 until TAK-536 is titrated to the maximum dose (0.8 mg/kg) 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. If TAK-536 is already titrated to the maximum dose (0.8 mg/kg) and the subjects blood pressure is still not reduced to the target blood pressure, the subject 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 in the treatment period and the influence of antihypertensive drugs as a prior treatment in subjects who were taking them. In addition, the Run-in Period allows the opportunity to assess subject compliance with the study procedures 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]

A population pharmacokinetic model was developed based on data from 85 subjects (33 for pediatric patients aged ≥6 to <16 years [TAK-536/OCT-101 and TAK-536/CPH-103] and 52 for healthy adults [TAK-536/CPH-101]). Then, a virtual population of subjects was generated and were uniformly distributed by age from ≥2 to <6 years and by sex based on pediatric body weight data in Japanese children [8] and equally allocated to TAK-536 doses range from 0.1 to 1.0 mg/kg. This virtual population was composed of a total of 28800 subjects, 3600 subjects for each age (ie, 2, 3, 4, 5 years of age) and sex.

The population pharmacokinetic model was then used to simulate the exposures (C_{max} and AUC) of TAK-536 following a single oral dose of each dose for each age and sex category for the virtual pediatric population. Results simulated with the virtual population were compared with actual parameters of C_{max} and AUC (TAK-536/CPH-001) following a single oral dose of TAK-536 10-80 mg in Japanese healthy subjects. Based on the simulation, estimated exposures in pediatric patients aged from ≥2 to <6 years after receiving TAK-536 0.1, 0.2, 0.4 or 0.8 mg/kg are similar to or lower than those in healthy adults receiving TAK-536 5, 10, 20 or 40 mg, respectively. In TAK-536/OCT-101 study for subjects with hypertension aged ≥6 to <16 years, safety and tolerability were evaluated at TAK-536 2.5, 5, 10 and 20 mg in subjects weighing <50 kg. Similarly, these dose levels were selected as the exposures at each dose level would be similar to or lower than that in adults at doses of TAK-536 5, 10, 20, 40 mg.

In this study, using 0.1, 0.2, 0.4 or 0.8 mg/kg in subjects who are over 25 kg will result in doses that exceed TAK-536/OCT-101 doses (2.5, 5, 10, and 20 mg). Therefore, to avoid this, a dosing cap is set to reflect the doses used in TAK-536/OCT-101 pediatric subjects <50 kg.

[Justification for the Regimen]

Based on the results of the food effect study for TAK-536 (Azilsartan-1005), food did not affect the pharmacokinetics of TAK-536 in adults. In this study the subjects may receive the study drug before or after breakfast.

[Justification of Endpoints]

Based on the ICH-E11 guideline, efficacy data from a reference population may be extrapolated to pediatric subjects (target population) provided there is sufficient similarity in the course of the disease and the expected response to the therapy. For this study, the efficacy data from the reference population of older pediatric subjects aged 6 years and older (TAK-536/OCT-101 and AR14.001) can be extrapolated to the younger age subjects less than 6 years of age. In the same guideline, it is stated that safety data is required in the target population; therefore, safety was set as a primary endpoint for this study.

Variables commonly used to evaluate the safety of antihypertensive medication were selected as the primary endpoints. In addition, anthropometric data is included to assess the safety of TAK-536 on growth and development in this pediatric population.

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 [9] and JSH2019 [6].

Plasma concentrations of TAK-536 will be measured in order to evaluate the pharmacokinetics of TAK-536 in pediatric patients with hypertension aged 2 to less than 6 years.

[Justification for Study Duration]

a) Run-in Period

It is defined 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 in this study. This period would be equaled at least 5 half-lives of the relevant drug; the period is defined as 2 weeks in accordance with the half-life of antihypertensive drugs [10]. The subjects whose blood pressures meet the inclusion criteria 1 week (at the earliest) after receiving placebo during the Run-in Period should enter the Treatment Period in consideration of subject safety.

b) Treatment Period

JSH2019 [6] recommends that low-dose therapy with a single antihypertensive drug should be initiated first for the treatment of the hypertensive patients, and the effect must be evaluated at 2- to 4-week intervals. The dose should be increased slowly with the speed to achieve the target blood pressure. Additionally, in phase 3 studies (TAK-536/CCT-005 and TAK-536/OCT-101), a decrease of office trough sitting diastolic and systolic blood pressures started at Week 2. An 8-week period was set as the optional titration period with 3 titration point and 2 or 4 weeks for each titration point for evaluating the safety and tolerability. In addition, 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 (0.8 mg/kg).

After Week 12, 40 weeks was set as the Treatment Period 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 this study.

c) 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 on temporary suspension or early termination are satisfied.

- 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 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.
3. A 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 (refer to Table 5.a); office sitting diastolic or systolic blood pressure ≥95th percentile for essential hypertension without concomitant hypertensive organ damage, and ≥90th percentile for secondary hypertension with concomitant CKD, diabetes mellitus, heart failure or hypertensive organ damage.

   In addition, subjects need to meet the following criteria:

   If currently treated with any antihypertensive drugs at the start of the Run-in Period: Subject has a documented 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).

   If currently untreated with any antihypertensive drugs at the start of the Run-in Period: Subject meets the above criteria for hypertension on 3 separate time points including screening and the end of the Run-in Period (Week 0). In addition, for a subject with essential hypertension without hypertensive organ damage, the subject does not respond to non-pharmacological therapy such as diet modification or exercises for at least 3 months within 1 year prior to the start of screening.

   *Japanese is defined as those who are in Japan, are born in Japan and have Japanese parents and Japanese maternal and paternal grandparents.
4. The subject is male or female and aged 2 to less than 6 years at the time of informed consent.
5. At screening, the subject has not less than minus 2 standard deviations from mean weight for age of reference population shown in the table of pediatric body weight by the Japanese Society for Pediatric Endocrinology[8].
6. The subject is able to swallow the study drug.
7. A subject who has undergone kidney transplantation is eligible if he/she underwent the transplantation, 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 [computed tomography] scan or MRI [magnetic resonance imaging]) excluding transplanted kidney arterial stenosis. A subject on immunosuppressive therapy with a stable dose at least 30 days prior to screening is eligible.

8. The subject, judged by the investigator or subinvestigator, who can safely discontinue the therapy with RAS inhibitors for 2 weeks prior to the Treatment Period. This period may change to between 1 and 4 weeks depending on the subject's duration of Run-in Period.

7.1.1 Rationale of Inclusion Criteria

1. 2. 6. These were set as the standard requirements for clinical studies in pediatric subjects.

3. This inclusion criterion was set according to the criteria for initiation of Pharmacotherapy indicated in the Japanese guidelines, ie, JCS2018 Guideline on the Clinical Examinations for Decision Making of Diagnosis and Drug therapy in Pediatric Patients with Congenital Heart Disease and Cardiovascular Disorder (JCS2018 Yasukochi) [3] and Evidence-based Clinical Practice Guideline for CKD 2018 [13]. In both guidelines, reference blood pressure value of hypertension in the US guideline for children in the 50th percentile for height (categorized by age and gender) was adopted as reference blood pressure value for Japanese children. Thus, it was reflected in Table 5.a.

   The criteria, "to meet the hypertension criteria on 3 separate time points" was set for subjects untreated with any antihypertensive drugs at the start of the Run-in Period, in accordance with the 2 guidelines mentioned above as well as JSH2019 [6].

   In the guidelines of JCS2018 Yasukochi and JSH2019, non-pharmacotherapy is recommended for the treatment of essential hypertension without hypertensive organ damage before starting pharmacotherapy. Additionally, in JSH2019, it is recommended that blood pressure should be measured every 3 months during non-pharmacotherapy. According to these guidelines, the criterion "a subject with essential hypertension without hypertensive organ damage does not respond to non-pharmacological therapy for at least 3 months within 1 year prior to the start of the screening" was set.

4. The lower limit of age is set as 2 years old based on the nonclinical study results. In the series of juvenile toxicity studies using post-natal day (PND) 0, 7, 14, or 21 rats, more pronounced renal toxicities were observed, while the kidney findings in PND 21 rats were comparable to those in adult rats, indicating that younger juvenile rats whose kidney is immature were more sensitive to the pharmacologic effect of ARBs. For human, the kidney is expected to be morphologically and functionally matured at the age of 2 [14]. Thus, the lower limit of age is set as 2 years old in this study.

5. The weight limit was set from a subject safety perspective reffering to the criterion of World Health Organization (WHO) for "underweight", ie, weight for age <-2 standard deviations of the WHO Child Growth Standards median.

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. The investigator's judgment on ability to discontinue RAS therapy for 2 weeks is needed 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 surgical therapy.

2. The subject previously received therapy with azilsartan.
3. The subject has poorly controlled hypertension indicated by an office sitting systolic blood pressure higher by at least 22 mmHg and/or an office sitting diastolic blood pressure higher by at least 17 mmHg than the 95th percentiles of the reference blood pressure values of children by gender and age (refer to the Table 5.a).
4. The subject has a diagnosis of malignant or accelerated hypertension.
5. The subject was noncompliant (compliance*: <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, urogenital, 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 uncorrected aortic valvular disease, or is scheduled to undergo a medical procedure affecting blood pressure during the study (eg, correction of arterial anomaly).

   Note: This does not apply to subjects who received medical procedure(s) (eg, surgery for aortic coarctation) before the study and investigator or subinvestigator assess that subject's condition is stable at screening.

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.

7.2.1 Rationale 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.

7.3 Excluded Medications and Treatments

7.3.1 Excluded Medications

Subjects and subjects' parent or the subjects' legal guardian must be instructed not to take any medications including over-the-counter (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.

A subject can continue the conventional therapy for the concurrent medical conditions without changing daily dosage except the excluded medications.

<During Run-in Period and Treatment Period before Week 12>

The following medications will not be allowed.

(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

<During Treatment Period after Week 12>

The following medications will not be allowed.

(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

[Rationale for Excluded Medications]

<During the Run-in Period and Treatment Period before Week 12>

(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.

<During Treatment Period after Week 12>

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

(2), (4)-(6) These drugs are excluded because they could be used chronically and 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.

7.3.2 Medications Permitted with Conditions

Certain medications will be permitted with conditions in consideration of subject safety between Week 0 and 12 in which TAK-536 is titrated. Details of the following permitted medications (start and end date of administration, generic name or commercial name, total daily doses, route of administration) should be recorded in the electronic case report form (eCRF). These medications and the conditions for their use are as follows:

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 by the investigator or subinvestigator. The antihypertensive drug should be administered with 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.

Antihypertensives, in particular BBs, should be tapered off gradually, as it may cause withdrawal syndrome, in which symptoms such as palpitations, restlessness, hypertension, headache would be observed upon abrupt discontinuation.

2. Steroids:

For subjects who are receiving steroid therapy (oral, topical or inhaled), the dosage and administration should not be changed after study drug administration is initiated unless there are medical indications.

Hydrocortisone or equivalent dose to hydrocortisone for other steroids are permitted for subjects with adrenal insufficiency. The highest dose per day should be capped at 15 mg/m^2 which is recommended for chronic adrenal insufficiency in childhood in the guideline [15].

Prednisolone or equivalent dose to prednisolone for other steroids are permitted in subjects after renal transplantation or with glomerular disease. The highest dose per day should be capped at 60 mg/m^2 which is recommended for steroid sensitive nephrotic syndrome in the guideline [16].

Especially for subjects who need higher dose of steroids (eg, 60 mg/m^2 of prednisolone), the investigator or subinvestigator need to confirm these subjects' safety and consider whether continuous administration of the study drug is acceptable. Additionally, pulse therapy with extremely high dose of steroid (eg, >60 mg/m^2 of prednisolone) is prohibited.

3. Central nervous system stimulants, non-central nervous system stimulants:

Use for treatment of attention deficit/hyperactivity disorder is permitted but its dosage and administration should not be changed as much as possible after study drug administration is initiated.

7.4 Diet, Fluid, Activity Control

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

1. The subject's parent or the subject's legal guardian should ask the investigator or subinvestigator by telephone for instructions or visit the study site, as soon as the subject experiences vomiting or diarrhea frequently throughout the study.
2. The investigator or subinvestigator will explain the possibility of excessive reduction in the blood pressure associated with TAK-536 treatment to the subject's parent or the subject's legal guardian. The subject's parent or the subject's legal guardian should make the subject rest in a supine position, as soon as the subject experiences any symptoms suggesting decreased blood pressure (eg, dizziness, lightheadedness, etc.) outside the study site on days other than the scheduled visit, and ask the investigator or subinvestigator by telephone for further instructions, or visit the study site, if the symptoms did not subside.
3. The subject's parent or the subject's legal guardian should ask the investigator or subinvestigator by telephone for instructions, or visit the study site, as soon as the subject experiences 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. The subject should not eat or bathe within 1 hour before office blood pressure measurement, no intake of any caffeine containing product within 30 minutes before the measurement.
5. The subject should comply with and not to change a fixed diet (eg, caloric and salt intake) and/or exercise therapies, if performed, throughout the study.
6. The subject should avoid food with high salt content, to take adequate hydration, and to maintain a routine sleep, behavior and caffeine intake. In addition, the subject should avoid excessive drinking/eating, significant change of diet (eg, excessively high-fat diet), excessive exercise, and staying up late. The subject will maintain a regular lifestyle on the day before visit days.
7. The subject's parent or the subject's legal guardian should inform the investigator or subinvestigator before receiving treatment from another doctor, or to provide details of treatment the subject received in case of reporting afterwards. If subject receives treatment by another doctor, the subject's parent or the subject's legal guardian should inform another doctor of his/her participation in this study before the treatment, as far as possible.
8. The subject's parent or the subject's legal guardian should consult the investigator or subinvestigator before the subject's using or changing the dosage of any drug not prescribed by the investigator or subinvestigator (including vitamins supplements, OTC drugs, and herbal preparations). The subject's parent or the subject's legal guardian will promptly provide the details when the subject uses any such drug.
9. The subject should visit the study site at the scheduled times to undergo examinations and tests by the investigator or subinvestigator. The subject's parent or the subject's legal

guardian will promptly inform the investigator or subinvestigator when the subject is unable to visit the study site as scheduled.

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 eCRF using the following categories. For subject failure, refer to Section 9.1.12.

1. 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 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%).

2. Significant Protocol deviation. The discovery after the start of the first dose of study drug 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.
3. 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.
4. Voluntary withdrawal. The subject (or the subject's parent or legal guardian) 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 (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. 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 22 mmHg and/or an office sitting diastolic blood pressure is persistently higher by at least 17 mmHg than the 95th 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 before Week 12 or with the addition of any other antihypertensive drugs other than RAS inhibitors during the Treatment Period after Week 12.
7. 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 (or the subject's parent or legal guardian) 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 the eCRF. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL STUDY 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 study 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 granules (placebo for the Run-in Period)	White to nearly white granules	Contains no TAK-536 in 1 g
TAK-536 granules (active drug for the Treatment Period)	White to nearly white granules	Contains 10 mg of TAK-536 in 1 g

   Manufacturing: Nipro Pharma Corporation

2. Package and labeling

- Package

  Study drugs will be dispensed in bottles.

- Labeling

  Each bottle indicates the following information: the drug is for the study use only, study drug name, study number, subject identification number, medication identification number, the sponsor's name and address, batch number, and storage condition, and expiration date.

8.1.2 Storage

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

TAK-536 granules will be subdivided into sachets by the on-site pharmacist (site designee) at each site. The subjects' parent or the subjects' legal guardian will be instructed not to store in direct sunlight, high temperatures or high humidity. TAK-536 granules should be administered immediately after the sachet is torn off.

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.

During the Run-in Period, subjects will orally receive the study drug for the Run-in Period once daily, before or after breakfast. The placebo study drug during the Run-in Period will be provided with equivalent daily amount (mg) as they would receive for TAK-536 0.1 mg/kg dose. During the Treatment Period, study drugs will be dosed according to the subject's body weight. After the initial dose (0.1 mg/kg [not exceeding 2.5 mg/day]), subjects will orally receive any of TAK-536 0.2 mg/kg (not exceeding 5 mg/day), 0.4 mg/kg (not exceeding 10 mg/day), 0.8 mg/kg (not exceeding 20 mg/day) once daily, before or after breakfast. For dose titration method, see Section 6.1.

At Week 12, 24 and 40, subject's body weight is measured and the dose is adjusted according to the body weight.

The investigator or subinvestigator may select the timing of the study drug administration (ie, before or after breakfast) in consideration of subject lifestyle but should not change this timing throughout the study. Regular doses on days except for the visits will be administered no later than 9:00 AM, regardless of the specified dosing timing (ie, before or after breakfast). The study drug should be administered at the almost same time every day throughout the study (acceptable range is ± 3hours) except the visit day. In case of a missed dose, the subject should take only one dose of the study drug for the day; instructions should be provided to parents or legal guardians that the daily dose should not be doubled on account of the missed dose. On the day before a scheduled visit, subject must take the study drug 24 hours (acceptable range, 21 to 27 hours) before office blood pressure measurement on the following 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.

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 eCRFs according to Section10.0.

Serious adverse events (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 in response to symptoms.

8.2 Study Drug Assignment and Dispensing Procedures

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

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed at the site. The site will maintain source documents in addition to entering data into the interactive response technology system (IRT).

In case subjects cannot visit the site due to the COVID-19 associated event/issue (e.g. subjects or their care givers who tested positive for COVID-19 or is close contact, or site shutdown due to COVID-19, etc), additional study drug may be provided to the subjects to cover extended periods between on-site visits. Study drug may be shipped directly from investigational sites to subjects' residences by a contracted logistics provider (Direct to Patient [DTP] shipment) or the subject's parent or the subject's legal guardian may receive directly at investigational site. DTP shipment will be performed if the investigator determines that treatment can be continued after confirming the subject's condition by phone or using a data communication device and be provided in compliance with applicable laws, regulations or temporary emergency measures. The investigator's decision must be documented in the source documents.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (site designee) will receive the pharmacy manual 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 investigator or designee and the on-site pharmacist (site designee) must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects

enrolled in the study. To document appropriate use of sponsor supplied drug, the on-site pharmacist (site designee) must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the on-site pharmacist (site designee) must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, the on-site pharmacist (site designee) should acknowledge the receipt of the shipment in the IRT. If there are any discrepancies between the packing list versus the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The on-site pharmacist (site designee) will immediately return unused study drugs to the sponsor after the study is closed at the study 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 are described in Section15.2.

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.

Consent to participate in the study will be obtained from any subject's parent or the subject's legal guardian 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 obtained; 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 resolved within 1 year prior to signing of informed consent form. 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 the start of Run-in Period (Week -2).

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) 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 prior to first dose examination.

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: Height is

recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

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

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then BMI=$79.2/1.76^2$=25.56818 kg/m^2

9.1.5 Vital Sign Procedure

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

Office blood pressure should be measured at the time of trough (approximately 21 to 27 hours after the latest dose, ie, 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.

<Arm for measurement>

The right arm should be used to measure office blood pressure. 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 after the subject has been sitting at rest and recorded in the subject source documents and eCRF. These should be measured in a sitting position. For subjects who are unable to assume a sitting position, the measurements can be obtained while in other positions such as a supine position. In this case, all measurements should be conducted in the same position during the study.

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. 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 study collaborator.

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.

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, 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 (including visit at Week 6, when performed), and for 1 week from the day before the visit at Week 12 of the Treatment Period.

The subject should measure blood pressure 2 times in a row with the blood pressure cuff applied to the right arm. 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 the eCRF. 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 22 mmHg and/or a home sitting diastolic blood pressure which is higher by at least 17 mmHg than the 95th 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 the sponsor. 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 the medications permitted with conditions (see 7.3.2), the daily dosage and unit of concomitant medications until Week 12 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 form. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the first test after signing of informed consent form, according the judgment of the investigator. The condition (ie, 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 and the maximum total volume of blood for the study is approximately 73 mL. The volume of blood will be determined at each site.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis [c]
Red blood cell count	Hemoglobin A1c/Hemoglobin [a]	Qualitative tests for glucose, pH, protein, occult blood, ketones
White blood cell count with differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes)	ALT	Quantitative tests for protein, creatinine, albumin
Hemoglobin	Albumin	Protein/creatinine ratio, albumin/creatinine ratio, specific gravity
Hematocrit	Alkaline phosphatase (ALP)	
Platelets	AST	
	Bilirubin (Total bilirubin)	
	Blood urea nitrogen (BUN) [b]	
	Calcium	
	Chloride [b]	
	Creatinine [b]	
	Creatine kinase	
	Cystatin C	
	Estimated Glomerular Filtration Rate [b]	
	Gamma-glutamyl transferase (GGT)	
	Glucose	
	Cholesterol (Total cholesterol)	
	Triglyceride	
	Phosphate	
	Potassium [b]	
	Sodium [b]	
	Protein (Total protein)	
	Lactate dehydrogenase (LDH)	

[a] Only for subjects with diabetes mellitus
[b] The laboratory tests associated with renal parameters and potassium should be performed to confirm the safety and tolerability when TAK-536 is titrating (including unscheduled visit).

[c] Urine samples will be collected when possible.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis (acceptable under the fed condition). The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

The laboratory tests associated with renal parameters and potassium should be performed to confirm the safety and tolerability when TAK-536 is titrating (including unscheduled visit).

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 [17]

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, 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 (refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on reporting of abnormal liver function tests).

If 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 (refer to Section 10.2.3).

The investigator or subinvestigator is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the reference ranges including the archival records for the laboratory used.

9.1.10 ECG Procedure

A resting 12-lead ECG will be measured. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The investigator 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 ($QT/RR^{0.33}$).

9.1.11 Pharmacokinetic Sample Collection

According to the study schedule (Appendix A), pharmacokinetic sample should be collected before study drug administration at one of the 4 visits (Week 2, 4, 8, and 12). Also, if possible, pharmacokinetic sample is collected around 2 hours (acceptable time window is 1 to 3 hours) after study drug administration at the same visit. At other 3 visits, if possible, pharmacokinetic samples are collected before study drug administration and/or around 2 hours (acceptable time window is 1 to 3 hours) after study drug administration.

On the visit of Week 16, pharmacokinetic sample should be collected around 2 hours (acceptable time window is 1 to 3 hours) after study drug administration.

9.1.11.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (one 1-mL sample per scheduled time) for pharmacokinetic analysis of TAK-536 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.

9.1.11.2 Bioanalytical Method

Plasma concentrations of TAK-536, M-I, and M-II will be measured by HPLC/MS/MS (high-performance liquid chromatography with tandem mass spectrometry) at CMIC Pharma Science Co., Ltd.

9.1.12 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent form. If the subject is withdrawn before the start of the Treatment Period, the investigator or subinvestigator should complete the eCRF.

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

- AE.
- Screen Failure <specify reason>.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

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

9.1.13 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

Subjects will be required to bring study drug containers/unused study drugs to each dispensing site visit. Compliance with study drug (amount of dispense and return) between the visits, 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 (Compliance: <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.

In unavoidable circumstances (eg, a widespread disease outbreak such as COVID-19 pandemic or natural disaster), exceptions may be consulted for alternative visits or assessments for conducting subject visits with approval by the Medical Monitor and/or sponsor.

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. See Section 9.1.12 for procedures for documenting screening failures.

Procedures to be completed at Screening include:

- Informed consent.
- Demographics, medical history, and medication history.
- Physical examination.

- Vital signs.
- Weight, height.
- Concomitant medications.
- Concurrent medical conditions.
- Screening clinical laboratory tests.
- Resting 12-lead ECG.
- AE assessment.

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

The study drug for the Run-in Period (TAK-536 placebo) 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 for the Run-in Period will be started from the next day.

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

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 9.1.12 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, 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.

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 who terminate the study early 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 measured 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 continued to receive the study drug beyond Week 24.

9.3.6 Follow-up Period: Week 54

The follow-up Period will begin the 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 at the end of this follow-up period but care should be taken for subject safety.

9.3.7 Post Study Care

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 form 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 test values and ECG findings:

- Changes in laboratory test values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, 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 or ECG re-test and/or continued monitoring of an abnormal value or finding 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 test 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 form) 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 form 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 concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes 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, worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. 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 the start of study drug, 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…").
- If the subject experiences a worsening or complication of an AE after any change in the study drug, 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 intensity of AEs:

- If the subject experiences changes in intensity 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 intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent form 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 recorded 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 form 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 (including seizure and epilepsy)	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis (including interstitial lung disease)
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
COVID-19 related disease	COVID-19 pneumonia

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.1.4 AEs of Special Interest (AESI)

An AE of Special Interest (AESI) (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 and instructions provided for investigator or subinvestigator as to how and when they should be reported to Takeda. The list of AESIs in this study is in Section 10.2.1.3

10.1.5 Intensity of AEs

The different categories of intensity (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

The relationship 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 possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications 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 medications and concurrent treatments.

10.1.7 Causality to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship 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 investigator or subinvestigator.

10.1.9 Stop 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 Frequency

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 Concerning Study Drug

- 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.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.

- Dose 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".
- Resolved/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's parent or the subject's legal guardian signs the informed consent form. 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 stop date.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not applicable for the AE that occurred before the study drug administration).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning 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. In addition to these risks, hyperkalemia is also known as a risk caused by the pharmacological effect of ARB. Hence, the following AEs related to hypotension, renal impairment or hyperkalemia will be investigated as AESIs 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.

[Hyperkalemia-related AE]

Blood potassium increased, Hyperkalaemia

If any of these AESIs occur during the Treatment Period or the Follow-up Period, it should be reported to the sponsor.

An AESI eCRF should be completed, and signed by the investigator immediately or within 1 business day of first onset or notification of the event from the subject, the subject's parent or the subject's legal guardian. However, as a back-up, if required, the AESI Form should be completed and reported to the sponsor (described in the separate contact information list) within 1 business day.

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 eCRF should be completed, and signed by the investigator immediately or within 1 business day of the first onset or notification of the event from the subject, the subject's parent or legal guardian. However, as a back-up, if required, the SAE Form should be completed and reported to the sponsor (described in the separate contact information list) within 1 business day.

The information should be provided as completely 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 and dose (during the Treatment Period).
- 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.

Reporting SAEs that occur before the first dose of study drug will follow the procedure described for SAEs.

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 Medical Monitor 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 update SAE eCRF or complete a follow-up SAE form immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the sponsor, 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/ the head of the study site. 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, medical history and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using WHO Drug Dictionary.

12.1 CRFs (Electronic)

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

The sponsor or its designee will supply study 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 e-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 results of pharmacokinetics conducted at the analytical institute will not be recorded into the eCRFs.

After the lock of the 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 the sponsor or its designee. 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 study site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, the investigator and the head of the study 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 study 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 study.

In addition, the investigator and the head of the study 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 prior to first subject enrolled 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 all subjects complete Week 24 and 52 in the Treatment Period, the data until Week 24 and 52 in the Treatment Period will be analyzed separately after being locked.

13.1.1 Analysis Sets

13.1.1.1 Safety Analysis Set

The safety analysis set will consist of all subjects who were enrolled and received at least 1 dose of study drug for the Treatment Period. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

13.1.1.2 Full Analysis Set

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

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the safety analysis set.

13.1.3 Efficacy Analysis

(1) Secondary endpoints and analytical methods

[Secondary endpoints]

Change from baseline in office trough sitting diastolic and systolic blood pressure, proportion of subjects who achieve the target blood pressure at Week 12 and 52 (LOCF)

The short term efficacy and long term efficacy will be mainly evaluated by Week 12 (LOCF) and Week 52 (LOCF), respectively.

[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 pointand Week 12 and 52 (LOCF). The case plots will be also provided.

Summary statistics and 2-sided 95% confidence intervals for mean values will be calculated 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 and Week 12 and 52 (LOCF) during the Treatment Period.

The proportion of subjects who achieve the target blood pressure at each time point and Week 12 and 52 (LOCF) during the Treatment Period will be summarized with blood pressure values measured under stable condition.

In the analysis of Week 12 (LOCF), the above analysis will be conducted with data which are obtained before dosage of the medications permitted with conditions (see Section 7.3.2) is changed in the Treatment Period.

(2) Confidence coefficient

Confidence coefficient: 0.95 (2-sided estimates)

13.1.4 Pharmacokinetic Analysis

[Secondary endpoints]

Plasma concentrations of TAK-536

[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 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, and pharmacokinetic parameters (eg, C_{max} and AUC) in the subjects will be estimated, if possible. An analysis plan and results will be provided separately from those of this study.

13.1.5 Safety Analysis

Primary endpoints and analytical methods

[Primary endpoints]

- AEs
- Resting 12-lead ECG parameters
- Anthropometric measurements (weight, height, and BMI])
- Laboratory test values

- Vital sign measurements (office sitting 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 TEAE is defined as any AE occurring after the start of TAK-536 administration, and until the end of Follow-up Period (or the test performed at early termination).

The incidence of TEAEs listed below will be analyzed. TEAEs will be coded using 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) Resting 12-lead ECG parameters, anthropometric measurements (weight, height, and BMI), laboratory test values, and vital sign measurements (office sitting 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. The number and percentage of Markedly Abnormal Values (MAV) for serum chemistry will be provided.

13.2 Interim Analysis and Criteria for Early Termination

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

13.3 Determination of Sample Size

Total of 10 subjects to enter the Treatment Period.

[Rationale for Determination of Sample Size]

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

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 head of the study 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 sponsor's 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 or 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. Should other unavoidable circumstances arise (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster) that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. Deviations from the protocol-specified procedures will be recorded as related to COVID-19. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study 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 study site as soon as possible and an approval from IRB should be obtained.

The investigator or subinvestigator should document all protocol deviations. 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 head of the study 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 (ie, 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 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 must be obtained and submitted to the sponsor or designee before commencement of the study (ie, 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 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.

Study 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 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, 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. 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 form. The informed consent form must be approved by both of the IRB and sponsor prior to use.

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 detailed elements of the informed consent form to a subject's parent or the subjects' legal guardian. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

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. 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. The investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form 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 in the subject's medical record. Copies of the signed informed consent form shall be given to the subject's parent, or the subject's legal guardian.

All revised informed consent forms must be reviewed and signed by the relevant subject's parent or the subject's legal guardian in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject's parent, or legal guardian should receive a copy of the revised informed consent 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 the monitor or the sponsor's designee, 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's parent, or the subject's legal guardian as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, 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 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 needs 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 registerall interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with facility names, 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 and/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 study

subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator or subinvestigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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