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

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

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

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

PROTOCOL

A Randomized, Open Label, 2-Period, 2-Treatment, Cross-over Phase 1 Study to Evaluate the Bio-equivalence of Single Oral Dose of TAK-536 Pediatric Formulation and TAK-536 Commercial Formulation in Healthy Adult Male Subjects

A Phase 1, Bio-equivalence Study of TAK-536 Pediatric Formulation

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka, Japan		
Study Number:	Azilsartan-1004		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-536		
Date:	22 Dec 2016	**Version/Amendment Number:**	First Version

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the annex.

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 Council for Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Clinical Study Sponsor:
Takeda Pharmaceutical Company Limited</td><td colspan="2">Compound:
TAK-536</td></tr>
<tr><td>Study Title:
A Randomized, Open Label, 2-Period, 2-Treatment, Cross-over Phase 1 Study to Evaluate the Bio-equivalence of Single Oral Dose of TAK-536 Pediatric Formulation and TAK-536 Commercial Formulation in Healthy Adult Male Subjects</td><td>IND No.:
Not applicable</td><td>EudraCT No.:
Not applicable</td></tr>
<tr><td colspan="2">Study Identifier: Azilsartan-1004</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="4">Study Design:
This study is conducted to evaluate the bio-equivalence of a single oral administration of TAK-536 pediatric formulation (granules) in comparison with a TAK-536 commercial formulation in healthy adult male subjects in an open label, 2-period, 2-treatment, cross-over design.
In case bio-equivalence is not demonstrated because the planned number of subjects is too small, an add-on subject study will be conducted.</td></tr>
<tr><td colspan="4">Primary Objective:
To evaluate the bio-equivalence of a single oral administration of TAK-536 pediatric formulation in comparison with a TAK-536 commercial formulation in Japanese healthy adult male subjects
Secondary Objective:
To evaluate the safety of a single oral administration of TAK-536 pediatric formulation in Japanese healthy adult male subjects</td></tr>
<tr><td colspan="4">Subject Population: Japanese healthy adult male subjects</td></tr>
<tr><td colspan="2">Planned Number of Subjects:
14 subjects (7 for each sequence)
In case an add-on subject study is conducted, the maximum number of subjects will be 120 in total (60 per sequence).</td><td colspan="2">Planned Number of Sites:
1 site</td></tr>
<tr><td colspan="2">Dose Levels:
Each subject will receive either TAK-536 commercial formulation or TAK-536 pediatric formulation in each period under the conditions described below.
1. TAK-536 commercial formulation (tablet)
The subject will orally receive one TAK-536 10 mg tablet with 200 mL water under fasted conditions in the morning (fasted for more than 10 hours after the last meal on the day before the study drug administration [Day 1]).
2. TAK-536 pediatric formulation (granules)
The subject will orally receive one sachet of TAK-536 granules containing 10 mg TAK-536 with 200 mL water under fasted conditions in the morning (fasted for more than 10 hours after the last meal on the day before the study drug administration [Day 1]).</td><td colspan="2">Route of Administration:
Oral</td></tr>
</table>

Duration of Treatment:	**Study Length:**
Single dose×2 period (with a washout period of at least 6 days)	Hospitalization for 4 days and 3 nights+1 day for a follow-up examination in each period

Criteria for Inclusion:

1. In the opinion of the investigator or sub-investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a Japanese healthy adult male.
4. The subject is aged 20 to 35 years, inclusive, at the time of informed consent.
5. The subject weighs at least 50.0 kg, and has a body mass index (BMI) between 18.5 and 25.0 kg/m^2, inclusive, at Screening.

Criteria for Exclusion:

1. The subject has suspected hypotension with associated physical findings, such as dizziness postural, facial pallor, or cold sweats based on evaluation/physical examination at Screening, on the day before the study drug administration (Day -1) in Period 1, or up to the study drug administration on the Period 1.
2. The subject has received any study drug within 16 weeks (112 days) prior to the study drug administration in Period 1.
3. The subject has received TAK-536 or TAK-491 in a previous clinical study or as a therapeutic agent.
4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results.
5. The subject has a known hypersensitivity to any component of the formulation of TAK-536 or any angiotensin II receptor blocker (ARB).
6. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use) at Screening.
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 2 years prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
8. The subject has taken any excluded medication, supplements, dietary products or food products during the time periods listed in Section 7.3.
9. The subject has any current or recent (within 6 months) gastrointestinal diseases that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
10. The subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1 of Period 1.
11. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, or serological reactions for syphilis at Screening.
12. The subject has poor peripheral venous access.
13. The subject has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of the study drug administration in Period 1.
14. The subject has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of the study drug administration in Period 1.
15. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of the study drug administration in Period 1.
16. The subject has an abnormal (clinically significant) electrocardiogram (ECG) at Screening or prior to the study drug administration in Period 1.
17. The subject has abnormal laboratory values that suggest a clinically significant underlying disease, or subject with

the following laboratory abnormalities at Screening or prior to the study drug administration in Period 1: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5×the upper limits of normal (ULN).

18. The subject who, in the opinion of the investigator or sub-investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

Criteria for Evaluation and Analyses:

Primary endpoints

Pharmacokinetics: AUC_{48} and C_{max} of TAK-536.

Secondary endpoints

Pharmacokinetics: AUC_{∞}, t_{max}, MRT, and λ_z.

Safety: adverse events (AEs), vital signs (sitting blood pressure, sitting pulse [beats per minute], and body temperature), weight, resting 12-lead ECGs, and laboratory test results (hematology, serum chemistry, and urinalysis).

Statistical Considerations:

(1) Plasma drug concentration

For plasma concentration of TAK-536, descriptive statistics will be provided by visit for each formulation (TAK-536 commercial formulation, TAK-536 pediatric formulation). In addition, the plasma concentration-time profiles will be also provided.

For pharmacokinetic parameters except $AUMC_{last}$ and $AUMC_{\infty}$, descriptive statistics will be provided. For the ratio between each formulation (TAK-536 pediatric formulation/TAK-536 commercial formulation) for pharmacokinetic parameters AUC_{48} and C_{max}, descriptive statistics will be provided.

(2) Assessment of bio-equivalence on pharmacokinetic parameters

The difference in the least square means between formulations (TAK-536 pediatric formulation - TAK-536 commercial formulation) and the two-sided 90% confidence interval will be provided using a crossover analysis of variance (ANOVA) model. The ANOVA model will include log-transformed (natural log) pharmacokinetic parameters AUC_{48} and C_{max} as dependent variable, and formulation, group, and period as independent variables. For log-transformed (natural log) pharmacokinetic parameters AUC_{last}, AUC_{∞}, $MRT_{\infty,ev}$, λ_z, and non-natural log tansformed t_{max}, same analyses will be performed.

Sample Size Justification:

Based on the currently available results of the studies conducted to date, the residual sum of squares of pharmacokinetic parameters C_{max} and AUC_{48} in the present study was assumed to be 0.13 and 0.08, respectively. For 6 subjects per sequence (total of 12 subjects per formulation), in two one-sided t-tests [H_0: $\ln(\mu)\leq\ln(\theta_1)$, $\ln(\mu)\geq\ln(\theta_2)$; H_1: $\ln(\theta_1)<\ln(\mu)<\ln(\theta_2)$; where $\mu=\mu_t/\mu_s$, μ_t was the population mean for the pediatric formulation, μ_s was the population mean for the TAK-536 commercial formulation, $\theta_1=0.80$, and $\theta_2=1.25$] with a one-sided significance level of 5% and alternative hypothesis $\mu=0.95$, more than 90% power of simultaneous detection of the bio-equivalence for pharmacokinetic parameters C_{max} and AUC_{48}. Taking into account possible occurence of dropouts during the study and feasibility, 7 subjects per sequence (total of 14 subjectsper formulation) were set.

In case bio-equivalence cannot be demonstrated with the number of subjects initially planned on account of insufficient subjects, an add-on subject study will be conducted in accordance with the Guideline for Bioequivalence Studies of Generic Products. The maximum number of subjects in the add-on subject study is 120 (60 per sequence), which is determined based on study feasibility, but is not on statistical consideration. The number of subjects in the add-on subject study will be determined based on the result of the interim analysis in this study and the currently available results of the studies conducted to date.

3.0 LIST OF ABBREVIATIONS

ACE	angiotensin converting enzyme
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
OTC	over-the-counter
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TPC	Takeda Pharmaceutical Company Limited
ULN	upper limits of normal

4.0 INTRODUCTION

4.1 Background

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

Pediatric hypertension is classified into essential hypertension and secondary hypertension as described for adults. Although essential hypertension in children is generally mild, such patients are at a high risk of cardiovascular disease including left ventricular hypertrophy and carotid intima-media wall thickening as well as organ damage, eg, renal dysfunction [4][5]. Furthermore, essential hypertension in children can track into adult essential hypertension with patients' growth [6]. The possibility of secondary hypertension, in contrast, increases with a younger age and the majority cases are severe. Hypertension caused by renal diseases (renal hypertension) accounts for 60% to 80% of children with secondary hypertension, and chronic renal failure requires particular attention. Therefore, it is necessary to prevent deterioration of renal function and progression of organ damage.

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

The Japanese Society of Hypertension Guidelines for the Management of Hypertension 2014 (JSH2014) [7] recommends that drug therapy should be considered after non-pharmacological interventions (dietary and exercise therapy) are primarily performed since essential hypertension in children is often mild. For patients with secondary hypertension and patients with target organ damage, diabetes mellitus, or chronic kidney disease (CKD), drug therapy is highly recommended to prevent the development and progression of organ damage.

JSH2014 [7] and the Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases by the Japanese Circulation Society[8] recommend angiotensin II receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers as first-choice drugs for pediatric patients. In particular, more strict blood pressure management is recommended for hypertension with CKD or diabetes mellitus than that for hypertension without complications. Hypertension with such complications is recommended to be treated with ARBs having antiproteinuric effects and inhibitory effects of CKD progression in addition to ACE inhibitors.

While a number of antihypertensive drugs for adults are available in Japan, only 4 drugs are indicated for hypertension in children, valsartan being the only ARB among them. Only one drug among ACE inhibitors is indicated for patients younger than 6 years old. Furthermore, none of the approved drugs have formulations designed for pediatric patients. Therefore, treatment options for pediatric patients with hypertension are not sufficient.

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

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

4.2 Rationale for the Proposed Study

Upon beginning the development of TAK-536 for infants and children (from 1 year old to less than 6 years old), TPC decided that pediatric patients, who have difficulty swallowing tablets, require pediatric formulations to ensure individually targeted dose adjustment and treatment adherence.

TPC then decided to evaluate the bio-equivalence of TAK-536 pediatric formulation in comparison with a TAK-536 10 mg commercial formulation in healthy adult male subjects in accordance with the partial revision of the Guideline for Bioequivalence Studies of Generic Products (hereafter referred to as the Guideline for Bioequivalence Studies of Generic Products) [9].

This protocol is designed in accordance with Good Clinical Practice (GCP).

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To evaluate the bio-equivalence of a single oral administration of TAK-536 pediatric formulation in comparison with a TAK-536 commercial formulation in Japanese healthy adult male subjects.

5.1.2 Secondary Objective

To evaluate the safety of a single oral administration of TAK-536 pediatric formulation in Japanese healthy adult male subjects.

5.2 Endpoints

5.2.1 Primary Endpoints

Pharmacokinetics: AUC_{48} and C_{max} of TAK-536.

5.2.2 Secondary Endpoints

Pharmacokinetics: AUC_{∞}, t_{max}, MRT, and λ_z.

Safety: adverse events (AEs), vital signs (sitting blood pressure, sitting pulse, and body temperature), weight, resting 12-lead electrocardiograms (ECGs), and laboratory test results (hematology, serum chemistry, and urinalysis).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

1. Study Design

This study is conducted to evaluate the bio-equivalence of a single oral administration of TAK-536 pediatric formulation (granules) in comparison with a TAK-536 commercial formulation in healthy adult male subjects in an open label, 2-period, 2-treatment, cross-over design.

In case bio-equivalence is not demonstrated because the planned number of subjects is too small, an add-on subject study will be performed.

2. Sample size

A total of 14 subjects (7 for each sequence) will be enrolled in this study.

In case an add-on subject study is conducted, the maximum number of subjects will be 120 (60 per sequence).

3. Dose and mode of administration

The dosage and number of subjects are presented in Table 6.a. Each subject will receive either TAK-536 commercial formulation (tablet) or TAK-536 pediatric formulation (granules) in each period under the conditions described below.

1) TAK-536 commercial formulation (TAK-536 10 mg tablet)

The subject will orally receive one TAK-536 10 mg tablet with 200 mL water under fasted conditions in the morning (fasted for more than 10 hours after the last meal on the day before the study drug administration [Day 1]).

2) TAK-536 pediatric formulation (TAK-536 granules)

The subject will orally receive one sachet of TAK-536 granules containing 10 mg TAK-536 with 200 mL water under fasted conditions in the morning (fasted for more than 10 hours after the last meal on the day before the study drug administration [Day 1]).

Table 6.a Dosage and Number of Subjects

Sequence	Dose		Number of Subjects	Administration Condition
	Period 1	Period 2		
a	One sachet of TAK-536 granules (10 mg/sachet)	One tablet of TAK-536 10 mg	7	Fasted
b	One tablet of TAK-536 10 mg	One sachet of TAK-536 granules (10 mg/sachet)	7	

Add-on Subject Study (if conducted)

Sequence	Dose		Maximum Number of Subjects	Administration Condition
	Period 1	Period 2		
a	One sachet of TAK-536 granules (10 mg/sachet)	One tablet of TAK-536 10 mg	60	Fasted
b	One tablet of TAK-536 10 mg	One sachet of TAK-536 granules (10 mg/sachet)	60	

4. Planned number of study sites

One study site

5. Planned duration of subject participation and number of visits of each subject in the study

Subjects will be screened for enrollment from 4 weeks (28 days) to 2 days (the day before admission) before the study drug administration (Day -28 to Day -2) in Period 1. Subjects will be admitted to the study site on the day before the study drug administration (Day -1) in both Periods 1 and 2, and will be hospitalized under medical supervision for 4 days (until 48 hours after the study drug administration). They will undergo daily examinations from the day before the study drug administration (Day -1) and observations during their hospitalization according to the study schedule specified in Appendix A, and will be discharged from the study site on Day 3 after confirmation of safety by the investigator or sub-investigator. Subjects will return to the study site for follow-up examinations on Day 6. A washout period of at least 6 days will be placed between the study drug administrations in Periods 1 and 2.

Subjects will visit the study site 5 times, including the visit for screening examinations, in this study. They will be hospitalized for a total of 8 days in Periods 1 and 2.

The examinations scheduled on the day before the study drug administration (Day -1) in Period 2 can be replaced with the follow-up examinations (Day 6) in Period 1, if they are scheduled on the same day. If this is the case, the subject will visit the study site 4 times in this study.

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

Figure 6.a Schematic of Study Design (Period 1 and Period 2)

Element	Screening		Treatment (TAK-536 10 mg)*				
Day	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	…	Day 6
	Visit	Hospitalization					Visit
Content	Informed Consent, Screening	Admission	Study Drug Administration		Discharge		Follow-up Examination

*: A washout period of at least 6 days will be placed between the study drug administrations in Period 1 and Period 2. The examinations scheduled on the day before the study drug administration (Day -1) in Period 2 can be replaced with the follow-up examinations (Day 6) in Period 1, provided that they are scheduled on the same day. If this is the case, the subject will visit the study site 4 times in this study.

6.2 Justification for Study Design, Dose, and Endpoints

1. Justification for the Study Design

In accordance with the Guideline for Bioequivalence Studies of Generic Products [9], a 2-period, 2-treatment, cross-over design, which allows bio-equivalence evaluation with minimal effect on inter-subject variation, was selected for this study.

2. Justification for the Study Population

The study population will be healthy adult males in accordance with the Guidance on Clinical Investigation of Medicinal Products in the Pediatric Population [10] and the Guideline for Bioequivalence Studies of Generic Products [9].

3. Justification for Dose

Three formulations of TAK-536 tablets (10 mg, 20 mg, and 40 mg) are marketed for adult patients, and TAK-536 pediatric formulations are being developed for infants and children (from 1 year old to less than 6 years old) who have difficulty swallowing these tablets. Weight-based dosing is planned in this age category. The clinically recommended general dose is considered to be lower than the lowest daily dose of 20 mg for adult patients. Considering the above, 10 mg is selected as the dose of the study drug, since a TAK-536 10 mg tablet with the lowest strength is considered to be the most suitable as a standard among the commercial formulations.

4. Justification for the Washout Period

The elimination half-life of TAK-536 after a single administration of TAK-536 10 mg tablet is 13.1 hours. When TAK-536 10 mg was administered once under fasted conditions in a phase 1, single dose study conducted in Japan, plasma TAK-536 concentration was 9 ng/mL at 72 hours after the administration in the subject with detectable plasma TAK-536 levels for the longest duration. It was assumed in accordance with the Guideline for Bioequivalence Studies of Generic Products [9] that the plasma TAK-536 level would be below the lower limit of quantification

(<1 ng/mL) at 65.5 hours, which is equivalent to 5 times the elimination half-life (13.1 hours), after this time point (72 hours). The duration of washout period in this study will therefore be at least 6 days, in which drug is considered to be eliminated in living body.

5. Justification for the Endpoints

1) Justification for the Pharmacokinetic Endpoints

In accordance with the Guideline for Bioequivalence Studies of Generic Products [9], AUC_{48} and C_{max} of TAK-536 will be eavaluated. The plasma concentration will be evaluated until 48 hours postdose for TAK-536, the time point when their AUC_t is over 80% of their AUC_∞.

2) Justification for the Safety Examinations, Observations, and Endpoints

AEs, vital signs (sitting blood pressure, sitting pulse, and body temperature), weight, resting 12-lead ECGs, and laboratory test results (hematology, serum chemistry, and urinalysis) were set as standard endpoints used for assessing safety in clinical pharmacology studies.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

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

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

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

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

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 the study drug administration in Period 1.

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 sub-investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form prior to the initiation of any study procedures.
3. The subject is a Japanese healthy adult male.
4. The subject is aged 20 to 35 years, inclusive, at the time of informed consent.
5. The subject weighs at least 50.0 kg, and has a body mass index (BMI) between 18.5 and 25.0 kg/m^2, inclusive, at Screening.

7.1.1 Justification of Inclusion Criteria

1. to 4. These are the standard inclusion criteria used in clinical pharmacology studies.

5. In accordance with "Law Enforcement Regulation on Securing a Stable Supply of Safe Blood Products," the Ministry of Health and Welfare Ordinance No.22 (1956) [11], which recommends against collecting 400 mL blood from individuals weighing less than 50.0 kg because of its possible harmful effects on health, subjects in this study should weigh at least 50.0 kg. The acceptable BMI range is based on the diagnostic criteria for obesity proposed by the Japan Society for the Study of Obesity [12].

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 suspected hypotension with associated physical findings, such as dizziness postural, facial pallor, or cold sweats based on evaluation/physical examination at Screening, on the day before the study drug administration (Day -1) in Period 1, or up to the study drug administration on the Period 1.
2. The subject has received any study drug within 16 weeks (112 days) prior to the study drug administration in Period 1.
3. The subject has received TAK-536 or TAK-491 in a previous clinical study or as a therapeutic agent.
4. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results.

5. The subject has a known hypersensitivity to any component of the formulation of TAK-536 or any ARB.
6. The subject has a positive urine drug result for drugs of abuse (defined as any illicit drug use) at Screening.
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 2 years prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
8. The subject has taken any excluded medication, supplements, dietary products or food products during the time periods listed in Section 7.3.
9. The subject has any current or recent (within 6 months) gastrointestinal diseases that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention).
10. The subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1 of Period 1.
11. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, or serological reactions for syphilis at Screening.
12. The subject has poor peripheral venous access.
13. The subject has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of the study drug administration in Period 1.
14. The subject has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of the study drug administration in Period 1.
15. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of the study drug administration in Period 1.
16. The subject has an abnormal (clinically significant) ECG at Screening or prior to the study drug administration in Period 1.
17. The subject has abnormal laboratory values that suggest a clinically significant underlying disease, or subject with the following laboratory abnormalities at Screening or prior to the study drug administration in Period 1: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5×the upper limits of normal (ULN).
18. The subject who, in the opinion of the investigator or sub-investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

7.2.1 Justification of Exclusion Criteria

1. This was set in consideration of the subject's safety.

2.	This minimum time interval from the previous clinical study has been established to exclude the possible influence of the previous clinical study in order to ensure the safety of subjects, with reference to the General Considerations for Clinical Trials (Pharmaceutical Safety Bureau Notification No.380, April 21, 1998) [13], and Standard Intervals to be Observed between Participation in Clinical Studies [14].
3.	This criterion has been established since bias may be generated in the safety evaluation. TAK-491 has been included in this criterion since TAK-491 is a prodrug of TAK-536 and its previous use may lead to bias in the safety evaluation, as with the previous use of TAK-536.
4. to 7., 12., 18.	These criteria have been established as the standard exclusion criteria for conducting a clinical pharmacology study.
8.	This criterion has been established to exclude any influence on the laboratory test values at Screening and the safety and pharmacokinetic evaluations after study treatment.
9. to 11., 16., 17	To enroll healthy adult male subjects in accordance with the Guideline for Bioequivalence Studies of Generic Products [9].
13. to 15.	These criteria have been established in accordance with the Law Enforcement Regulation on Securing a Stable Supply of Safe Blood Products [11].

7.3 Excluded Medications, Supplements, Dietary Products

Use of the concomitant drugs (prescribed or over-the-counter [OTC] drugs) and consumption of dietary products listed in Table 7.a is prohibited until the specified period.

Table 7.a Prohibited Medications, Supplements, Dietary Products or Food Products

From 4 weeks (28 days) before the study drug administration in Period 1 to the day of discharge (Day 3) in Period 2	From 72 hours before the study drug administration to the day of discharge (Day 3) in each period
Concomitant Drugs (prescribed or OTC drugs) Vitamins, Chinese herbal medicines, dietary products containing St. John's wort, Korean ginseng, kava kava, ginkgo, or melatonin	Foods and beverages containing grapefruit (juice, pulp), Seville-type (sour) oranges, pineapple (juice, pulp), caffeine or alcohol

OTC: over-the-counter

Subjects must be instructed not to take any medications including OTC products, without first consulting with the investigator or sub-investigator.Use of prohibited concomitant drugs will be allowed when the investigator or sub-investigator deem it necessary to use any of the concomitant drugs for reasons including treatment of an AE.

7.4 Diet, Fluid, Activity Control

The investigator or sub-investigator and study collaborator should instruct subjects to follow the following requirements. Subjects will be kept under the supervision of the investigator or sub-investigator during hospitalization.

1. Foods

On the day of blood collection for laboratory tests (screening examination and follow-up examinations), the subjects must finish the last meal at least 8 hours before visiting the study site.

During hospitalization, the subjects take given meals and are not allowed to take any other food. Meal menus will be same for each period.

On the day of the study drug administration (Day 1) in each period, the subjects must fast from at least 10 hours before the study drug administration to 4 hours after the study drug administration. On the days other than the above, the subjects will be instructed to have breakfast at 9:00, lunch at 13:00 and dinner at 19:00 (approximate time). The subject can choose not to have breakfast on Day 3 (the day of discharge).

Excessive drinking and eating should be avoided during the entire study period including follow-up examinations.

2. Beverages

On the day of the study drug administration (Day 1) for both periods, the subjects should be prohibited from drinking any liquid from 1 hour before to 4 hours after the study drug administration, with the exception of water (200 mL) taken with the study drug.

3. Smoking

Smoking is not allowed during the study period.

4. Body position and exercises

Supine position is not allowed for 4 hours after the study drug administration, unless it is required for examinations. The subjects will engage in 15 minutes of light exercise a day during hospitalization.

The subjects should abstain from excessive exercise after signing of the informed consent until completion of follow-up examination in Period 2. The subjects will be instructed to lead the same kind of daily life in Period 2 as that in Period 1, and lead a regular life throughout the washout period between the study drug administrations.

5. Blood donation after study completion

Blood donation is not allowed for at least 12 weeks after the final examination of this study. The investigator or sub-investigator will instruct the subjects on the prohibition of blood donation.

6. Other

If a subject visits another medical institution during the study period, the investigator or sub-investigator should be informed of the circumstances and therapy in advance whenever

possible, and should communicate to the medical institution about the subject's participation in the study.

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 electronic case report form (eCRF) using the following categories. For screen failure subjects who will discontinue or withdraw prior to the start of the study drug administration in Period 1, refer to Section 9.1.12.

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

- Liver Function Test 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 9.1.8), 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%).

- The subject used any prohibited concomitant drugs (prescribed or OTC drugs) or foods listed in Table 7.a during the specified period when the investigator or sub-investigator deem it necessary to use any of the concomitant drugs for reasons including treatment of an AE.

3. Protocol deviation.

- The discovery after the first dose of study drug in Period 1 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.
- The subject used any prohibited concomitant drugs (prescribed or OTC drugs) or foods and the like listed in Table 7.a during the specified period.

4. Lost to follow-up. The subject did not return to the study site and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.

5. Withdrawal by subject. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
6. Study terminated by sponsor. The sponsor terminates the study.
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 sub-investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his 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 sub-investigator. In addition, efforts should be made to perform all procedures scheduled for Early Termination Visit if possible.

A subject who discontinues the study after the study drug administration in Period 1 will not be replaced with a reserve subject (see Section 9.3.1). If a subject has not received the study drug as scheduled during Period 1 owing to any reason occurring before the study drug administration, a reserve subject will be allowed to participate in the study.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications 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

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. Code name, chemical name, strength, and formulation

Code name: TAK-536

Generic name: Azilsartan (JAN)

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

Strength:

- TAK-536 tablet: Contains 10 mg of TAK-536 in 1 tablet
- TAK-536 granules: Contains 10 mg of TAK-536 in 1 g

Formulation:

- TAK-536 tablet: Pale-yellowish red film-coated tablet
- TAK-536 granules: White to nearly white granules

2. Packaging

- TAK-536 tablet: Each press through package (PTP) sheet contains 14 tablets of TAK-536. Ten sheets are packaged in a box.
- TAK-536 granules: Each aluminum strip sachet contains 1 g of TAK-536 granules containing 10 mg TAK-536. Twenty sachets are packaged in a box.

3. Labeling

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

4. Manufacturing

TAK-536 tablets are manufactured by TPC. TAK-536 granules are manufactured by [redacted].

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 its 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

Each subject will receive either TAK-536 commercial formulation (tablet) or TAK-536 pediatric formulation (granules) in each Period as described below.

1. TAK-536 commercial formulation (tablet)

The subject will orally receive one TAK-536 10 mg tablet with 200 mL water under fasted conditions in the morning (fasted for more than 10 hours after the last meal on the day before the study drug administration [Day 1]).

2. TAK-536 pediatric formulation (granules)

The subject will orally receive one sachet of TAK-536 granules containing 10 mg TAK-536 with 200 mL water under fasted conditions in the morning (fasted for more than 10 hours after the last meal on the day before the study drug administration [Day 1]).

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) 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 eCRF(s) according to Section 10.0.

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

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

8.2 Study Drug Assignment and Dispensing Procedures

The study is conducted in an open label manner.

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment according to the randomization code. Subjects will be assigned to receive a 4-digit enrollment number. This 4-digit number will be used by the study site to facilitate the prelabeling of pharmacokinetic samples and will be a subject identifier used on all PK sample collections.. It should also be contained on the pharmacokinetic transport tubes shipped to the bioanalytical

laboratory, and will be used by the laboratory to report the subject data results. This 4-digit number does not replace the 3-digit subject identification number. In case it becomes necessary to replace a subject before the study drug administration in Period 1 after randomization, the reserve subject will replace the scheduled subject and receive the study drug for the initial subject will be used.

8.3 Randomization Code Creation and Storage

The designee of the sponsor will generate the randomization code. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage, and management of the study drugs created by the sponsor, and follow the procedures for manage the sponsor-supplied drug supplies. A copy of these procedures will be provided to the investigator as well. The manual will provide instructions on ensuring appropriate receipt, handling, storage, management, and dispensation of the sponsor-supplied drug. The manual will also describe procedures for the collection of unused study drugs from the subject and their return to the sponsor, or the destruction of unused supplies.

The 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 by the investigator or sub-investigator. For each procedure, subjects are to be assessed by the same investigator, sub-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 Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

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

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, caffeine consumption, alcohol use and smoking classification of the subject.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved within 1 year prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to the eligibility criteria, stopped within 4 weeks (28 days) prior to signing of informed consent.

9.1.3 Physical Examination Procedure

Physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other.

Any Clinically Significant findings/changes on a pretreatment physical examination assessed by the investigator or sub-investigator will be recorded as an AE or a concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.7.

On a post treatment physical examination, any Clinically Significant findings/changes compared with a result of a pretreatment physical examination, as determined by the investigator or sub-investigator, will be recorded as an AE in source documentation and on the AE eCRF described in Section 10.0.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured with shoes off. The BMI is calculated using metric units with the formula provided below. Height is recorded in centimeters (cm) without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

$$BMI = \text{weight (kg)}/\text{height (m)}^2$$

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

Weight and BMI should be reported to 1 decimal place by rounding. Height in centimeters will be rounded to the nearest integer. Thus, in the above example BMI would be reported as 25.6 kg/m^2.

9.1.5 Vital Sign Procedure

Vital signs will include sitting systolic blood pressure and diastolic blood pressure (resting more than 5 minutes) (in mmHg), sitting pulse (beats per minute), and body temperature (axillary) (°C).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within an acceptable time window (see Appendix A).

9.1.6 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 signing of informed consent through the end of the study, and all medications including vitamin supplements, OTC medications, and Chinese herbal medicines, must be recorded in the eCRF. Documentation will include generic medication name, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

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

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken following a minimum 8 hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

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

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells (RBC) White blood cells (WBC) with differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes) Hemoglobin Hematocrit Platelets	ALT AST ALP GGT Total bilirubin Total protein Albumin Creatinine BUN Potassium Sodium Chloride Calcium Inorganic phosphorus Total cholesterol Fasting triglyceride Uric acid LDH Creatine kinase Fasting glucose	pH Specific gravity Qualitative tests for glucose, protein, occult blood, ketone body, bilirubin, and urobilinogen

Only for eligibility assessment:

Serum (immunology tests)	Urine (urine drug tests)
HBsAg, HCV antibody, HIV antigen/antibody, serum test for syphilis	phencyclidine, benzodiazepines, cocaine, antihypnotic agents, cannabinoids, opioids, barbiturates, and tricyclic antidepressants

Note: The investigator or sub-investigator will report the results of immunology and urine drug tests directly to subjects. The sponsor will confirm the overall test results ("Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered the study drug.

The local laboratory will perform laboratory tests for hematology, serum chemistry, and urinalysis. The results of laboratory tests will be returned to the investigator or sub-investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, ALP, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted (Refer to Section 7.5 and Section 10.2.3 for the appropriate guidance on reporting abnormal liver function tests).

The investigator will maintain a copy of the reference ranges for the laboratory used.

All clinically significant laboratory abnormalities must be recorded as an AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 ECG Procedure

A resting 12-lead ECG will be recorded. The investigator or sub-investigator (or a qualified observer at the study site) will interpret the ECG findings using one of the following categories: within normal or abnormal. In the case that the ECG findings is abnormal, the investigator or sub-investigator (or a qualified physician at the study site) will judge if it is clinically significant.

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QTc interval (corrected by the Fredericia's formula).

When 12-lead ECG measurements are scheduled at the same time as blood draws, the blood draw will take priority and 12-lead ECGs will be obtained within an acceptable time window (see Appendix A).

9.1.10 Pharmacokinetic Sample Collection

9.1.10.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (one 3-mL sample per scheduled time) for pharmacokinetic analysis of TAK-536 will be collected into Vacutainers containing ethylenediaminetetraacetic acid dipotassium salt dihydrate (EDTA) according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in a separately defined "Procedure for Handling Samples for Drug Concentration Measurement".

Blood samples for determination of TAK-536 will be collected according to Table 9.b

Table 9.b Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Dosing Day	Scheduled Time
TAK-536	Plasma	Day 1 of each period	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 hours postdose

The actual time of sample collection will be recorded on the source document and eCRF.

If the subject is prematurely terminating from the study within 48 hours after the study drug administration, the blood sample for TAK-536 will be collected at early termination.

9.1.10.2 Bioanalytical Methods

Plasma concentration of TAK-536 will be measured by high-performance liquid chromatography with tandem mass spectrometry (LC/MS/MS method) at [redacted]

9.1.11 Pharmacokinetic Parameters

The following pharmacokinetic parameters of TAK-536 will be determined from the concentration-time profile up to 48 hours after study drug administration based on

non-compartmental analysis. Scheduled sampling times will be used for the estimation of pharmacokinetic parameters in principle.

Symbol/Term	Definition
Plasma	
AUC_t	Area under the concentration-time curve from time 0 to t.
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration.
$AUMC_{last}$	Area under the first moment concentration-time curve from time 0 to time of last quantifiable concentration.
$MRT_{last,ev}$	Mean residence time after extravascular administration from time 0 to time of last quantifiable concentration, calculated as $MRT_{last}=AUMC_{last}/AUC_{last}$
C_{max}	Maximum observed concentration.
t_{max}	Time of first occurrence of C_{max}.
AUC_∞	Area under the concentration-time curve from time 0 to infinity, calculated as $AUC_\infty=AUC_{last}+C_{last}/\lambda_z$.
λ_z	Terminal disposition phase rate constant.
$t_{1/2z}$	Terminal disposition phase half-life, calculated as $\ln(2)/\lambda_z$.
CL/F	Apparent clearance after extravascular administration, calculated as Dose/AUC_∞ after single dosing.
$AUMC_\infty$	Area under the first moment concentration-time curve from time 0 to infinity, calculated as $AUMC_\infty=AUMC_{last}+lqc\times tlqc/\lambda_z+lqc/\lambda_z^2$, where tlqc is the time of last quantifiable concentration and lqc is the last quantifiable concentration.
$MRT_{\infty,ev}$	Mean residence time after extravascular administration, calculated as $AUMC_\infty/AUC_\infty$.
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration.

9.1.12 Documentation of Subjects Failure

Investigator or sub-investigator must account for all subjects who sign informed consent. If the subject discontinues the study before the study drug administration in Period 1, the investigator or sub-investigator should complete the eCRF.

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

- Death.
- AE.
- Screen Failure (failed inclusion criteria or did meet exclusion criteria) <specify reason>.
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject <specify reason>.
- Study terminated by sponsor.

- Sample size sufficient.
- Other <specify reason>.

Subject identification numbers assigned to subjects who discontinued the study before the study drug administration in Period 1 should not be reused. If the reserve subject participates in the study, the same subject identification number of the subject who discontinued the study can be used.

9.1.13 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization and are recorded on the eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation at the study site in Period 1 and Period 2. Following each administration of the study drug, appropriate mouth checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study drug supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent.

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 point(s).

9.3.1 Screening

9.3.1.1 Screening

Subjects will be screened for enrollment between 4 weeks (28 days) and 2 days (the day before admission to the study site for Period 1) before the study drug administration in Period 1, after obtaining informed consent. Subjects will be screened in accordance with the predefined inclusion and exclusion criteria described in Section 7.0.

The investigator or sub-investigator will assess each subject for eligibility for participation in the study and inform the subject of the assessment result.

Considering that some of the subjects who are found eligible during screening examinations are unable to participate in the study for any reason before the study drug administration (Day 1) in Period 1, additional subjects who are found eligible during screening examinations will stand by as reserve subjects for Period 1 only. For Period 2, only those subjects who are scheduled to receive the study drug will be admitted to the study site on the day before the study drug administration (Day -1). Subjects who drop out of the study after the study drug administration in Period 1 will not be replaced.

The subjects will undergo the examinations, observations, and assessments specified for screening (see Appendix A).

9.3.1.2 Admission (Day -1)

The subjects will be admitted to the study site on the day before the study drug administration (Day -1) in Period 1 and Period 2 and will undergo the specified examinations, observations, and assessments (see Appendix A).

9.3.2 Randomization (Day 1)

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized as described in Section 8.2. Subjects will receive the study drug of Period 1 at the study site under the supervision of the investigator or designee, as described in Section 9.2. The procedure for documenting Subject failure in Period 1 is described in Section 9.1.12.

9.3.3 Treatment Phase (Days 1 to 3)

The subjects will undergo the specified examinations, observations, and assessments in Period 1 and Period 2 (see Appendix A).

9.3.4 Day of Discharge (Day 3)

The subjects will be discharged from the study site after confirming that the subjects are in good health by the specified examinations, observations, and assessments in Period 1 and Period 2 (see Appendix A).

9.3.5 Early Termination

The reason for discontinuation must be documented in the source document and eCRF.

When a subject prematurely withdraws from the study after the study drug administration in Period 1, he will undergo the examinations, observations, and evaluations scheduled for Day 3 (day of discharge) as far as possible. The blood samples for plasma drug concentration measurement should be collected and analyzed only in the case of early termination within 48 hours after the study drug administration.

For all subjects receiving the study drug, the investigator must complete the Subject Status eCRF page.

9.3.6 Follow-up Examination (Day 6)

The subjects will undergo the specified examinations, observations, and assessments scheduled for the follow-up examination in Period 1 and Period 2 (see Appendix A).

For all subjects receiving the study drug, the investigator must complete the Subject Status eCRF page.

9.4 Blood Sampling Volume and Frequency

Total blood sampling volume for an individual subject are shown in Table 9.c.

Table 9.c Approximate Blood Volume

Sample Type	Volume/Sample	Number of Samples	Total Volume
Screening (clinical laboratory tests, immunology tests)	19 mL	1	19 mL
Clinical laboratory tests (hematology, serum chemistry)	9 mL	8	72 mL
Plasma drug concentration (TAK-536)	3 mL	32	96 mL
		Total	187 mL

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

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

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), 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 sub-investigator for any reason.

AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG 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 sub-investigator 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 values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. The first examination after the informed consent (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition after informed consent is signed, the worsening should be recorded appropriately as an AE. The investigator or sub-investigator 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. The investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a pre-existing degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), 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 sub-investigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the study drug, the worsening should be recorded as a new AE. The investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. The investigator or sub-investigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

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

Preplanned surgeries or procedures:

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

Overdose:

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

10.1.3 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure (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

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 Severity of AEs

The different categories of severity are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.5 Causality of AEs to Study Drugs

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

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug is at least a reasonable possibility, ie, the relationship 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.

10.1.6 Relationship of AEs to Study Procedures

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

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

10.1.7 Start Date

The start date of AEs will be determined in the following criteria;

AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the investigator or sub-investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed old values or findings or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment from signing of informed consent	The date that a worsening or complication of the condition was noted first by the subject and/or the investigator or sub-investigator should be recorded.
Laboratory values that showed normal in the first examination after signing of informed consent or the examination right before the start of the study drug showed abnormal in the subsequent test.	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The first examination after signing of informed consent or the examination right before the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms.	The date of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

10.1.8 End Date

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

10.1.9 Pattern of Adverse Event

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

10.1.10 Action Taken with Study Drug

The action taken with the study drug should be defined using the following categories:

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.

- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE, the AE that occurred before the study drug administration.

10.1.11 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/Not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up examination.

10.2.1.2 AE Reporting

At each study visit, the investigator or sub-investigator 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 concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and end date and time.
3. Pattern.
4. Severity.
5. Investigator's or sub-investigator's opinion of the causality between the event and administration of study drug(s) (related or not related).
6. Investigator's or sub-investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure.
7. Action taken with study drug (not applicable for the AE that occurred before the study drug administration).
8. Outcome of event.
9. Seriousness.
10. Timing of occurrence (after administration of study drug)

10.2.2 Collection and Reporting of SAEs

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

An SAE should be reported by the investigator or sub-investigator to the sponsor (see Annex) within 1 business day of the first onset or notification of the SAE, along with any relevant information. The investigator should submit the detailed SAE Form to the sponsor within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's or sub-investigator's name.
- Name of the study drug(s).
- Causality assessment.

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

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified after the study drug administration in Period 1, the event (treatment-emergent only) should be recorded as an SAE and reported as per Section 10.2.2. The investigator or sub-investigator must contact the 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 9.1.8 must also be performed.

10.3 Follow-up of SAEs

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

All SAEs should be followed up until resolution or permanent outcome of the event.

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, IRBs, and 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 the study drug/sponsor supplied drug or that would be sufficient to consider changes in the administration of the study drug/sponsor supplied drug 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 including concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Case Report Forms (Electronic)

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

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.

Corrections 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 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 following data will not be recorded directly into the eCRFs.

- Laboratory results
- Measurement results of drug concentrations

After the lock of the study database, any change of, modification of or addition to the data on eCRFs should be made by the investigator or sub-investigator with use of change and modification records of eCRFs (Data Clarification Form) provided by the sponsor.

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. 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

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

13.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: pharmacokinetic analysis set and safety analysis set. The pharmacokinetic analysis set is defined as "all subjects who received the study drug, completed the minimum protocol-specified procedures without any major protocol deviations, and were evaluable for pharmacokinetics." The safety analysis set is defined as "all subjects who received the study drug."

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Main demographics and other baseline characteristics will be summarized overall and by treatment group using the pharmacokinetic analysis set and the safety analysis set.

13.1.3 Pharmacokinetic Analysis

The following statistical analyses will be performed on the pharmacokinetic analysis set.

1. Plasma drug concentrations

For plasma concentration of TAK-536, descriptive statistics will be provided by visit for each formulation (TAK-536 commercial formulation, TAK-536 pediatric formulation). In addition, the plasma concentration-time profiles will be also provided.

For pharmacokinetic parameters except $AUMC_{last}$ and $AUMC_{\infty}$, descriptive statistics will be provided. For the ratio between each formulation (TAK-536 pediatric formulation/TAK-536 commercial formulation) for pharmacokinetic parameters AUC_{48} and C_{max}, descriptive statistics will be provided.

2. Assessment of bio-equivalence on pharmacokinetic parameters

The difference in the least square means between formulations (TAK-536 pediatric formulation - TAK-536 commercial formulation) and the two-sided 90% confidence interval (CI) will be provided using a crossover analysis of variance (ANOVA) model. The ANOVA model will include log-transformed (natural log) pharmacokinetic parameters AUC_{48} and C_{max} as dependent variable, and formulation, group, and period as independent variables. For log-transformed (natural log) pharmacokinetic parameters AUC_{last}, AUC_{∞}, $MRT_{\infty,ev}$,λ_z, and non-natural log tansformed t_{max}, same analyses will be performed.

3. Methods of data transformation and handling of missing data

Details will be described in the Statistical Analysis Plan.

4. Significance level, confidence coefficient

- Significance level: 5% (one-sided test, assessment of bio-equivalence)
  5% (two-sided test, other than assessment of bio-equivalence)
- Confidence coefficient: 90% (two-sided, assessment of bio-equivalence)
  95% (two-sided, other than assessment of bio-equivalence)

5. Interpretation of bio-equivalence assessment

The bio-equivalence of the formulations (TAK-536 commercial formulation and TAK- 536 pediatric formulation) will be evaluated according to the criteria set forth in the Guideline for Bioequivalence Studies of Generic Products [9]. The formulations will be considered bioequivalent if the 90% CIs (two-sided) of the differences in the means of the natural log-transformed AUC_{48} and C_{max} of TAK-536 between the TAK-536 commercial formulation and the TAK-536 pediatric formulation fall within the range of ln(0.80) – ln(1.25).

When the 90% CIs will not fall within the range of ln(0.80) – ln(1.25) with an add-on subject study, the formulations will be considered bioequivalent if the differences in the means of the natural log-transformed parameters AUC_{48} and C_{max} of TAK-536 between the TAK-536 commercial formulation and the TAK-536 pediatric formulation fall within the range of ln(0.90) – ln(1.11), and the results of the dissolution test meet the conditions specified in the Guideline for Bioequivalence Studies of Generic Products. However, above provision will be applicable only if a combined number of subjects in this study and an add-on subject study is 30 subjects or greater.

13.1.4 Safety Analysis

The following statistical analyses will be performed on the safety analysis set.

1. Adverse events (treatment emergent adverse events)

A treatment emergent adverse event (TEAE) is defined as an event whose date of onset occurs on or after the start of study drug.

TEAEs will be coded using the MedDRA dictionary. The frequency distribution will be provided using the system organ class and the preferred term for each treatment as follows:

- All TEAEs
- Drug-related TEAEs
- Intensity of TEAEs
- Intensity of drug-related TEAEs
- TEAEs leading to study drug discontinuation
- Serious TEAEs

2. Laboratory test results, resting 12-lead ECGs, and vital signs (sitting blood pressure, sitting pulse [beats per minute], and body temperature), weight

For continuous variables, the observed values and the changes from baseline will be summarized by treatment for each visit using descriptive statistics. Case plots for the observed values will also be provided for each treatment.

For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided for each treatment.

13.2 Interim Analysis and Criteria for Early Termination

Interim analysis will be conducted due to judgment of necessity of an add-on subject study for the bioequivalence for TAK-536 commercial formulation and TAK-536 pediatric formulation.

13.2.1 Timing of Interim Analysis

An interim analysis will be performed after the database lock for the total of 14 subjects (7 per sequence).

13.2.2 Statistical Analysis Plan for Interim Analysis

The interim analysis will be the same analysis in 13.1.3 2. The further details are described in the SAP finalized prior to the database lock for interim analysis.

13.3 Determination of Sample Size

A total of 14 subjects (7 per sequence)

In case an add-on subject study is conducted, the maximum number of subjects will be 120 (60 per sequence).

[Rationale for the sample size]

Based on the currently available results of the studies conducted to date, the residual sum of squares of pharmacokinetic parameters C_{max} and AUC_{48} in the present study was assumed to be 0.13 and 0.08, respectively. For 6 subjects per sequence (total of 12 subjects per formulation), in two one-sided t-tests [H_0: $\ln(\mu)\leq\ln(\theta_1)$, $\ln(\mu)\geq\ln(\theta_2)$; H_1: $\ln(\theta_1)<\ln(\mu)<\ln(\theta_2)$; where $\mu=\mu_t/\mu_s$, μ_t was the population mean for the pediatric formulation, μ_s was the population mean for the TAK-536 commercial formulation, $\theta_1=0.80$, and $\theta_2=1.25$] with a one-sided significance level of 5% and alternative hypothesis $\mu=0.95$, more than 90% power of simultaneous detection of the bio-equivalence for pharmacokinetic parameters C_{max} and AUC_{48}. Taking into account possible occurence of dropouts during the study and feasibility, 7 subjects per sequence (total of 14 subjects per formulation) were set.

In case bio-equivalence cannot be demonstrated with the number of subjects initially planned on account of insufficient subjects, an add-on subject study will be conducted in accordance with the Guideline for Bioequivalence Studies of Generic Products [9]. The maximum number of subjects in the add-on subject study is 120 (60 per sequence), which is determined based on study feasibility, but is not on statistical consideration. The number of subjects in the add-on subject study will be determined based on the result of the interim analysis in this study and the currently available results of the studies conducted to date.

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 the head of the study site guarantee access to source documents by the sponsor or its designee (CRO [contract research organization]) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or the 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, sub-investigator 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 sub-investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the 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 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 the IRB should be obtained.

The investigator or sub-investigator should document all protocol deviations.

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], Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and the head of the study site will 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 absence 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 form 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 the site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives the 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 incentives should not exert undue influence for participation. Payments to subjects 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 describe 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 is free to withdraw at any time without giving a reason and without prejudice to his 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 the IRB and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator or sub-investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject 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 determines he will participate in the study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-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 sub-investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects 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 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 trial database or documentation via a subject 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 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 or sub-investigator 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 register all 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 investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

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Appendix A Schedule of Study Procedures (Period 1 and Period 2)

Element	**Screening**		**Treatment (a)**				
Study Day	**Day -28 to Day -2** (Screening Visit)	**Day -1** (Admission)	**Day 1**	**Day 2**	**Day 3** (Discharge)	**Early Termination**	**Day 6 (b)** (Follow-up Examination)
Hospitalization		X	X	X	X		
Informed consent	X						
Inclusion/exclusion criteria (c)	X		X				
Demographics and medical history	X						
Medication history	X						
Physical examination (d)	X	X	X	X	X	X	X
Vital signs (e)	X		X	X	X	X	X
Weight/BMI/height (f)	X		X		X	X	X
Concomitant medications	X	X	X	X	X	X	X
Resting 12-lead ECGs (g)	X		X		X	X	X
Laboratory tests (h)	X		X	X	X	X	X
Immunology and urine drug tests	X						
Study drug administration			X				
Plasma concentrations(i)			X	X	X	X (j)	
AE assessment (k)	X	X	X	X	X	X	X

AE: Adverse event, ECG: Electrocardiogram

(a) A washout period of at least 6 days will be placed between the study drug administrations in Period 1 and Period 2.

(b) The examinations scheduled on the day before the study drug administration (Day -1) in Period 2 can be replaced with the follow-up examinations (Day 6) in Period 1, provided that they are scheduled on the same day.

(c) Inclusion/exclusion criteria will be confirmed at Screening and before the study drug administration in Period 1, but will not be confirmed on Day 1 in Period 2.

(d) Physical examination will be performed at Screening, Day -1, predose, 4, 24, 48 hours postdose and Day 6.

(e) The sitting blood pressure (resting more than 5 minutes), sitting pulse, and body temperature (axillary) will be measured at Screening, predose, 4, 24 and 48 hours postdose, and Day 6.

(f) The subjects are weighed at Screening, predose, 48 hours postdose, and Day 6. Height is measured only at screening for calculation of BMI.

(g) The resting 12-lead ECG will be measured at Screening, predose, 48 hours postdose and Day 6.

(h) Laboratory tests include hematology, serum chemistry, and urinalysis. Samples will be collected at Screening, predose, 24, 48 hours postdose and Day 6.

(i) Blood samples for PK assessments will be collected at predose (from waking-up to immediately before the study drug administration), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 hours postdose.

(j) The blood samples for plasma drug concentration measurement should be collected and analyzed only in the case of early termination within 48 hours after the study drug administration.

(k) Collection of AEs will commence from the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up examination in Period 2.

Acceptable Time Windows for Study Procedures

Safety Tests/Observations (Period 1 and Period 2)

As per the Protocol		**Acceptable Time Window**
Tests/Observation Item	**Designated Time Window**	
Physical examination	Screening	From 28 days to 2 days before the study drug administration
	Day -1	same as on the left
	Before the study drug administration	From waking-up to immediately before the study drug administration
	4 hours postdose	±30 minutes
	24 and 48 hours postdose	±120 minutes
	Follow-up examination (Day 6)	±1 day
Height	Screening	From 28 days to 2 days before the study drug administration
Weight	Screening	From 28 days to 2 days before the study drug administration
	Before the study drug administration	From waking-up to immediately before the study drug administration
	48 hours postdose	±120 minutes
	Follow-up examination (Day 6)	±1 day
Vital sign (sitting blood pressure, sitting pulse, and body temperature)	Screening	From 28 days to 2 days before the study drug administration
	Before the study drug administration	From waking-up to immediately before the study drug administration
	4 hours postdose	±30 minutes
	24 and 48 hours postdose	±120 minutes
	Follow-up examination (Day 6)	±1 day
Resting 12-lead ECGs	Screening	From 28 days to 2 days before the study drug administration
	Before the study drug administration	From waking-up to immediately before the study drug administration
	48 hours postdose	±120 minutes
	Follow-up examination (Day 6)	±1 day
Laboratory tests (Blood)	Screening	From 28 days to 2 days before the study drug administration
	Before the study drug administration	From waking-up to immediately before the study drug administration
	24 and 48 hours postdose	±120 minutes
	Follow-up examination (Day 6)	±1 day
Laboratory tests (Urine)	Screening	From 28 days to 2 days before the study drug administration
	Before the study drug administration	From waking-up to immediately before the study drug administration
	24 and 48 hours postdose	From waking-up to +120 minutes
	Follow-up examination (Day 6)	±1 day

Pharmacokinetics Test/Observations (Period 1 and Period 2)

As per the Protocol		**Acceptable Time Window**
Tests/Observation Item	**Designated Time Window**	
Plasma drug concentration	Before the study drug administration	From waking-up to immediately before the study drug administration
	0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 12 hours postdose	±5 minutes
	16, 24, and 48 hours postdose	±15 minutes

Appendix B Responsibilities of the Investigator

1. Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety, and wellbeing of human subjects.
2. When a part of the important procedures related to the study are delegated to the sub-investigator or the study collaborator, prepare the lists of procedures to be delegated and responsible personnel, submit the lists to the head of the study site in advance to get them accepted.
3. Prepare a written informed consent form, and update as appropriate.
4. Confirm the contents of the clinical study agreement.
5. Provide necessary information on the protocol, medications, and responsibilities of individual personnel to the sub-investigator and study collaborator, and provide guidance and supervision.
6. Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing, and obtain the written consent.
7. Assume responsibility for all the medical judgement related to the study.
8. Ensure in collaboration with the head of the study site that sufficient medical treatment on all clinically significant adverse events related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
9. If a subject is consulting other medical institution or other department, and the subject agrees, notify the physician of the medical institution or department of the subject's participation in the study, as well as the end and termination of the study in writing, and document such records.
10. In case of urgent report of a SAE, immediately notify the head of the study site and the sponsor in writing.
11. Prepare correct and complete eCRFs, and submit them to the sponsor with electronic signature.
12. Check and confirm the contents of eCRFs prepared by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
13. Discuss any proposal from the sponsor including update of the protocol.
14. Notify the head of the study site of the end of the study in writing.

A Randomized, Open Label, 2-Period, 2-Treatment, Cross-over Phase 1 Study to Evaluate the Bio-equivalence of Single Oral Dose of TAK-536 Pediatric Formulation and TAK-536 Commercial Formulation in Healthy Adult Male Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Statistical Approval	27-Dec-2016 05:32 UTC
[redacted]	Clinical Pharmacology Approval	27-Dec-2016 06:06 UTC
[redacted]	Clinical VP Approval	27-Dec-2016 06:36 UTC