Title: A Randomized, Open-Label, Cross-over Phase 1 Study to Evaluate the Food Effect of Single Oral Dose of TAK-536 Pediatric Formulation in Healthy Adult Male Subjects

NCT Number: NCT03434977

Protocol Approve Date: 08-Dec-2017

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Note; This document was translated into English as the language on original version was Japanese.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Open-Label, Cross-over Phase 1 Study to Evaluate the Food Effect of Single Oral Dose of TAK-536 Pediatric Formulation in Healthy Adult Male Subjects

A Phase 1 Food Effect Study of TAK-536 Pediatric Formulation

Study Identifier: Azilsartan-1005

Compound: TAK-536

Date: 08 December 2017

Version/Amendment Number: Initial Version

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceutical Company Limited	**Compound:** TAK-536
Study Identifier: Azilsartan-1005	**Phase:** 1

Protocol Title: A, Randomized, Open-Label, Crossover Phase 1 Study to Evaluate the Food Effect of Single Oral Dose of TAK-536 Pediatric Formulation in Healthy Adult Male Subjects

Trial Design:

This is an open-label, 2×2 crossover study to assess the food effect on the pharmacokinetics (PK) and safety of a single oral dose of TAK-536 10 mg granules (contains 10 mg of TAK-536 in 1 g) in Japanese healthy adult male subjects under fasted or fed condition in the morning.

Prior to study drug administration in Period 1, eligible subjects will be randomized to either Sequence A or Sequence B with 1:1 ratio. Subjects will receive TAK-536 either in the morning under fasted condition (fasted overnight for at least 10 hours prior to the study drug administration) or in the morning under fed condition (at 30 minutes after starting breakfast).

Hospitalization will be for 4 days and 3 nights. At least 6-day washout interval will be placed between the study drug administrations in Periods 1 and 2.

Sequences	Number of Subjects	Dose of TAK-536	Regimen	
			Period 1	Period 2
A	6	TAK-536 10 mg granules (TAK-536 10 mg)	Single oral dose under fasted condition	Single oral dose under fed condition
B	6	TAK-536 10 mg granules (TAK-536 10 mg)	Single oral dose under fed condition	Single oral dose under fasted condition

Trial Primary Objective:

To assess the food effect on the PK following single oral administration of TAK-536 pediatric formulation in Japanese healthy adult male subjects

Secondary Objective:

To assess the food effect on the safety of a single oral administration of TAK-536 pediatric formulation in Japanese healthy adult male subjects

Trial Subject Population: Japanese healthy adult male subjects

Planned Number of Subjects:	**Planned Number of Sites:**
12 subjects (6 for each sequence)	1 site
Dose Levels: Each subject will receive the study drug under one of the following treatment conditions in each period. 1. One sachet of TAK-536 10 mg granules (TAK-536 10 mg) will be administered orally with 200 mL of water in the morning under fasted condition (fasted overnight for at least 10 hours prior to the study drug administration). 2. One sachet of TAK-536 10 mg granules (TAK-536 10 mg) will be administered orally with 200 mL of water in the morning under fed condition (at 30 minutes after starting breakfast).	**Route of Administration:** Oral

Duration of Treatment:	**Planned Trial Duration:**
Single dose×2 periods (with at least 6-day washout interval)	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 ages 20 to 35 years inclusive at the time of informed consent.
5. The subject weighs at least 50.0 kg, and has a 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 in 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 hypersensitivity to any component of the formulation of TAK-536 or any angioteosin II receptor blockers (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 medications, 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 prior to the start of the study drug administration in Period 1) 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 the 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: ALT and/or 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

PK: Plasma concentrations and PK parameters of unchanged TAK-536 (C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{1/2z}$, MRT, λ_z, CL/F, and V_z/F).

Secondary endpoints

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

Statistical Considerations:

PK:

The following statistical analyses will be performed on the PK analysis set:

For plasma concentration of unchanged TAK-536, descriptive statistics will be provided by time point for each treatment condition (fed and fasted condition). In addition, the plasma concentration-time profiles will be provided with both conditions on the same graph.

For PK parameters, descriptive statistics will be provided by each treatment condition.

The difference in the least square means between treatment conditions (fed - fasted) 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) PK parameters other than t_{max} as dependent variable, and treatment condition, group, and period as independent variables. For non-natural log transformed t_{max}, same analyses will be performed.

Safety:

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

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

The frequency distribution will be provided for all TEAEs, drug-related TEAEs, intensity of all TEAEs, intensity of drug-related TEAEs, TEAEs leading to study drug discontinuation and serious TEAEs by treatment condition. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The frequency distribution will be provided using the system organ class and the preferred term for each treatment condition.

For continuous variables of clinical laboratory tests and other safety measurements, the observed values and the changes from baseline will be summarized by treatment condition for each time point using descriptive statistics. Case plots for the observed values will also be provided for each treatment condition. 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 condition.

Sample Size Justification:

A total of 12 subjects, with 6 subjects in each sequence were considered the sufficient sample size to evaluate the PK and safety of TAK-536. The sample size is not based on statistical consideration.

2.0 STUDY SCHEMATIC

Figure 2.a Schematic of Study Design

Element	Screening		Treatment (TAK-536 10 mg Pediatric Formulation) Period 1 and Period 2*				
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

*: There will be at least 6-day washout interval between the study drug administrations 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, provided that they are scheduled on the same day.

3.0 SCHEDULE OF STUDY PROCEDURES (PERIOD 1 AND PERIOD 2)

	Screening		Treatment (a) (Period 1 and Period 2)				
Study Day:	**Days -28 to -2 (Screening)**	**Day -1 (Admission)**	**Day 1**	**Day 2**	**Day 3 (Discharge)**	**Early Termination**	**Day 6 (b) (Follow-up)**
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 and height (f)	X		X		X		X
Concomitant medications	X	X	X	X	X	X	X
12-lead ECG (g)	X		X		X	X	X
Laboratory tests (h)	X		X	X	X	X	X
Urine drug and alcohol screen tests	X						
Immunology tests	X						
Study drug administration			X				
Plasma concentrations (i)			X	X	X	X (j)	
AE assessment (k)	X	X	X	X	X	X	X

(a) There will be at least 6-day washout interval between the study drug administrations in Periods 1 and 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) Check of the inclusion/exclusion criteria will be done at Screening and before the study drug administration in Period 1 and not be done 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 rate, and body temperature (axillary) will be measured at Screening, predose, 4, 24, 48 hours postdose and Day 6.
(f) Weight will be measured at Screening, predose, 48 hours postdose and Day 6. Height will be measured only at Screening for calculation of BMI.
(g) The 12-lead ECG will be measured at Screening, predose, 48 hours postdose and Day 6.
(h) Laboratory tests include hematology, serum chemistry, and urinalysis. Blood samples will be collected at Screening, predose, 24, 48 hours postdose and Day 6 after fasting for at least 8 hours.
(i) PK blood samples will be collected at predose (from waking-up to immediately before the study drug administration) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 hours postdose.
(j) Measured only if the subject discontinues the study within 48 hours after the study drug administration.
(k) The collection of AEs will commence from the time the subject signs the informed consent at Screening and continue until the follow-up examination in Period 2.

4.0 INTRODUCTION

4.1 Background

Hypertension develops 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 Estimates, 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 highly 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 2012 [8] recommend 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 essential 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

Clinical Pharmacokinetic Studies of Pharmaceuticals [9] specifies that the effects of food on gastrointestinal absorption should be evaluated since absorption from the gastrointestinal tract is likely to be affected by food in the case of study drugs that are administered orally. Therefore, this study was designed to evaluate the food effect on the pharmacokinetics and safety of TAK-536 after administration of the TAK-536 pediatric formulation.

This protocol has been prepared in accordance with Good Clinical Practice (GCP).

4.3 Benefit/Risk Profile

There will be no benefit to subjects in this study other than receiving physical examinations and obtaining information about their general health. Instead, patients with pediatric hypertension may benefit in the future from what can be learned in this study.

Although subjects who participate in this study will have risks of adverse events and others associated with administration of the study drug, they will be informed about possible risk with the informed consent form before participation of this study, and are free to withdraw from the study at any time without giving a reason (Section 13.2).

Clinical safety information is provided in clinical results in adults and package insert. For further information on TAK-536, please refer to the Investigator's Brochure.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study was designed based on the following hypothesis:

- No major differences between fasted and fed conditions in the pharmacokinetics (PK) and safety will be found after the single oral dose of TAK-536 pediatric formulation. No clinically significant food-effect will be found.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

To assess the food effect on the PK following single oral administration of TAK-536 pediatric formulation in Japanese healthy adult male subjects

5.2.2 Trial Secondary Objective

To assess the food effect on the safety of a single oral administration of TAK-536 pediatric formulation in Japanese healthy adult male subjects

5.3 Endpoints

5.3.1 Primary Endpoint

PK: Plasma concentrations and PK parameters of unchanged TAK-536 (C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{1/2z}$, MRT, λ_z, CL/F, and V_z/F)

5.3.2 Secondary Endpoints

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

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is an open-label, 2×2 crossover study to assess the food effect on the PK and safety of a single oral dose of TAK-536 pediatric formulation in Japanese healthy adult male subjects under fasted or fed condition in the morning.

The dosage, treatment condition, and number of subjects are shown in Table 6.a. Each subject will receive the study drug under one of the following treatment conditions in each period.

1. One sachet of TAK-536 10 mg granules (TAK-536 10 mg) will be administered orally with 200 mL of water in the morning under fasted condition (fasted overnight for at least 10 hours prior to study drug administration).
2. One sachet of TAK-536 10 mg granules (TAK-536 10 mg) will be administered orally with 200 mL of water in the morning under fed condition (at 30 minutes after starting breakfast).

Table 6.a Dosage, Treatment Condition, and Number of Subjects

Sequences	Number of Subjects	Dose of TAK-536	Regimen	
			Period 1	Period 2
A	6	TAK-536 10 mg Granules (TAK-536 10 mg)	Single oral dose under fasted condition	Single oral dose under fed condition
B	6	TAK-536 10 mg Granules (TAK-536 10 mg)	Single oral dose under fed condition	Single oral dose under fasted condition

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 and observations from the day before the study drug administration (Day -1) during their hospitalization according to the study schedule specified in Section 3.0, 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. At least 6-day washout interval 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 (refer to Section 2.0 for a schematic of the study design).

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.

6.2 Rationale for Trial Design, Dose, and Endpoints

6.2.1 Rationale of Trial Design

In accordance with Clinical Pharmacokinetic Studies of Pharmaceuticals [9], a 2-period, 2-treatment, crossover design, which allows food effect evaluation on PK and safety with minimal effect on inter-subject variation, was selected for this study.

6.2.2 Rationale for Dose

TAK-536 pediatric formulation, 1% film-coated granules, is being developed for pediatric patients younger than 6 years old who have a difficulty in swallowing tablets. Generally, maximum amount of the pediatric granule formulation which pediatric patients can take orally at one time is estimated to be 1 g, equivalent to 10 mg of TAK-536 based on 1% concentration of TAK-536. It is assumed that many patients will take 10 mg of TAK-536 at a maximum. Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies by FDA[10] recommends to investigate the food effect with an estimated maximum dose. Considering the above, 10 mg is selected as the dose of this study.

6.2.3 Rationale for 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 [11] and Clinical Pharmacokinetic Studies of Pharmaceuticals [9].

6.2.4 Rationale for Washout Period

When a single oral dose of TAK-536 10 mg was administered under fasted condition to Japanese healthy adult subjects, plasma concentration of unchanged TAK-536 was 9 ng/mL at 72 hours after the administration in the subject with the highest plasma TAK-536 level. It was assumed that the plasma unchanged TAK-536 level would be below the lower limit of quantification (<1 ng/mL) at 6 days (3 days after the time point of C_{max}) after the administration based on the half-life of TAK-536 (about 13 hours). The Japanese Guideline for Bioequivalence Studies of Generic Products [12] recommends that there should be a washout period at least 5 times longer than the apparent half-life of the investigational drug between the two treatments to be compared within subjects. Thus, the washout period in this study was set as 6 days (144 hours), which is more than 5 times longer than the apparent elimination half-life of TAK-536.

6.2.5 Rationale for Endpoints

6.2.5.1 Rationale for Pharmacokinetic Endpoints

The plasma concentration of unchanged TAK-536 will be evaluated to determine the food effect on PK after the administration of TAK-536. The plasma concentration will be evaluated until 48 hours postdose for TAK-536, the time point when its AUC_{last} is expected to be over 80% of its AUC_{∞}.

6.2.5.2 Rationale for Safety Endpoints

AEs, vital signs, resting 12-lead ECGs, weight and laboratory test results are set as standard endpoints used for assessing safety in clinical pharmacology studies.

6.2.6 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this study, the collection of blood samples for TAK-536 PK is the critical procedure since PK is set as the primary endpoint. The examination regarding safety is also the critical procedure since safety is set as the secondary endpoint. Critical procedures are listed below:

- At any postdose time point, the blood samples for TAK-536 PK need to be collected as close to the nominal time point as possible.
- The other procedures should be completed as close to the nominal time as possible, either before or after these nominal times.
- When ECG and/or vital signs measurements are scheduled at the same time as PK sampling, the blood draw will take priority and ECG and/or vital signs will be obtained within an acceptable time window (see Appendix B).
- The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor.
- Any unscheduled procedures required for the urgent evaluation of safety concerns, regardless of the content of procedures, will take precedence over all routine scheduled procedures.

6.3 Trial Beginning and End/Completion

6.3.1 Definition of Beginning of the Trial

The overall study begins when the first subject signs the trial's informed consent form.

6.3.2 Definition of End of the Trial

The overall trial ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit, discontinues from the trial or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.3.3 Definition of Trial Discontinuation

Study discontinuation due to non-safety-related reasons, such as:

- A finding (eg, PK, pharmacodynamics, efficacy, biologic targets) from the other nonclinical or clinical studies results with the study drug in the study discontinuation for non-safety related reasons.
- Data from drugs classified in the same class, or methodologies used in this study become available and results in the study being stopped for a non-safety related reason.

- Study discontinuation due to non-scientific and non-safety-related reasons, such as slow enrollment.

Study discontinuation due to safety reasons, such as:

- Early termination due to unanticipated concerns of safety to the subjects arising from the other clinical or nonclinical studies with the study drug.
- Early termination due to unanticipated concerns of safety observed in the other drugs classified in the same class.

6.3.4 Criteria for Premature Termination or Suspension of the Trial

6.3.4.1 Criteria for Premature Termination or Suspension of Trial

The study will be completed as planned unless 1 or more of the following criteria are met 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 objective or compromises subject safety.

6.3.4.2 Procedure for Premature Termination or Suspension of the Trial

In the event that the Sponsor, an institutional review board (IRB), or a regulatory authority elects to terminate or suspend the study, 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.

6.3.5 Criteria for Premature Termination or Suspension of a Site

6.3.5.1 Criteria for Premature Termination or Suspension of a Site

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.

6.3.5.2 Procedures for Premature Termination or Suspension of a Site

In the event that the Sponsor, an IRB, or a regulatory authority elects to terminate or suspend of the 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

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 ages 20 to 35 years inclusive at the time of informed consent.
5. The subject weighs at least 50.0 kg, and has a BMI between 18.5 and 25.0 kg/m^2, inclusive, at Screening.

[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 [13], 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 [14].

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 in 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 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 medications, 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 prior to the start of the study drug administration in Period 1) 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 the 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 virus 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: ALT and/or 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.

[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 "General Considerations for Clinical Trials," Pharmaceutical Safety Bureau Notification No.380 (April 21, 1998) [15], and "Standard Intervals to be Observed between Participation in Clinical Studies" [16].
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 PK evaluations after study treatment.
9. to 11., 16., 17	To enroll healthy adult male subjects in accordance with "Partial Revision of the Guideline for Bioequivalence Studies of Generic Products," Pharmaceutical and Food Safety Bureau Notification No. 0229-10 (February 29, 2012) [12].
13. to 15.	These criteria have been established in accordance with "Law Enforcement Regulation on Securing a Stable Supply of Safe Blood Products," the Ministry of Health and Welfare Ordinance No.22 (June 25, 1956) [13].

7.3 Excluded Medications, Supplements, Dietary Products

Use of excluded agents (prescribed or over-the-counter [OTC] drugs) and dietary products is listed in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary 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 deems it necessary to use any of the concomitant drugs for reasons including treatment of an AE.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

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 the same for each period.

On the day of the study drug administration (Day 1) under fasted condition 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. The subjects will be instructed to have lunch at 13:00 and dinner at 19:00 (approximate time). Under fed condition, the subjects will have breakfast at 8:30 (approximate time) and will have the study drug at 30 minutes after starting the breakfast. The subjects will have lunch at 13:00 and dinner at 19:00 (approximate time).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.

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 drink provided as a part of breakfast (under fed condition) and water (200 mL) taken with the study drug.

7.4.2 Activity

Smoking is not allowed during the study period.

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.

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.

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 Documentation of Subject Failure

The investigator or sub-investigator must account for all subjects who sign informed consent. If a subject discontinues the study before the study drug administration in Period 1, the investigator or sub-investigator should complete the electronic case report form (eCRF).

The primary reason for subject failure is to be 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>.

7.6 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories. For screen failure subjects who discontinue or withdraw prior to the start of the study drug administration in Period 1, refer to Section 7.5.

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 10.2.9.3 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 (LFT) Abnormalities
     - ALT or AST >8×ULN, or
     - ALT or AST >5×ULN and persists for more than 2 weeks, or
     - ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN or international normalized ratio (INR) >1.5, or

- ALT or AST >3×ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

3. Protocol deviation.

   - The discovery after the 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.

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.

7.7 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 7.6. 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.

7.8 Subject Replacement

A subject who discontinues the study after the study drug administration in Period 1 will not be replaced with a reserve subject. 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

8.1 Clinical Study Drug

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: Contains 10 mg of TAK-536 in 1 g

Formulation: White to nearly white granules

8.1.1 Clinical Study Drug Labeling

Each aluminum strip sachet contains 1 g of TAK-536 granules containing 10 mg TAK-536. Twelve sachets are packaged in a box.

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.

8.1.2 Clinical Study Drug Inventory and Storage

Study drug is 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. 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 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.

8.1.4 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedure for handling, storage, and management of study drug created by the Sponsor, and follow the procedure to manage the Sponsor-supplied drug supplies. The investigator will also receive the procedure from the Sponsor. The procedure will provide instructions on ensuring appropriate receipt, handling, storage, management, and dispensation of the sponsor-supplied drug. The procedure will also stipulate the methods for collection of unused study drugs from the subject and their return to the sponsor, or other disposal 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 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 Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 13.2.

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

9.1.1.1 Assignment of Subject Identification Numbers

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

9.1.1.2 Study Drug Assignment

The study is conducted in an open label manner.

Subjects will be assigned to each sequence, 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 PK samples and will be a subject identifier used on all PK sample collections. It should also be contained on the PK 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 initial subject and receive the study drug scheduled for the initial subject.

9.1.2 Inclusion and Exclusion

For the eligibility, each subject will be assessed in accordance with the inclusion and exclusion criteria described in Section 7.0.

9.1.3 Medical History/Demography

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 this study that resolved within 1 year prior to

signing of informed consent. Ongoing conditions or diseases are considered concurrent medical conditions.

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.

9.1.4 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.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

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.

9.2.2 Height and Weight

A subject should have weight and height measured with shoes off. Height is recorded in centimeters (cm) without decimal places by rounding. Weight is collected in kilograms (kg) with 1 decimal place.

9.2.3 BMI

BMI is calculated using the formula provided below.

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

BMI should be reported to 1 decimal place by rounding. The inclusion criterion for BMI will be assessed based on a rounded value.

9.2.4 Vital Signs

Vital signs will include sitting systolic blood pressure and diastolic blood pressure (resting more than 5 minutes) (mmHg), sitting pulse rate (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 B).

9.2.5 12-Lead ECG

A resting 12-lead ECG will be recorded. The investigator or sub-investigator (or a qualified physician 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 are 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 Fridericia'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 B).

9.2.6 Study Drug Administration

Each subject will receive TAK-536 pediatric formulation under one of the following treatment conditions in each period.

1. One sachet of TAK-536 10 mg granules (TAK-536 10 mg) will be administered orally with 200 mL of water in the morning under fasted condition (fasted overnight for at least 10 hours prior to study drug administration).
2. One sachet of TAK-536 10 mg granules (TAK-536 10 mg) will be administered orally with 200 mL of water in the morning under fed condition (at 30 minutes after starting breakfast).

9.2.7 AE Monitoring

AE monitoring begins after the signing of informed consent. A complete description of AE collections and procedures is provided in Section 10.2.

9.2.8 Laboratory Procedures and Assessments

All samples will be collected in accordance with the separately defined laboratory procedures. Laboratory samples will be taken following a minimum 8 hour overnight fast on the days stipulated in the study schedule (see Section 3.0).

9.2.8.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Red blood cells (RBC)	Hemoglobin
White blood cells (WBC) with differential (neutrophils, basophils, eosinophils, lymphocytes, monocytes)	Hematocrit
	Platelets

Serum Chemistry

Serum Chemistry evaluations will consist of the following standard chemistry panel:

ALT	Sodium
AST	Chloride
ALP	Calcium
GGT	Inorganic phosphorus
Total bilirubin	Total cholesterol
Total protein	Fasting triglyceride
Albumin	Uric acid
Creatinine	LDH
BUN	Creatine kinase
Potassium	Fasting glucose

Urinalysis

Urinalysis will consist of the following tests:

pH	Qualitative tests for glucose, protein, occult blood, ketone body, bilirubin, and urobilinogen
Specific gravity	

Other

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

HBsAg=hepatitis B surface antigen, HCV=hepatitis C virus, HIV=human immunodeficiency virus.
Note: The investigator or sub-investigator will inform 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 7.6 and Section 10.2.9.4 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.

9.3 PK Samples

Blood samples for PK analysis of TAK-536 will be collected according to the study schedule specified in Section 3.0. Instructions for sample processing and shipment are provided in a separately defined procedure.

9.3.1 PK Measurements

The following PK parameters of unchanged TAK-536 will be determined from the plasma concentration-time profile up to 48 hours after the study drug administration based on non-compartmental analysis. Actual sampling times, instead of scheduled sampling times, will be used in all PK computations.

The following PK parameters will be calculated from plasma concentrations of TAK-536, unless otherwise specified:

Symbol/Term	Definition
Plasma	
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity.
C_{max}	Maximum observed plasma concentration (observed value).
t_{max}	Time of first occurrence of C_{max} (observed value).
MRT	Mean residence time.
λ_z	Terminal disposition phase rate constant.
$t_{1/2z}$	Terminal disposition phase half-life.
CL/F	Apparent clearance after extravascular administration.
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration.

9.3.1.1 Plasma for PK Measurements

Blood samples (one 3-mL sample per scheduled time) for PK analysis of unchanged TAK-536 will be collected into Vacutainers containing ethylenediaminetetraacetic acid dipotassium salt dihydrate (EDTA-2K) according to the schedule specified in Table 9.a.

Table 9.a Collection of Plasma Samples for PK Analysis

Analyte	Sample Type	Dosing Day (Periods 1 and 2)	Scheduled Time
Unchanged 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 unchanged TAK-536 measurement will be collected at early termination.

9.3.2 Confinement

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 Section 3.0, and will be discharged from the study site on Day 3 after confirmation of safety by the investigator or sub-investigator.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of 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 the treatment or study participation.

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

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.

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters may be considered 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 re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. The first examination after the informed consent (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a

worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). 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 condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature. The investigator or sub-investigator should ensure that the AE term recorded captures the change from baseline in the condition (eg, "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. 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 the first administration of study drug or after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators or sub-investigators 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 a change in the severity of an AE that is not associated with a change in study drug, the event should be captured once with the maximum severity recorded.

Pre-planned surgeries or procedures:

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

Elective surgeries or procedures:

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

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. It is up to the investigator or sub-investigator to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

- 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. AEs associated with an overdose will be documented on an AE page of the eCRF according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.9.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence in a clinical investigation subject who has signed the 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. Results in 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
	Acute liver failure
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizure	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/Stevens-Johnson syndrome	
	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.

10.2 AE Procedures

10.2.1 Assigning Severity of AEs

The different categories of severity are:

Mild: An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The causality of each AE to the study drug 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 drugs and concurrent treatments, may also be responsible.

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

10.2.3 Assigning Causality of AEs to Study Procedures

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

The causality should be assessed as Related if the investigator or 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.

10.2.4 Start Date

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

10.2.5 End Date

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

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken With Study Treatment

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

10.2.8 Outcome

- Recovered/resolved – subject returned to the first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages; the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; 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 become 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 – an AE that is 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.

10.2.9 Collection and Reporting of AEs, SAEs, and Abnormal LFTs

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent until the follow-up examination.

10.2.9.2 Reporting AEs

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 an SAE 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. Nonserious AEs that begin prior to the first exposure to study drug, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

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

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Intensity.
- Investigator's or sub-investigator's opinion of the causality between the event and administration of study drug (related or not related).
- Investigator's or sub-investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure.
- Action taken with study drug.
- Outcome of event.
- Seriousness.
- Timing of occurrence (after the administration of study drug).

10.2.9.3 Reporting SAEs

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

An SAE should be reported by the investigator or sub-investigator to the Sponsor 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.

SAE Follow-Up

If the information which 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 the other written documentation and submit it to the Sponsor immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be submit to the Sponsor, if requested.

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

10.2.9.4 Reporting of Abnormal LFTs

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, the event should be recorded as an SAE and reported as per Section 10.2.9.3. 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 9.2.8 must also be performed.

10.2.10 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs and the head of the study site. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted 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 or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

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

11.1.1 Analysis Sets

In this study, two kinds of analysis sets are defined: PK analysis set and safety analysis set.

11.1.1.1 Safety Analysis Set

The safety analysis set is defined as "all subjects who received at least one dose of the study drug".

11.1.1.2 PK Analysis Set

The PK 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 PK".

11.1.2 Analysis of Demography 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.

11.1.3 PK Analysis

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

1. Plasma drug concentrations

   For plasma concentration of unchanged TAK-536, descriptive statistics will be provided by time point for each treatment condition (fed and fasted condition). In addition, the plasma concentration-time profiles will be also provided with both conditions on the same graph.

   For PK parameters, descriptive statistics will be provided by each treatment condition.

2. Assessment of food effect on PK parameters

   The difference in the least square means between treatment conditions (fed-fasted) 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) PK parameters other than t_{max} as dependent variable, and treatment condition, group, and period as independent variables. For non-natural log transformed t_{max}, same analyses will be performed.

3. Methods of data transformation and handling of missing data

   Details will be described in the SAP.

4. Significance level, confidence coefficient

   Confidence coefficient: 90% (two-sided)

11.1.4 Safety Analysis

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

11.1.4.1 AEs

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 Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The frequency distribution will be provided using the system organ class and the preferred term for each treatment condition as follows:

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

11.1.4.2 Clinical Laboratory Evaluation

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

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

11.1.4.3 Vital Signs

The observed values and the changes from baseline will be summarized by treatment condition for each time point using descriptive statistics. Case plots for the observed values will also be provided for each treatment condition.

11.1.4.4 Other Safety Parameters

For ECG parameters, the observed values and the changes from baseline will be summarized by treatment condition for each time point using descriptive statistics. Case plots for the observed values will also be provided for each treatment condition.

For 12-lead ECG interpretation, shift tables showing the number of subjects in each category at baseline and each post-baseline time point will be provided for each treatment condition.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

11.3 Determination of Sample Size

A total of 12 subjects (6 per sequence)

[Sample size justification]

A total of 12 subjects, with 6 subjects in each sequence were considered sufficient sample size to evaluate the PK and safety of TAK-536. The sample size is not based on statistical consideration.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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 study site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the Sponsor or its designee, including but not limited to the Investigator's Binder, trial 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.

12.2 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 changes 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 IRB should be obtained.

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

12.3 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 study 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], the 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 study site guarantee access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 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 (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 A.

13.1 IRB Approval

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

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

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

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and Sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date the 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.

13.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy

reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

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).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

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

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

13.4.2 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.

13.4.3 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.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the study 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.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

A separate contact information list (Protocol Annex 1) will be provided to the study site.

14.1.2 Investigator Agreement

A separate agreement will be provided to the study site.

14.1.3 Study-Related Responsibilities

A separate contact information list (Protocol Annex 1) will be provided to the study site.

14.1.4 List of Abbreviations

Term	Definition
ACE	angiotensin converting enzyme
AE	adverse event
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BMI	body mass index
CKD	chronic kidney disease
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
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent AE

15.0 DATA HANDLING AND RECORDKEEPING

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

15.1 eCRFs

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

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

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

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. Reasons for significant corrections should additionally be included.

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 into the eCRFs:

- Laboratory results
- Measurement results of drug concentrations

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or sub-investigator with use of change and modification records of the eCRFs. The investigator must review the data change for completeness and accuracy, and must e-sign.

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

15.2 Record Retention

The investigator or the head of the study site agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, 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 relevant essential 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 for 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 for the study.

In addition, the investigator and the head of the study site should retain the relevant essential documents until the receipt of a Sponsor-issued notification that states the retention is no longer required.

16.0 REFERENCES

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17.0 APPENDICES

Appendix A 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 activities related to the study are delegated to a sub-investigator or the study collaborator, prepare the lists of activities 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 other written information, 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 care for all clinically significant AEs related to the study are provided to subjects throughout and beyond the period when subjects participate in the study, upon obtaining consent from the subject.
9. If a subject consults other medical institution or other department, 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. Determine the need of emergency key code blinding of a subject in case of emergency. [For double-blined studies only.]
12. Prepare correct and complete eCRFs, and submit them to the Sponsor with electronic signature.
13. 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.
14. Discuss any proposal from the Sponsor including update of the protocol.
15. Notify the head of the study site of the end of the study in writing.

Appendix B Acceptable Time Window for Study Procedure

Acceptable time window for safety examination/test/observations (Periods 1 and 2)

As per the Protocol		Acceptable Time Window
Tests/Observation Item	**Designated Time Point**	
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 signs (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 ECG	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

As per the Protocol		Acceptable Time Window
Tests/Observation Item	**Designated Time Point**	
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

Acceptable time window for PK blood sampling (Periods 1 and 2)

As per the Protocol		Acceptable Time Window
Tests/Observation Item	**Designated Time Point**	
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

Total blood sampling volume for an individual subject is shown below.

		Number of Samples			Total Volume
Sample Type	**Volume**	**Screening**	**Period 1**	**Period 2**	**(mL)**
Clinical laboratory tests samples	16 mL at Screening/ 10 mL at other time points	1	4	4	96
PK samples for TAK-536	3 mL	0	16	16	96
			Total blood sampling volume		192

A Randomized, Open-Label, Cross-over Phase 1 Study to Evaluate the Food Effect of Single Oral Dose of TAK-536 Pediatric Formulation in Healthy Adult Male Subjects

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	06-Mar-2018 00:40 UTC