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

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

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

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

Note; This document was translated into English and the language in original document was Japanese.

STATISTICAL ANALYSIS PLAN

Final Analysis

STUDY NUMBER: Azilsartan-1004

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

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

PHASE 1

Version: 1

Date: 18 May 2017

[redacted]

Based on:

Protocol Version: Original (First Version)

Protocol Date: 22 December 2016

1.1 Approval Signatures

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

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

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

4.0 OBJECTIVES

4.1 Primary Objectives

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

4.2 Secondary Objectives

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

4.3 Additional Objectives

Not applicable in this study.

4.4 Study Design

1. Study Design

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

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

2. Sample size

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

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

3. Dose and mode of administration

The dosage and number of subjects are presented in Table 4.a. Each subject will receive either TAK-536 commercial formulation (tablet) or TAK-536 pediatric formulation (granules) in each period under the conditions described below.

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

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

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

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

Table 4.a Dosage and Number of Subjects

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

Add-on Subject Study (if conducted)

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

4. Planned number of study sites

One study site

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

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

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

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

A schematic of the study design is included as Figure 4.b. A schedule of assessments is listed in Appendix A (protocol).

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

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

Figure 4.b Schematic of Study Design (Period 1 and Period 2)

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

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

5.1.2 Secondary Endpoints

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

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

6.0 DETERMINATION OF SAMPLE SIZE

A total of 14 subjects (7 per sequence)

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

[Rationale for the sample size]

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

In case bio-equivalence cannot be demonstrated with the number of subjects initially planned on account of insufficient subjects, an add-on subject study will be conducted in accordance with the Guideline for Bioequivalence Studies of Generic Products [1]. The maximum number of subjects in the add-on subject study is 120 (60 per sequence), which is determined based on study feasibility, but is not on statistical consideration. The number of subjects in the add-on subject study will be determined based on the result of the interim analysis in this study and the currently available results of the studies conducted to date.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

- Treatment-emergent adverse event (TEAE): Adverse events that occurred after the start of the study drug administration
    * Among the TEAEs, those that occurred from the start of the study drug administration in Period 1 to before the start of the study drug administration in Period 2 are deemed as "TEAEs that occurred in Period 1" and those that occurred after the start of the study drug administration in Period 2 as "TEAEs that occurred in Period 2."
- Pretreatment event(PTE):Adverse events that occurred after obtaining the consent but before the start of the study drug administration
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV)(%): Standard deviation / Mean x 100
- QTcF interval: QT interval corrected with Fridericia's correction
- Formulations:
    - TAK-536 commercial formulation
    - TAK-536 pediatric formulation
- Treatment group:
    - a (TAK-536 pediatric formulation→TAK-536 commercial formulation)
    - b (TAK-536 commercial formulation→TAK-536 pediatric formulation)

7.1.2 Definition of Study Days

- Total Study Time in each time interval (hour): Time and date of test/observation/assessment - Time and date of start of study drug administration in each time interval (rounded to the fourth decimal place)

7.1.3 Definition of Study Visit Windows

For items of examinations, observations, and assessments described below, evaluable data (i.e., non-missing data) will be handled according to the following rules.

Evaluable data within the visit window will be used. If more than one evaluable data exist within the same visit window, the examinations, observations, and assessments with the closest Study Time to the scheduled Study Time will be used. If there are two evaluable equidistant to the scheduled Study Time, the later data will be used. The size of difference from the Study Time will be determined based on the total Study Time in each time interval (hour) .

For items from examinations, observations, and assessments other than those described below, evaluable data will be handled as data at the corresponding visit based on the visits specified in the case report form. However, among the visits specified in the case report form, if the follow-up examination in Period 1 (Day 6) and the examination on the day before the study drug administration (Day -1) in Period 2 were conducted on the same day and only the evaluable data exists from either the follow-up examination (Day 6) for Period 1 or the day before the study drug administration (Day -1) for Period 2, that data will be handled though it were obtained at both visits.

Table 7.a Visit Window

Plasma drug concentration

Visit	Scheduled Study Time	Total Study Time in each time interval (hour)
Predose	Study Time (hour): 0	-5.000 - 0.000
0.5 Hour Postdose	Study Time (hour): 0.5	0.417 - 0.583
1 Hour Postdose	Study Time (hour): 1	0.917 - 1.083
1.5 Hours Postdose	Study Time (hour): 1.5	1.417 - 1.583
2 Hours Postdose	Study Time (hour): 2	1.917 - 2.083
2.5 Hours Postdose	Study Time (hour): 2.5	2.417 - 2.583
3 Hours Postdose	Study Time (hour): 3	2.917 - 3.083
3.5 Hours Postdose	Study Time (hour): 3.5	3.417 - 3.583
4 Hours Postdose	Study Time (hour): 4	3.917 - 4.083
5 Hours Postdose	Study Time (hour): 5	4.917 - 5.083
6 Hours Postdose	Study Time (hour): 6	5.917 - 6.083
8 Hours Postdose	Study Time (hour): 8	7.917 - 8.083
12 Hours Postdose	Study Time (hour): 12	11.917 - 12.083
16 Hours Postdose	Study Time (hour): 16	15.750 - 16.250
24 Hours Postdose	Study Time (hour): 24	23.750 - 24.250
48 Hours Postdose	Study Time (hour): 48	47.750 - 48.250

7.2 Analysis Sets

- Pharmacokinetic (PK) Analysis Set: All subjects who received the study drug, completed the minimum protocol-specified procedures without any major protocol deviations, and were evaluable for pharmacokinetics
  - Any subject who meets the following criteria will be excluded from this analysis set:
    1) Deviations of protocol entry criteria
       - Deviations of inclusion criteria

         Inclusion criteria 3, 4, and 5
       - Deviations of exclusion criteria

         Exclusion criteria 2, 4, 6, 7, 8, 9, 10, 11, and 17

2) Deviations related to treatment procedure or dose

- Deviations related to dose

Deviations of dosage

Subjects who received a dose of the study drug other than the doses specified in the protocol

- Deviations of regimen

Deviations of dosing interval (number of days for washout)

Subjects who received the study drug in Period 2 without undergoing a washout period of more than 6 days after the study drug administration in Period 1

Deviations of dosing conditions

Subjects who did not orally receive a single dose of any study drug under fasted conditions in the morning (fasted for more than 10 hours before the study drug administration)

3) Deviations concerning excluded medication or therapy

- Deviations concerning concomitant medications

Administration of excluded medication

Subjects who consumed drugs (prescribed or over-the-counter drugs) described in Table 7. a "Prohibited Medications, Supplements, Dietary Products or Food Products" of the protocol's section 7.3 within the given time

4) Deviations concerning pharmacokinetic measurements

- Plasma drug concentration

No conduct/missing of examinations and assessments concerning pharmacokinetic variables

Subjects whose plasma drug concentration data of TAK-536 was missing or not used at more than 1 visit

5) Others

- Matters of subject management

Matters concerning foods and beverages

Subjects who consumed meals other than the provided meals during hospitalization

Subjects who consumed meals within 10 hours before the study drug administration

Subjects who consumed meals within 4 hours after the study drug administration

Subjects who consumed beverages other than water (200 mL) with the study drug from 1 hour before to 4 hours after the study drug administration

Subjects who consumed foods described in Table 7. a "Prohibited Medications, Supplements, Dietary Products or Food Products" of the protocol's section 7.3 within the given time

Matters concerning smoking

Subjects who smoked during hospitalization

Matters concerning body position

Subjects who took a supine position for 4 hours after the study drug administration, unless it was required for examination.

- Safety Analysis Set: All subjects who received the study drug

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variable(s):	Date First Subject Signed Informed Consent Form Date Last Subject Completed Study Drug Administration MedDRA Version SAS Version Used for Creating the Datasets
Analysis Method(s):	The following analysis will be performed for the above analysis variables. (1) Display of analysis variables

7.3.2 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s):	Randomization	[Eligible for Randomization, Not Eligible for Randomization]
	Primary Reason for Subject Not Being Eligible	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Sufficient Subject, Screening Failure, Study Termination by Sponsor, Voluntary Withdrawal, Other]
Analysis Method(s):	The following analysis will be performed for the above analysis variables. When calculating percentages for the primary reasons for subject not eligible for randomization, the total number of subjects who were not eligible for randomization will be used as the denominator. (1) Frequency distributions	

7.3.3 Disposition of Subjects

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Study Completion Status	[Completed All Planned Study Visits, Did Not Complete All Planned Study Visits]
	Reason for Discontinuation of Study Visits	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Study Termination by Sponsor, Voluntary Withdrawal, Other]
Analysis Method(s):	The following summaries will be provided by treatment group and by combining the treatment groups. When calculating percentages for the primary reasons for subject who did not complete all planned study visits, the total number of subjects who did not complete all planned study visits will be used as the denominator. (1) Frequency distributions	

7.3.4 Protocol Deviations and Analysis Sets

7.3.4.1 Protocol Deviations

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Protocol Deviations	[Deviations of Protocol Entry Criteria, Deviations Concerning Excluded Medication or Therapy, Noncompliance with Protocol, Deviations Related to Treatment Procedure or Dose, Deviations of Discontinuation Criteria, Major GCP Violations]
Analysis Method(s):	The following summaries will be provided by treatment group and by combining the treatment groups. The number of subjects with protocol deviations will be calculated and the details of deviations will be shown after classifying the contents of deviations into the above categories. A subject who has several categories will be counted once in each appropriate category. (1) Frequency distributions	

7.3.4.2 Analysis Sets

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Handling of Subjects in Analysis Sets	[Categories are based on the specifications in the List of Subject Evaluability Assignments]
	Inclusion/Exclusion of Analysis Set	
	Safety Analysis Set	[Included]
	PK Analysis Set	[Included]
Analysis Method(s):	The following summaries will be provided by treatment group for (1), and by treatment group and by combining the treatment groups for (2). For (1), a subject who has several categories will be counted once in each appropriate category. (1) Frequency distributions for handling of cases in each analysis set (2) Frequency distributions for number of cases included in each analysis set	

7.4 Demographic and Other Baseline Characteristics

Analysis Set:	Safety Analysis Set PK Analysis Set

Analysis Variable(s):	Age (years)	
	Height (cm)	
	Weight (kg) (prior to administration in Period 1)	
	BMI (kg/m^2) (prior to administration in Period 1)	
	Smoking Classification	[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]
	Alcohol Classification	[Everyday, 2 to 3 Days a Week, 2 to 3 Days a Month, Never]
	Caffeine Classification	[Yes, No]

Analysis Method(s): The following summaries will be provided by treatment group and by combining the treatment groups. In case an add-on subject study was conducted, the analysis will be performed for the study which was conducted with the originally planned number of subjects and for each add-on study.

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

7.5 Medical History and Concurrent Medical Conditions

Not applicable in this study.

7.6 Medication History and Concomitant Medications

Not applicable in this study.

7.7 Study Drug Exposure and Compliance

Not applicable in this study.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint

Not applicable in this study.

7.8.2 Secondary Efficacy Endpoint

Not applicable in this study.

7.8.3 Additional Efficacy Endpoint

Not applicable in this study.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applied in this study.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results or data determined to be non-evaluable according to this Statistical Analysis Plan will not be used for hypothesis testing and estimations.

Values below the lower limit of quantification in drug concentrations and laboratory test values will be treated as zero, and values above the upper limit of quantification in laboratory test values will be treated as the upper limit of quantification.

7.8.4.3 Multicenter Studies

Not applied in this study.

7.8.4.4 Multiple Comparison/Multiplicity

Not applied in this study.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applied in this study.

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

The bioequivalence of the formulations (TAK-536 commercial formulation and TAK- 536 pediatric formulation) will be evaluated according to the criteria set forth in the Guideline for Bioequivalence Studies of Generic Products [1]. The formulations will be considered bioequivalent if the 90% CIs (two-sided) of the differences in the means of the natural log-transformed AUC48 and Cmax of TAK-536 between the TAK-536 commercial formulation and the TAK-536 pediatric formulation fall within the range of ln(0.80) – ln(1.25).

When the 90% CIs do not fall within the range of ln(0.80) – ln(1.25) with an add-on subject study, the formulations will be considered bioequivalent if the differences in the means of the natural log-transformed parameters AUC48 and Cmax of TAK-536 between the TAK-536 commercial formulation and the TAK-536 pediatric formulation fall within the range of

ln(0.90) – ln(1.11), and the results of the dissolution test meet the conditions specified in the Guideline for Bioequivalence Studies of Generic Products. However, the above provision will be applicable only if the combined number of subjects in this study and an add-on subject study is 30 subjects or greater.

7.8.4.7 Examination of Subgroups

Not applied in this study.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma Concentrations

Analysis Set: PK Analysis Set
Analysis Variable(s): Plasma Concentrations of TAK-536
Visit: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 Hours Postdose
Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) Descriptive statistics will be provided for each formulation by visit.
(2) Mean and standard deviation will be plotted simultaneously for both formulations (vertical axis: normal scale).
(3) Mean will be plotted simultaneously for both formulations (vertical axis: common logarithmic scale).

7.9.1.2 Pharmacokinetic Parameters

Analysis Set: PK Analysis Set
Analysis Variable(s): Pharmacokinetic Parameters of TAK-536

AUC48	AUClast	Cmax
AUCinf	MRTlast,ev	tmax
Lambda z	t1/2z	CL/F
Vz/F	MRTinf,ev	

Analysis Method(s): The following analysis will be performed for the above analysis variables by formulation.

(1) Summary of Pharmacokinetic Parameters
For AUC48, AUClast, Cmax, and AUCinf, descriptive statistics, geometric mean, and CV will be provided.
For Tmax, descriptive statistics will be provided.
For all other variables, descriptive statistics and CV will be provided.

7.9.1.3 Treatment Ratio in Pharmacokinetic Parameters

Analysis Set: PK Analysis Set
Analysis Variable(s): Treatment Ratio of (TAK-536 commercial formulation/TAK-536 pediatric formulation) in AUC48 and Cmax of TAK-536
Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) Descriptive statistics will be provided for treatment ratio of pharmacokinetic parameters.

7.9.1.4 Assessment of Bioequivalence

Primary Endpoints

Analysis Set: PK Analysis Set
Analysis Variable(s): Pharmacokinetic Parameters of TAK-536
AUC48 Cmax
Analysis Method(s): The following analysis will be performed for the above analysis variables. In case an add-on subject study was conducted, the analysis will be performed for the study which was conducted with the originally planned number of subjects and for each add-on study.

(1) The difference in the least square means between formulations (TAK-536 pediatric formulation – TAK-536 commercial formulation) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variables as dependent variable, and formulation, treatment group, and period as independent variables.

Secondary Endpoints

Analysis Set: PK Analysis Set
Analysis Variable(s): Pharmacokinetic Parameters of TAK-536

AUClast	AUCinf	MRTinf,ev
Lambda z	tmax	

Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) The difference in the least square means between formulations (TAK-536 pediatric formulation - TAK-536 commercial formulation) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variables other than tmax as dependent variable, and formulation, treatment group, and period as independent variables.

(2) The difference in the least square means between formulations (TAK-536 pediatric formulation – TAK-536 commercial formulation) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include non-natural log-transformed tmax as dependent variable, and formulation, treatment group, and period as independent variables.

7.9.1.5 Individual Plasma Concentrations

Analysis Set: All Subjects Who Entered the Treatment Period
Analysis Variable(s): Plasma Concentrations of TAK-536

Visit: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 Hours Postdose

Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) Individual plasma concentrations will be plotted simultaneously for both formulations (vertical axis: normal scale).

7.9.1.6 Subject Data Listings for Pharmacokinetic Parameters

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s): Pharmacokinetic Parameters of TAK-536

AUC48	AUClast	MRTlast,ev
Cmax	tmax	AUCinf
Lambda z		

Measuring points of estimating Lambda z (start point, end point, and number of points) and adjusted R-squared contribution rate

t1/2z	CL/F	Vz/F
MRTinf,ev		

Analysis Method(s): Subject data listings including the following variables will be displayed.

(1) Subject ID, subject number, treatment group, dose, and timing

7.9.1.7 Subject Data Listings for Treatment Ratio in Pharmacokinetic Parameters

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variable(s): Treatment Ratio of (TAK-536 commercial formulation/TAK-536 pediatric formulation) in AUC48 and Cmax of TAK-536

Analysis Method(s): Subject data listings including the following variables will be displayed.

(1) Subject ID, subject number, and treatment group

7.9.2 Pharmacodynamic Analysis

Not applicable in this study.

7.10 Other Outcomes

Not applicable in this study.

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set
Analysis Variable(s): TEAE
Categories: Relationship to Study Drug [Related, Not Related]
Intensity [Mild, Moderate, Severe]
Analysis Method(s): The following analysis will be performed for the above analysis variables by formulation.

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

TEAEs will be counted according to the rules below. When calculating percentages for TEAE, the number of subjects who were treated by that formulation in the safety analysis set will be used as the denominator.

[Number of subjects with TEAEs]

- In case of "frequency distributions by relationship to study drug"
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- In case of "frequency distributions by intensity"
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- In case of distributions other than the above
  A subject with multiple occurrences of TEAE will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

7.11.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set: Safety Analysis Set
Analysis Variable(s): TEAE
Categories: Intensity [Mild, Moderate, Severe]
Analysis Method(s): The following analysis will be performed for the above analysis variables by formulation.
TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

(1) All TEAEs by SOC and PT
(2) All TEAEs by SOC
(3) All TEAEs by PT
(4) Drug-Related TEAEs by SOC and PT
(5) Intensity of All TEAEs by SOC and PT
(6) Intensity of Drug-Related TEAEs by SOC and PT
(7) TEAEs Leading to Study Drug Discontinuation by SOC and PT
(8) Serious TEAEs by SOC and PT

The method of counting events when conducting each frequency distribution will be as follows:
[Number of subjects with TEAEs]

- In case of "frequency distributions by SOC and PT, by SOC only, or PT only"
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT. Also, when calculating percentages for TEAE, the number of subjects who were treated by that formulation in the safety analysis set will be used as the denominator.
- In case of "frequency distributions by SOC and PT"
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Also, when calculating percentages for TEAE, the number of subjects who were treated by that formulation in the safety analysis set will be used as the denominator.

7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis Variable(s): PTE
Analysis Method(s): The following analysis will be performed for the above analysis variables.
PTEs will be coded using the MedDRA and will be summarized

using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) All PTEs by SOC and PT
(2) Serious PTEs by SOC and PT

The method of counting events when conducting each frequency distribution will be as follows:

[Number of subjects with PTEs]

- A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s): Hematology

RBC	WBC	Hemoglobin
Hematocrit	Platelets	
WBC Differentials (Neutrophil, Basophil, Eosinophil, Lymphocyte, and Monocyte)		

Serum Chemistry

ALT	AST	
Alkaline Phosphatase		
GGT	Total Bilirubin	Total Protein
Albumin	Creatinine	Urea Nitrogen
Potassium	Sodium	Chloride
Calcium	Iinorganic Phosphorus	Total Cholesterol
Fasting Triglycerides	Urine Acid	LDH
Creatine Kinase		Fasting Glucose

Categories: Results of determination based on reference values
[Below lower limit of reference value, Within the range of reference value, Over upper limit of reference value]

Visit: Predose, 24 and 48 Hours Postdose, Follow-up Examination (Day 6)

Analysis Method(s): The following analysis will be performed for the above analysis variables by formulation.

(1) Descriptive statistics for observed values for each visit and changes (each visit after administration-predose) will be provided.
(2) Case Plots
(3) A shift table for each visit before and after administration will be provided for the results of determination based on the

reference values.

7.11.2.2 Urinalysis

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	Specific Gravity pH Glucose Protein Blood Ketone Body Bilirubin Urobilinogen
Categories:	Results of determination based on reference values [Below lower limit of reference value, Within the range of reference value, Over upper limit of reference value]
Visit:	Predose, 24 and 48 Hours Postdose, Follow-up Examination (Day 6)
Analysis Method(s):	For specific gravity, summaries (1) to (3) will be provided by formulation. For each variable other than specific gravity, summaries (3) will be provided. (1) Descriptive statistics for observed values for each visit and changes (each visit after administration-predose) will be provided. (2) Case Plots (3) A shift table for each visit before and after administration will be provided for the results of determination based on the reference values.

7.11.3 Vital Signs and Weight

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	Body Temperature(armpit) Sitting Systolic Blood Pressure Sitting Diastolic Blood Pressure Sitting Pulse Rate Weight
Visit:	Body Temperature (armpit), Sitting Systolic Blood Pressure, Sitting Diastolic Blood Pressure, Sitting Pulse Rate: Predose, 4, 24, and 48 Hours Postdose, Follow-up Examination (Day 6) Weight: Predose, 48 Hours Postdose, Follow-up Examination (Day 6)
Analysis Method(s):	The following analysis will be performed for the above analysis variables by formulation.

(1) Descriptive statistics for observed values for each visit and changes (each visit after administration-predose) will be provided.
(2) Case Plots

7.11.4 12-Lead ECGs

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	Heart Rate	
	RR Interval	
	PR Interval	
	QRS Interval	
	QT Interval	
	QTcF Interval	
	12-Lead ECG Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Visit:	Predose, 48 Hours Postdose, Follow-up Examination (Day 6)	
Analysis Method(s):	For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by formulation.	
	For 12-lead ECG, summaries (3) will be provided by formulation.	
	(1) Descriptive statistics for observed values for each visit and changes (each visit after administration-predose) will be provided.	
	(2) Case Plots	
	(3) A shift table for each visit before and after administration will be provided.	

7.11.5 Other Observations Related to Safety

Not applicable in this study.

7.12 Interim Analysis

An interim analysis will be conducted due an add-on subject study for the bioequivalence for TAK-536 commercial formulation and TAK-536 pediatric formulation.

7.13 Changes in the Statistical Analysis Plan

The analysis plan described in this Statistical Analysis Plan is the same as the analysis plan described in the protocol.

8.0 REFERENCES

1. Partial Revision of the Guideline for Bioequivalence Studies of Generic Products, Pharmaceutical and Food Safety Bureau Notification No. 0229-10 (February 29, 2012).

STATISTICAL ANALYSIS PLAN

Interim Analysis

STUDY NUMBER: Azilsartan-1004

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

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

PHASE 1

Version: 1

Date: 18 May 2017

[redacted]

Based on:

Protocol Version: Original (First Version)

Protocol Date: 22 December 2016

1.1 Approval Signatures

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

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.0 TABLE OF CONTENTS

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LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

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

4.0 OBJECTIVES

4.1 Primary Objectives

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

4.2 Secondary Objectives

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

4.3 Additional Objectives

Not applicable in this study.

4.4 Study Design

1. Study Design

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

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

2. Sample size

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

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

3. Dose and mode of administration

The dosage and number of subjects are presented in Table 4.a. Each subject will receive either TAK-536 commercial formulation (tablet) or TAK-536 pediatric formulation (granules) in each period under the conditions described below.

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

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

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

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

Table 4.a Dosage and Number of Subjects

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

Add-on Subject Study (if conducted)

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

4. Planned number of study sites

One study site

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

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

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

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

A schematic of the study design is included as Figure 4.b. A schedule of assessments is listed in Appendix A (protocol).

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

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

Figure 4.b Schematic of Study Design (Period 1 and Period 2)

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

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

5.1.2 Secondary Endpoints

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

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

6.0 DETERMINATION OF SAMPLE SIZE

A total of 14 subjects (7 per sequence)

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

[Rationale for the sample size]

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

In case bio-equivalence cannot be demonstrated with the number of subjects initially planned on account of insufficient subjects, an add-on subject study will be conducted in accordance with the Guideline for Bioequivalence Studies of Generic Products [1]. The maximum number of subjects in the add-on subject study is 120 (60 per sequence), which is determined based on study feasibility, but is not on statistical consideration. The number of subjects in the add-on subject study will be determined based on the result of the interim analysis in this study and the currently available results of the studies conducted to date.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV)(%): Standard deviation / Mean x 100
- Formulations:
  - TAK-536 commercial formulation
  - TAK-536 pediatric formulation
- Treatment group:
  - a (TAK-536 pediatric formulation→TAK-536 commercial formulation)
  - b (TAK-536 commercial formulation→TAK-536 pediatric formulation)

7.1.2 Definition of Study Days

- Total Study Time in each time interval (hour): Time and date of test/observation/assessment - Time and date of start of study drug administration in each time interval (rounded to the fourth decimal place)

7.1.3 Definition of Study Visit Windows

For items of examinations, observations, and assessments described below, evaluable data (i.e., non-missing data) will be handled according to the following rules.

Evaluable data within the visit window will be used. If more than one evaluable data exist within the same visit window, the examinations, observations, and assessments with the closest Study Time to the scheduled Study Time will be used. If there are two evaluable equidistant to the scheduled Study Time, the later data will be used. The size of difference from the Study Time will be determined based on the total Study Time in each time interval (hour).

For items from examinations, observations, and assessments other than those described below, evaluable data will be handled as data at the corresponding visit based on the visits specified in the case report form. However, among the visits specified in the case report form, if the follow-up examination in Period 1 (Day 6) and the examination on the day before the study drug administration (Day -1) in Period 2 were conducted on the same day and only the evaluable data exists from either the follow-up examination (Day 6) for Period 1 or the day before the study drug administration (Day -1) for Period 2, that data will be handled though it were obtained at both visits.

Table 7.a Visit Window

Plasma drug concentration

Visit	Scheduled Study Time	Total Study Time in each time interval (hour)
Predose	Study Time (hour): 0	-5.000 - 0.000
0.5 Hour Postdose	Study Time (hour): 0.5	0.417 - 0.583
1 Hour Postdose	Study Time (hour): 1	0.917 - 1.083
1.5 Hours Postdose	Study Time (hour): 1.5	1.417 - 1.583
2 Hours Postdose	Study Time (hour): 2	1.917 - 2.083
2.5 Hours Postdose	Study Time (hour): 2.5	2.417 - 2.583
3 Hours Postdose	Study Time (hour): 3	2.917 - 3.083
3.5 Hours Postdose	Study Time (hour): 3.5	3.417 - 3.583
4 Hours Postdose	Study Time (hour): 4	3.917 - 4.083
5 Hours Postdose	Study Time (hour): 5	4.917 - 5.083
6 Hours Postdose	Study Time (hour): 6	5.917 - 6.083
8 Hours Postdose	Study Time (hour): 8	7.917 - 8.083
12 Hours Postdose	Study Time (hour): 12	11.917 - 12.083
16 Hours Postdose	Study Time (hour): 16	15.750 - 16.250
24 Hours Postdose	Study Time (hour): 24	23.750 - 24.250
48 Hours Postdose	Study Time (hour): 48	47.750 - 48.250

7.2 Analysis Sets

- Pharmacokinetic (PK) Analysis Set: All subjects who received the study drug, completed the minimum protocol-specified procedures without any major protocol deviations, and were evaluable for pharmacokinetics
  - Any subject who meets the following criteria will be excluded from this analysis set:
    1) Deviations of protocol entry criteria
       - Deviations of inclusion criteria

         Inclusion criteria 3, 4, and 5
       - Deviations of exclusion criteria

         Exclusion criteria 2, 4, 6, 7, 8, 9, 10, 11, and 17
    2) Deviations related to treatment procedure or dose
       - Deviations related to dose

         Deviations of dosage

         Subjects who received a dose of the study drug other than the doses specified in the protocol
       - Deviations of regimen

         Deviations of dosing interval (number of days for washout)

Subjects who received the study drug in Period 2 without undergoing a washout period of more than 6 days after the study drug administration in Period 1

Deviations of dosing conditions

Subjects who did not orally receive a single dose of any study drug under fasted conditions in the morning (fasted for more than 10 hours before the study drug administration)

3) Deviations concerning excluded medication or therapy

- Deviations concerning concomitant medications

Administration of excluded medication

Subjects who consumed drugs (prescribed or over-the-counter drugs) described in Table 7. a "Prohibited Medications, Supplements, Dietary Products or Food Products" of the protocol's section 7.3 within the given time

4) Deviations concerning pharmacokinetic measurements

- Plasma drug concentration

No conduct/missing of examinations and assessments concerning pharmacokinetic variables

Subjects whose plasma drug concentration data of TAK-536 was missing or not used at more than 1 visit

5) Others

- Matters of subject management

Matters concerning foods and beverages

Subjects who consumed meals other than the provided meals during hospitalization

Subjects who consumed meals within 10 hours before the study drug administration

Subjects who consumed meals within 4 hours after the study drug administration

Subjects who consumed beverages other than water (200 mL) with the study drug from 1 hour before to 4 hours after the study drug administration

Subjects who consumed foods described in Table 7. a "Prohibited Medications, Supplements, Dietary Products or Food Products" of the protocol's section 7.3 within the given time

Matters concerning smoking

Subjects who smoked during hospitalization

Matters concerning body position

Subjects who took a supine position for 4 hours after the study drug administration, unless it was required for examination.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variable(s):	Date First Subject Signed Informed Consent Form Date Last Subject Completed Study Drug Administration MedDRA Version SAS Version Used for Creating the Datasets
Analysis Method(s):	The following analysis will be performed for the above analysis variables. (1) Display of analysis variables

7.3.2 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s):	Randomization	[Eligible for Randomization, Not Eligible for Randomization]
	Primary Reason for Subject Not Being Eligible	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Sufficient Subject, Screening Failure, Study Termination by Sponsor, Voluntary Withdrawal, Other]
Analysis Method(s):	The following analysis will be performed for the above analysis variables. When calculating percentages for the primary reasons for subject not eligible for randomization, the total number of subjects who were not eligible for randomization will be used as the denominator. (1) Frequency distributions	

7.3.3 Disposition of Subjects

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Study Completion Status	[Completed All Planned Study Visits, Did Not Complete All Planned Study Visits]
	Reason for Discontinuation of Study Visits	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Study Termination by Sponsor, Voluntary Withdrawal, Other]
Analysis Method(s):	The following summaries will be provided by treatment group and by combining the treatment groups. When calculating percentages for the primary reasons for subject who did not complete all planned study visits, the total number of subjects who did not complete all planned study visits will be used as the denominator. (1) Frequency distributions	

7.3.4 Protocol Deviations and Analysis Sets

7.3.4.1 Protocol Deviations

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Protocol Deviations	[Deviations of Protocol Entry Criteria, Deviations Concerning Excluded Medication or Therapy, Noncompliance with Protocol, Deviations Related to Treatment Procedure or Dose, Deviations of Discontinuation Criteria, Major GCP Violations]
Analysis Method(s):	The following summaries will be provided by treatment group and by combining the treatment groups. The number of subjects with protocol deviations will be calculated and the details of deviations will be shown after classifying the contents of deviations into the above categories. A subject who has several categories will be counted once in each appropriate category. (1) Frequency distributions	

7.3.4.2 Analysis Sets

Analysis Set:	All Subjects Who Were Eligible for Randomization	
Analysis Variable(s):	Handling of Subjects in Analysis Sets	[Categories are based on the specifications in the List of Subject Evaluability Assignments]
	Inclusion/Exclusion of Analysis Set	
	PK Analysis Set	[Included]
Analysis Method(s):	The following summaries will be provided by treatment group for (1), and by treatment group and by combining the treatment groups for (2). For (1), a subject who has several categories will be counted once in each appropriate category. (1) Frequency distributions for handling of cases in each analysis set (2) Frequency distributions for number of cases included in each analysis set	

7.4 Demographic and Other Baseline Characteristics

Analysis Set:	PK Analysis Set
Analysis Variable(s):	Age (years) Height (cm) Weight (kg) (prior to administration in Period 1)

	BMI (kg/m^2) (prior to administration in Period 1)	
	Smoking Classification	[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]
	Alcohol Classification	[Everyday, 2 to 3 Days a Week, 2 to 3 Days a Month, Never]
	Caffeine Classification	[Yes, No]
Analysis Method(s):	The following summaries will be provided by treatment group and by combining the treatment groups. (1) Frequency distributions for categorical variables and descriptive statistics for continuous variables	

7.5 Medical History and Concurrent Medical Conditions

Not applicable in this study.

7.6 Medication History and Concomitant Medications

Not applicable in this study.

7.7 Study Drug Exposure and Compliance

Not applicable in this study.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint

Not applicable in this study.

7.8.2 Secondary Efficacy Endpoint

Not applicable in this study.

7.8.3 Additional Efficacy Endpoint

Not applicable in this study.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applied in this study.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results or data determined to be non-evaluable according to this Statistical Analysis Plan will not be used for hypothesis testing and estimations.

Values below the lower limit of quantification in drug concentrations and laboratory test values will be treated as zero, and values above the upper limit of quantification in laboratory test values will be treated as the upper limit of quantification.

7.8.4.3 Multicenter Studies

Not applied in this study.

7.8.4.4 Multiple Comparison/Multiplicity

Not applied in this study.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applied in this study.

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

The bioequivalence of the formulations (TAK-536 commercial formulation and TAK- 536 pediatric formulation) will be evaluated according to the criteria set forth in the Guideline for Bioequivalence Studies of Generic Products [1]. The formulations will be considered bioequivalent if the 90% CIs (two-sided) of the differences in the means of the natural log-transformed AUC48 and Cmax of TAK-536 between the TAK-536 commercial formulation and the TAK-536 pediatric formulation fall within the range of ln(0.80) – ln(1.25).

When the 90% CIs do not fall within the range of ln(0.80) – ln(1.25) with an add-on subject study, the formulations will be considered bioequivalent if the differences in the means of the natural log-transformed parameters AUC48 and Cmax of TAK-536 between the TAK-536 commercial formulation and the TAK-536 pediatric formulation fall within the range of ln(0.90) – ln(1.11), and the results of the dissolution test meet the conditions specified in the Guideline for Bioequivalence Studies of Generic Products. However, the above provision will be applicable only if the combined number of subjects in this study and an add-on subject study is 30 subjects or greater.

7.8.4.7 Examination of Subgroups

Not applied in this study.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma Concentrations

Analysis Set: PK Analysis Set
Analysis Variable(s): Plasma Concentrations of TAK-536
Visit: Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 Hours Postdose
Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) Descriptive statistics will be provided for each formulation by visit.
(2) Mean and standard deviation will be plotted simultaneously for both formulations (vertical axis: normal scale).
(3) Mean will be plotted simultaneously for both formulations (vertical axis: common logarithmic scale).

7.9.1.2 Pharmacokinetic Parameters

Analysis Set: PK Analysis Set
Analysis Variable(s): Pharmacokinetic Parameters of TAK-536

AUC48	AUClast	Cmax
AUCinf	MRTlast,ev	tmax
Lambda z	t1/2z	CL/F
Vz/F	MRTinf,ev	

Analysis Method(s): The following analysis will be performed for the above analysis variables by regimen.

(1) Summary of Pharmacokinetic Parameters
For AUC48, AUClast, Cmax, and AUCinf, descriptive statistics, geometric mean, and CV will be provided.
For Tmax, descriptive statistics will be provided.
For all other variables, descriptive statistics and CV will be provided.

7.9.1.3 Treatment Ratio in Pharmacokinetic Parameters

Analysis Set: PK Analysis Set
Analysis Variable(s): Treatment Ratio of (TAK-536 commercial formulation/TAK-536 pediatric formulation) in AUC48 and Cmax of TAK-536
Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) Descriptive statistics will be provided for treatment ratio of pharmacokinetic parameters.

7.9.1.4 Assessment of Bioequivalence

Primary Endpoints

Analysis Set: PK Analysis Set
Analysis Variable(s): Pharmacokinetic Parameters of TAK-536
AUC48 Cmax
Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) The difference in the least square means between formulations (TAK-536 pediatric formulation – TAK-536 commercial formulation) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variables as dependent variable, and formulation, treatment group, and period as independent variables.

Secondary Endpoints

Analysis Set: PK Analysis Set
Analysis Variable(s): Pharmacokinetic Parameters of TAK-536
AUClast AUCinf MRTinf,ev
Lambda z tmax
Analysis Method(s): The following analysis will be performed for the above analysis variables.

(1) The difference in the least square means between formulations (TAK-536 pediatric formulation - TAK-536 commercial formulation) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variables other than tmax as dependent variable, and formulation, treatment group, and period as independent variables.

(2) The difference in the least square means between formulations (TAK-536 pediatric formulation – TAK-536 commercial formulation) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include non-natural log-transformed tmax as dependent variable, and formulation, treatment group, and period as independent variables.

7.9.1.5 Individual Plasma Concentrations

Not applicable at the time of interim analysis.

7.9.1.6 Subject Data Listings for Pharmacokinetic Parameters

Not applicable at the time of interim analysis.

7.9.1.7 Subject Data Listings for Treatment Ratio in Pharmacokinetic Parameters

Not applicable at the time of interim analysis.

7.9.2 Pharmacodynamic Analysis

Not applicable in this study.

7.10 Other Outcomes

Not applicable in this study.

7.11 Safety Analysis

Not applicable at the time of interim analysis.

7.12 Interim Analysis

An interim analysis will be conducted due an add-on subject study for the bioequivalence for TAK-536 commercial formulation and TAK-536 pediatric formulation.

7.13 Changes in the Statistical Analysis Plan

The analysis plan described in this Statistical Analysis Plan is the same as the analysis plan described in the protocol.

8.0 REFERENCES

1. Partial Revision of the Guideline for Bioequivalence Studies of Generic Products, Pharmaceutical and Food Safety Bureau Notification No. 0229-10 (February 29, 2012).