Title: A Phase 1, Randomized, Open-Label, Crossover Study to Evaluate the Bioequivalence of Single Oral Dose of TAK-438ASA tablet and Single Oral Dose of TAK-438 tablet plus Aspirin Enteric-Coated tablet (Study 1) and the Food Effect of Single Oral Dose of TAK-438ASA tablet (Study 2) in Healthy Adult Male Subjects

NCT Number: NCT03456960

Statistical Approve Date: 25-July-2018

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

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

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

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

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438ASA-1001

A Phase 1, Randomized, Open-Label, Crossover Study to Evaluate the Bioequivalence of Single Oral Dose of TAK-438ASA tablet and Single Oral Dose of TAK-438 tablet plus Aspirin Enteric-Coated tablet (Study 1) and the Food Effect of Single Oral Dose of TAK-438ASA tablet (Study 2) in Healthy Adult Male Subjects

[Study 1 (Pivotal)]

PHASE 1

Version: 1

Date: 25 July 2018

Prepared by:

PPD

Based on:

Protocol Version: Amendment 1

Protocol Date: 9 February 2018

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

ALP	alkaline phosphatse
ALT	alanine aminotransferase
AST	asparate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
GGT	gamma-glutamyl transferase
MedDRA	Medical Dictionary for Regulatory Activities
SOC	System Organ Class
TAK-438F	freebase of TAK-438
TEAE	treatment-emergent adverse event
PT	Preferred Term
PTE	pretreatment event

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the study is to evaluate the bioequivalence of a single-dose TAK-438ASA tablet to concomitant administration of a single-dose TAK-438 tablet 10 mg and aspirin enteric-coated tablet 100 mg in healthy Japanese adult male subjects.

4.2 Secondary Objectives

Not applicable for Study 1.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This study comprises a bioequivalence study (Study 1) and food effect study (Study 2).

Each of these studies includes Periods 1 and 2 in which subjects are scheduled for a confinement period of 4 days and 3 nights, with a washout period of at least 14 days between the study drug administrations in Periods 1 and 2.

Study 1: Bioequivalence study

This study is an open-label 2×2 crossover study to investigate the bioequivalence of TAK-438ASA tablet with concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet in a fasted (without breakfast) condition.

The pivotal study will consist of the pilot studies with the same design (inclusion/exclusion criteria, dose levels and conditions, and schedules). The pivotal study will be implemented in a total of 120 subjects per sequence. The bioequivalence was verified only for TAK-438F in the pilot study, the pivotal study will be implemented for testing the bioequivalence of only the unchanged aspirin for which bioequivalence has not been verified. If bioequivalence is not verified in the pivotal study, implementation of an add-on subject study will be considered.

The planned dose levels and dosing schedules of TAK-438ASA to be evaluated are outlined in Table 4.a.

Table 4.a Dose Levels and Dosing Schedules

Study 1: Bioequivalence study

Pivotal Study

Sequence	Number of Subjects	Period 1	Period 2
a	120	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg)	One TAK-438 tablet 10 mg + One aspirin enteric-coated tablet 100 mg
b	120	One TAK-438 tablet 10 mg + One aspirin enteric-coated tablet 100 mg	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg)
Dosing Condition		Fasted (without breakfast) condition	

Element	Screening	Period 1					Period 2			
Study Day	-28 to -2	-1	1	2	3		15	16	17	18
Visit/ Confinement	Visit	Confinement					Confinement			
Procedure	Informed consent Screening tests	Check-in/Examinations	Examinations/Randomization Administration of study drug for Period 1	Examinations	Examinations/Discharge	Washout	Check-in/Examinations	Administration of study drug for Period 2/Examinations	Examinations	Examinations/Discharge

Figure 4.a Schematic of the Study Design (with 14-day Washout Period)

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoint of the study is:

PK (plasma concentration)

- AUClast and Cmax of Unchanged Aspirin.

5.2 Secondary Endpoints

Secondary endpoints include:

PK (Plasma Concentration)

- AUCinf, tmax, MRTinf,ev and Lambda z of Unchanged Aspirin.

5.3 Safety Endpoints

Safety endpoints will be assessed through the following parameters:

Treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, weight, and 12-lead electrocardiogram (ECG).

6.0 DETERMINATION OF SAMPLE SIZE

Planned number of subjects is 120 per sequence (total of 240 subjects) in the pivotal study. Statistical basis for the sample size is presented below.

Assuming a root mean square error of 0.45 for PK parameters and a dropout rate of 10% based on the results of the pilot study, the power of two one-sided t-tests to verify the bioequivalence [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 is the mean for TAK-438ASA tablet, μ_s is the mean for the concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet, $\theta_1=0.80$, and $\theta_2=1.25$] at a one-sided significance level of 5% and $\mu=1.10$ would be 90% with a sample size of 120 subjects per sequence (total of 240 subjects).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

- TEAE: An adverse event whose date of onset occurs on or after the start of administration of the study drug
- PTE: Any untoward medical occurrence in a clinical investigation subject who has signed the informed consent to participate in a study but prior to administration of the study drug
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV) (%): Standard deviation / mean × 100
- Study Medication:
  - Fixed Dose Combination: TAK-438ASA Tablet
  - Free Combination: Concomitant Administration of TAK-438 Tablet and Aspirin Enteric-Coated Tablet
- Sequence:
  - Sequence a: Fixed Dose Combination -> Free Combination
  - Sequence b: Free Combination -> Fixed Dose Combination

7.2 Analysis Sets

- Safety analysis set: All subjects who received at least one dose of study drug.
- Pharmacokinetic analysis set: All subjects who received at least one dose of study drug, who had no major protocol deviation listed below, and whose pharmacokinetic data are evaluable, who were able to evaluate of pharmacokinetics.
  - Entry Criteria
    - Inclusion Criterion 4, Exclusion Criteria 1, 4, 7, 8, 9, 10, and 18
  - Concomitant Medication
    - Subjects who used of excluded agents (prescription or nonprescription) or dietary products is outlined in Table 7.a “Excluded Medications, Supplements, and Dietary Products” in Protocol 7.3 section within the designated period
  - Procedure Not Performed Per Protocol
    - Subjects who took food other than served meals during confinement

  - Subjects who took food from more than 10 hours before the study drug administration until 4 hours after the study drug administration
  - Subjects who drank some liquid other than those at the time of breakfast or the water (150 mL) which took the study drug from 1 hour before the study drug administration until 4 hours after the study drug administration
  - Subjects who smoked from 28 days before the start of study drug administration (Day 1) during Period 1 and throughout the study period
  - Subjects who remained in a supine position at times other than those necessary for various types of examinations until 4 hours after the study drug administration
- Study Medication
  - Subjects who violated the administration condition described in Protocol 9.2.6 section
  - Subjects who took the study drug Period 2 without a washout period of not less than 14 days after the study drug administration during Period 1
- Missing Pharmacokinetic Endpoint
  - Subjects who are missing at least 1 point in all data for plasma drug concentrations (Plasma drug concentrations: unchanged aspirin)

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: Date First Subject Signed Informed Consent Form
Date of Last Subject's Last Visit/Contact
MedDRA Version
SAS Version Used for Creating the Datasets

Analytical Methods: (1) Study Information
Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set: All Subjects Who Were Not Randomized

Analysis Variables: Age (years)
Gender [Male, Female]

Analytical Methods: (1) Screen Failures
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: Eligibility Status [Yes, No]
Primary Reason for Subject Not Being Eligible [Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Sample Size Sufficient, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Methods: (1) Eligibility for Randomization
Frequency distributions will be provided. When calculating the percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Disposition of Subjects

Analysis Set:	Randomized Set	
Analysis Variables:	Study Completion Status	[Completed Study, Prematurely Discontinued Study]
	Reason for Discontinuation of Study	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Methods: (1) Disposition of Subjects

Frequency distributions will be provided by sequence and overall. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued study will be used as the denominator.

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Analysis Set:	Randomized Set	
Analysis Variables:	Protocol Deviations	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Methods: (1) Protocol Deviations

Frequency distribution will be provided by sequence and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.5.2 Analysis Sets

Analysis Set:	Randomized Set	
Analysis Variables:	Reason for Excluded from Analysis Sets	[Categories are based on the specifications in the List of Subject Evaluability Assignments]

Analysis Sets
Safety Analysis Set [Included]
Pharmacokinetic Analysis Set [Included]

Analytical Methods: (1) Subjects Excluded from Analysis Sets
(2) Analysis Sets
Frequency distributions will be provided by sequence for (1) and by sequence and overall for (2). For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Sets: Safety Analysis Set
Pharmacokinetic Analysis Set

Analysis Variables: Age (years)
Height (cm)
Weight (kg) (Period 1 Day -1)
Body Mass Index (kg/m^2)
(Period 1 Day -1)
Consumption of Caffeine [Yes, No]
Consumption of Alcohol [Daily, A Few Times Per Week, A Few Times Per Month, No]
Smoking Classification [Never, Current, Former]

Analytical Methods: (1) Summary of Demographics and Other Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by sequence and overall.

7.5 Medical History and Concurrent Medical Conditions

Not applicable.

7.6 Medication History and Concomitant Medications

Not applicable.

7.7 Study Drug Exposure and Compliance

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Number of Times the Study Drug was Taken	[Once, Twice]
Analytical Methods:	(1) Study Drug Exposure and Compliance Frequency distributions will be provided by sequence.	

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint

Not applicable.

7.8.2 Secondary Efficacy Endpoint

Not applicable.

7.8.3 Additional Efficacy Endpoint

Not applicable.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

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

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

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

For the pivotal study in Study 1, the study drugs will be assessed for bioequivalence according to Partial Revision of the Guideline for Bioequivalence Studies of Generic Products, PFSB Notification No. 0229-10 issued on 29 February 2012. If the following criteria is satisfied, TAK-438ASA tablet and the concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet will be concluded to be bioequivalent.

- For both AUClast and Cmax of unchanged aspirin, the two-sided 90% CI of the difference in the means of log-transformed (natural log) parameter between the study medications is between 0.8 and 1.25, inclusive.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma Concentrations

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Plasma Concentrations of Unchanged Aspirin

Visit: Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, and 12 hours

Analytical Methods: The following summaries will be provided.

(1) Summary of Plasma Concentrations by Visit for Each Study Medication

(2) Mean and Standard Deviation Plot of Plasma Concentrations for Each Study Medication (Vertical Axis: Normal Scale)

(3) Mean Plot of Plasma Concentrations for Each Study Medication (Vertical Axis: Common Logarithmic Scale)

7.9.1.2 Pharmacokinetic Parameters

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Pharmacokinetic Parameters of Unchanged Aspirin

AUClast	Cmax	AUCinf
AUC12	tmax	CL/F
Vz/F	t1/2z	Lambda z
MRTinf,ev	MRTlast,ev	

AUClast and Cmax Ratios (TAK-438ASA tablet / concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet)

Analytical Methods: The following summaries will be provided.

(1) Summary of Pharmacokinetic Parameters

For AUClast, Cmax, AUCinf, and AUC12, descriptive statistics, geometric mean, and CV will be provided by study medication.

For tmax, descriptive statistics will be provided by study medication.

For study medication ratio (AUClast and Cmax), descriptive statistics will be provided.

For each variable other than AUClast, Cmax, AUCinf, AUC12, tmax, and study medication ratio (AUClast and Cmax),

descriptive statistics and CV will be provided by study medication.

7.9.1.3 Assessment of Bioequivalence

Primary Endpoints

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Pharmacokinetic Parameters of Unchanged Aspirin

AUClast Cmax

Analytical Methods: The following summaries will be provided.

(1) ANOVA for PK Parameters

The difference in the least square means between study medications (TAK-438ASA tablet – concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include a log-transformed (natural log) analysis variable as the dependent variable, and study medication, sequence, and period as independent variables.

(2) ANOVA for PK Parameters

For reference, the difference in the least square means between study medications (TAK-438ASA tablet − concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include an untransformed analysis variable as the dependent variable, and study medication, sequence, and period as independent variables.

Secondary Endpoints

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Pharmacokinetic Parameters of Unchanged Aspirin

AUCinf tmax MRTinf,ev

Lambda z

Analytical Methods: The following summaries will be provided.

(1) ANOVA for PK Parameters
The difference in the least square means between study medications (TAK-438ASA tablet − concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include a log-transformed (natural log) analysis variable as the dependent variable, and study medication, sequence, and period as independent variables.

(2) ANOVA for PK Parameters
The difference in the least square means between study medications (TAK-438ASA tablet − concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include an untransformed analysis variable as the dependent variable, and study medication, sequence, and period as independent variables.

7.9.1.4 Individual Plasma Concentrations

Analysis Set:	All Subjects Who Entered the Treatment Period
Analysis Variables:	Plasma Concentrations of Unchanged Aspirin
Visit:	Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, and 12 hours
Analytical Methods:	The following case plots will be provided. (1) Individual Plasma Concentrations for Each Study Medication (Vertical Axis: Normal Scale)

7.10 Other Outcomes

Not applicable.

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 Variables:	TEAE	
Categories:	Relationship to Study Drug	[Related, Not Related]
	Intensity	[Mild, Moderate, Severe]

Analytical Methods: The following summaries will be provided by study medication.

(1) Overview of Treatment-Emergent Adverse Events
   1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   2) Relationship of Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
   3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
   5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   6) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
   7) Serious Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
   8) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below. Percentages for each study medication will be based on the number of subjects who were treated by that study medication in the safety analysis set.

[Number of subjects]

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (i.e.,

Related and Not Related) will be counted once in the Related category.

- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3), and 6)
  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 Variables:	TEAE
Categories:	Intensity [Mild, Moderate, Severe]
Analytical Methods:	The following summaries will be provided using frequency distribution by study medication.

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) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(2) Treatment-Emergent Adverse Events by System Organ Class
(3) Treatment-Emergent Adverse Events by Preferred Term
(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(7) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(8) Treatment-Emergent Adverse Events of Special Interest by

System Organ Class

The frequency distribution will be provided according to the rules below.

[Number of subjects]

- Summary tables other than (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages for each study medication will be based on the number of subjects who were treated by that study medication in the safety analysis set.
- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAEs within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages for each study medication will be based on the number of subjects who were treated by that study medication in the safety analysis set.

7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: PTE

Analytical Methods: The following summaries will be provided using frequency distribution.

PTEs 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.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

[Number of subjects]

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE 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 Variables: Hematology

Erythrocytes	Leukocytes	
White Blood Cell Fractions (Neutrophils/Leukocytes, Eosinophils/Leukocytes, Basophils/Leukocytes, Monocytes/Leukocytes, Lymphocytes/Leukocytes)		
Hemoglobin	Hematocrit	Platelets

Serum Chemistry

ALT	Albumin	ALP
AST	Bilirubin	Protein
Creatinine	BUN	Creatine Kinase
GGT	Potassium	Sodium
Glucose	Chloride	

Visit: Predose, 48 hours

Analytical Methods: The following summaries will be provided by study medication.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Laboratory Test Results
Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.
For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

7.11.2.2 Urinalysis

Analysis Set: Safety Analysis Set

Analysis Variables: Specific Gravity
pH

Protein
Glucose

Visit: Predose, 48 hours

Analytical Methods: For specific gravity, summaries (1) to (3) will be provided by study medication. For each variable other than specific gravity, summaries (3) will be provided by study medication.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Urine Laboratory Test Results
Plots over time for each subject will be presented.

(3) Summary of Shifts of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.
For each urine laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

7.11.3 Vital Signs and Weight

Analysis Set: Safety Analysis Set

Analysis Variables: Temperature
Respiratory Rate
Systolic Blood Pressure
Diastolic Blood Pressure
Pulse Rate
Weight

Visit: Variables other than Weight
Predose, 2, 24, and 48 hours
Weight
Predose, 48 hours

Analytical Methods: The following summaries will be provided by study medication.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Vital Signs Parameters and Weight

7.11.4 12-Lead ECGs

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Heart Rate	
	RR Interval	
	PR Interval	
	QT Interval	
	QRS Interval	
	QTcF Interval	
	12-Lead ECG Interpretation	[Within Normal Limits, Abnormal, Not Clinically Significant, Abnormal, Clinically Significant]
Visit:	Predose, 2 and 48 hours	

Analytical Methods: For each variable other than 12-lead resting ECG interpretations, summaries (1) and (2) will be provided by study medication. For 12-lead resting ECG interpretation, summary (3) will be provided by study medication.

(1) Summary of ECG Parameters and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of ECG Parameters

Plots over time for each subject will be presented.

(3) Summary of Shift of 12-lead ECG Interpretation

Shift table showing the number of subjects in each category at Predose and each postdose visit will be provided.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

None.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438ASA-1001

A Phase 1, Randomized, Open-Label, Crossover Study to Evaluate the Bioequivalence of Single Oral Dose of TAK-438ASA tablet and Single Oral Dose of TAK-438 tablet plus Aspirin Enteric-Coated tablet (Study 1) and the Food Effect of Single Oral Dose of TAK-438ASA tablet (Study 2) in Healthy Adult Male Subjects

[Study 1 (Pilot) and Study 2]

PHASE 1

Version: 1

Date: 06 February 2018

Prepared by:

PPD

Based on:

Protocol Version: Initial

Protocol Date: 9 January 2018

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

ALP	alkaline phosphatse
ALT	alanine aminotransferase
AST	asparate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
GGT	gamma-glutamyl transferase
MedDRA	Medical Dictionary for Regulatory Activities
SOC	System Organ Class
TAK-438F	freebase of TAK-438
TEAE	treatment-emergent adverse event
PT	Preferred Term
PTE	pretreatment event

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the study is to evaluate the bioequivalence of a single-dose TAK-438ASA tablet to concomitant administration of a single-dose TAK-438 tablet 10 mg and aspirin enteric-coated tablet 100 mg in healthy Japanese adult male subjects (Study 1).

4.2 Secondary Objectives

The secondary objective of the study is to evaluate the food effect on PK following administration of TAK-438ASA tablet (Study 2).

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This study comprises a bioequivalence study (Study 1) and food effect study (Study 2).

Each of these studies includes Periods 1 and 2 in which subjects are scheduled for a confinement period of 4 days and 3 nights, with a washout period of at least 14 days between the study drug administrations in Periods 1 and 2.

Study 1: Bioequivalence study

This study is an open-label 2×2 crossover study to investigate the bioequivalence of TAK-438ASA tablet with concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet in a fasted (without breakfast) condition.

The study will consist of pilot and pivotal studies with the same design (inclusion/exclusion criteria, dose levels and conditions, and schedules). The pilot study will be implemented in a total of 12 subjects per sequence to provide a basis for sample size calculation to verify the bioequivalence in the pivotal study. The pivotal study will be implemented in a maximum of 202 subjects per sequence. If bioequivalence is verified for TAK-438 free base (TAK-438F) and unchanged aspirin in the pilot study, the pivotal study will not be implemented. If bioequivalence is verified only for TAK-438F or unchanged aspirin in the pilot study, the pivotal study will be implemented for testing the bioequivalence of only the compound for which bioequivalence has not been verified. If bioequivalence is not verified in the pivotal study, implementation of an add-on subject study will be considered. Any evidence from the pilot study suggesting difficulties in bioequivalence testing in the pivotal study may lead to the pivotal study not being implemented.

Study 2: Food effect study

This study will be an open-label 2×2 crossover food effect study for TAK-438ASA tablet.

The planned dose levels and dosing schedules of TAK-438ASA to be evaluated are outlined in Table 4.a.

Table 4.a Dose Levels and Dosing Schedules

Study 1: Bioequivalence study

Pilot study

Sequence	Number of Subjects	Period 1	Period 2
a	12	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg)	One TAK-438 tablet 10 mg + One aspirin enteric-coated tablet 100 mg
b	12	One TAK-438 tablet 10 mg + One aspirin enteric-coated tablet 100 mg	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg)
Dosing Condition		Fasted (without breakfast) condition	

Pivotal Study

Sequence	Number of Subjects*	Period 1	Period 2
a	Maximum of 202	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg)	One TAK-438 tablet 10 mg + One aspirin enteric-coated tablet 100 mg
b	Maximum of 202	One TAK-438 tablet 10 mg + One aspirin enteric-coated tablet 100 mg	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg)
Dosing Condition		Fasted (without breakfast) condition	

*Number of subjects required for the pivotal study is to be calculated based on the results from pilot study.

Study 2: Food effect study

Sequence	Number of Subjects	Period 1	Period 2
c	6	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg) taken in a fasted (without breakfast) condition	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg) taken in a fed (30 minutes after starting breakfast) condition
d	6	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg) taken in a fed (30 minutes after starting breakfast) condition	One TAK-438ASA tablet (a fixed dose combination containing TAK-438 10 mg and aspirin 100 mg) taken in a fasted (without breakfast) condition

Element	Screening	Period 1					Period 2			
Study Day	-28 to -2	-1	1	2	3		15	16	17	18
Visit/ Confinement	Visit	Confinement					Confinement			
Procedure	Informed consent Screening tests	Check-in/Examinations	Examinations/Randomization Administration of study drug for Period 1	Examinations	Examinations/Discharge	Washout	Check-in/Examinations	Administration of study drug for Period 2/Examinations	Examinations	Examinations/Discharge

Figure 4.a Schematic of the Study Design (Studies 1 and 2, with 14-day Washout Period)

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoint of the study is:

Study 1:

PK (plasma concentration)

- AUClast and Cmax of TAK-438F.
- AUClast and Cmax of Unchanged Aspirin.

5.2 Secondary Endpoints

Secondary endpoints include:

Study 1:

PK (Plasma Concentration)

- AUCinf, tmax, MRTinf,ev and Lambda z of TAK-438F.
- AUCinf, tmax, MRTinf,ev and Lambda z of Unchanged Aspirin.

Study 2:

PK (Plasma Concentration)

- AUCinf, AUCt, AUClast, Cmax, tmax and t1/2z of TAK-438F and its Metabolites (M-I, M-II, M-III and M-IV-Sul).
- AUCinf, AUCt, AUClast, Cmax, tmax and t1/2z of Unchanged Aspirin and its Metabolite (Salicylic Acid).

PK (Urine Concentration)

- Aet, fe,t and CLR of TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul).
- Aet, fe,t and CLR of Unchanged Aspirin and its Metabolites (Salicylic Acid and Salicyluric Acid).

5.3 Safety Endpoints

Safety endpoints will be assessed through the following parameters:

Treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, weight, and 12-lead electrocardiogram (ECG).

6.0 DETERMINATION OF SAMPLE SIZE

Study 1:

Planned number of subjects is 12 per sequence (total of 24 subjects) in the pilot study, and a maximum of 202 per sequence (total of 404 subjects) in the pivotal study. Statistical basis for the sample size is presented below.

Assuming a root mean square error of 0.20 for PK parameters in the pilot study, the power of two one-sided t-tests to verify the bioequivalence [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 is the mean for TAK-438ASA tablet, μ_s is the mean for the concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet, $\theta_1=0.80$, and $\theta_2=1.25$] at a one-sided significance level of 5% and $\mu=0.95$ to 1.05 would be 89% to 96% with a sample size of 12 subjects per sequence (total of 24 subjects).

In the case that the pivotal study will be implemented, the number of subjects will be recalculated based on the results from the pilot study. Assuming a maximal root mean square error of 0.57 for PK parameters in the pivotal study, which is based on the results from preceding studies of TAK-438 and the bioequivalence study of another combination tablet using the same aspirin enteric-coated tablet (AG-1749ASA/CPH-001), two one-sided t-tests with a one-sided significance level of 5% and $\mu=0.90$ to 1.10 would need a maximum of 202 subjects per sequence (total of 404 subjects) to provide 90% power to verify the bioequivalence.

Study 2:

Planned number of subjects is 6 per sequence (total of 12 subjects) to evaluate the PK and safety of TAK-438ASA. This sample size has not been determined by statistical considerations.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

- TEAE: An adverse event whose date of onset occurs on or after the start of administration of the study drug
- PTE: Any untoward medical occurrence in a clinical investigation subject who has signed the informed consent to participate in a study but prior to administration of the study drug
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV) (%): Standard deviation / mean × 100
- Study Medication:
  - Fixed Dose Combination: TAK-438ASA Tablet
  - Free Combination: Concomitant Administration of TAK-438 Tablet and Aspirin Enteric-Coated Tablet
- Dosing Condition:
  - Fasted: TAK-438ASA Tablet Taken in a Fasted (Without Breakfast) Condition
  - Fed: TAK-438ASA Tablet Taken in a Fed (30 Minutes After Starting Breakfast) Condition
- Sequence:
  - Sequence a: Fixed Dose Combination -> Free Combination
  - Sequence b: Free Combination -> Fixed Dose Combination
  - Sequence c: Fasted Condition -> Fed Condition
  - Sequence d: Fed Condition -> Fasted Condition
- AUCt:
  - AUC48: TAK-438F in Study 1, TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul) in Study 2
  - AUC12: Unchanged Aspirin in Study 1
  - AUC24: Unchanged Aspirin and its Metabolite (Salicylic Acid) in Study 2
- fe,t (Study 2 only):
  - fe,48: TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul) and TAK-438F+M-1+M-II+M-III+M-IV-Sul

- fe,24: Unchanged Aspirin and its Metabolites (Salicylic Acid and Salicyluric Acid), and Unchanged Aspirin + Salicylic Acid + Salicyluric Acid

- Aet (Study 2 only):
  - Ae48: TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul)
  - Ae24: Unchanged Aspirin and its Metabolites (Salicylic Acid and Salicyluric Acid)

7.2 Analysis Sets

- Safety analysis set: All subjects who received at least one dose of study drug.
- Pharmacokinetic analysis set: All subjects who received at least one dose of study drug, who had no major protocol deviation listed below, and whose pharmacokinetic data are evaluable, who were able to evaluate of pharmacokinetics.
  - Entry Criteria
    - Inclusion Criterion 4, Exclusion Criteria 1, 4, 7, 8, 9, 10, and 18
  - Concomitant Medication
    - Subjects who used of excluded agents (prescription or nonprescription) or dietary products is outlined in Table 7.a “Excluded Medications, Supplements, and Dietary Products” in Protocol 7.3 section within the designated period
  - Procedure Not Performed Per Protocol
    - Subjects who took food other than served meals during confinement
    - Study 1 only: Subjects who took food from more than 10 hours before the study drug administration until 4 hours after the study drug administration
    - Study 2 only: Subjects who took food from more than 10 hours before the study drug administration until 4 hours after the study drug administration under the fasted condition without breakfast or subjects who took food during the 4 hours after the study drug administration under the fed condition with breakfast
    - Subjects who drank some liquid other than those at the time of breakfast or the water (150 mL) which took the study drug from 1 hour before the study drug administration until 4 hours after the study drug administration
    - Subjects who smoked from 28 days before the start of study drug administration (Day 1) during Period 1 and throughout the study period
    - Subjects who remained in a supine position at times other than those necessary for various types of examinations until 4 hours after the study drug administration

- Study Medication
  - Subjects who violated the administration condition described in Protocol 9.2.6 section
  - Subjects who took the study drug Period 2 without a washout period of not less than 14 days after the study drug administration during Period 1
- Missing Pharmacokinetic Endpoint
  - Subjects who are missing at least 1 point in all data for plasma drug concentrations (Plasma drug concentrations: TAK-438F and unchanged aspirin in Study 1, TAK-438F and its metabolites [M-I, M-II, M-III, and M-IV-Sul], unchanged aspirin and its metabolite [salicylic acid] in Study 2)

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variables:	Date First Subject Signed Informed Consent Form Date of Last Subject's Last Visit/Contact MedDRA Version SAS Version Used for Creating the Datasets
Analytical Methods:	(1) Study Information Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:	All Subjects Who Were Not Randomized
Analysis Variables:	Age (years) Gender [Male, Female]
Analytical Methods:	(1) Screen Failures Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variables:	Eligibility Status [Yes, No] Primary Reason for Subject Not Being Eligible [Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Sample Size Sufficient, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]
Analytical Methods:	(1) Eligibility for Randomization Frequency distributions will be provided. When calculating the percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Disposition of Subjects

Analysis Set:	Randomized Set	
Analysis Variables:	Study Completion Status	[Completed Study, Prematurely Discontinued Study]
	Reason for Discontinuation of Study	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Methods: (1) Disposition of Subjects

Frequency distributions will be provided by sequence and overall for each study. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued study will be used as the denominator.

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Analysis Set:	Randomized Set	
Analysis Variables:	Protocol Deviations	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Methods: (1) Protocol Deviations

Frequency distribution will be provided by sequence and overall in each study for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.5.2 Analysis Sets

Analysis Set:	Randomized Set	
Analysis Variables:	Reason for Excluded from Analysis Sets	[Categories are based on the specifications in the List of Subject Evaluability Assignments]

	Analysis Sets	
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]
Analytical Methods:	(1) Subjects Excluded from Analysis Sets	
	(2) Analysis Sets	

Frequency distributions will be provided by sequence for (1) and by sequence and overall for (2) in each study. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Sets:	Safety Analysis Set	
	Pharmacokinetic Analysis Set	
Analysis Variables:	Age (years)	
	Height (cm)	
	Weight (kg) (Period 1 Day -1)	
	Body Mass Index (kg/m^2) (Period 1 Day -1)	
	Consumption of Caffeine	[Yes, No]
	Consumption of Alcohol	[Daily, A Few Times Per Week, A Few Times Per Month, No]
	Smoking Classification	[Never, Current, Former]
Analytical Methods:	(1) Summary of Demographics and Other Baseline Characteristics	

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by sequence and overall for each study.

7.5 Medical History and Concurrent Medical Conditions

Not applicable.

7.6 Medication History and Concomitant Medications

Not applicable.

7.7 Study Drug Exposure and Compliance

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Number of Times the Study Drug was Taken	[Once, Twice]
Analytical Methods:	(1) Study Drug Exposure and Compliance Frequency distributions will be provided by sequence for each study.	

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint

Not applicable.

7.8.2 Secondary Efficacy Endpoint

Not applicable.

7.8.3 Additional Efficacy Endpoint

Not applicable.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

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

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

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

In Study 1, the study drugs will be assessed for bioequivalence according to Partial Revision of the Guideline for Bioequivalence Studies of Generic Products, PFSB Notification No. 0229-10 issued on 29 February 2012. If any of the following criteria is satisfied, TAK-438ASA tablet and the concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet will be concluded to be bioequivalent.

- For both AUClast and Cmax of TAK-438F and unchanged aspirin, the two-sided 90% CI of the difference in the means of log-transformed (natural log) parameter between the study medications is between 0.8 and 1.25, inclusive.
- For both AUClast and Cmax of TAK-438F and unchanged aspirin, the difference in the means of log-transformed (natural log) parameter between the study medications is between 0.90 and 1.11, inclusive. Furthermore, the results of the elution test satisfy the requirements specified in Partial Revision of the Guideline for Bioequivalence Studies of Generic Products.

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis (Pilot BE Study)

7.9.1.1 Plasma Concentrations

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Plasma Concentrations of TAK-438F and Unchanged Aspirin

Visit: TAK-438F

Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours

Unchanged Aspirin

Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, and 12 hours

Analytical Methods: For Study 1, the following summaries will be provided.

(1) Summary of Plasma Concentrations by Visit for Each Study Medication

(2) Mean and Standard Deviation Plot of Plasma Concentrations for Each Study Medication (Vertical Axis: Normal Scale)

(3) Mean Plot of Plasma Concentrations for Each Study Medication (Vertical Axis: Common Logarithmic Scale)

7.9.1.2 Pharmacokinetic Parameters

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Pharmacokinetic Parameters of TAK-438F and Unchanged Aspirin

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

AUClast and Cmax Ratios (TAK-438ASA tablet / concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet)

Analytical Methods: For Study 1, the following summaries will be provided.

(1) Summary of Pharmacokinetic Parameters

For AUClast, Cmax, AUCinf, and AUCt, descriptive statistics, geometric mean, and CV will be provided by study medication.

For tmax, descriptive statistics will be provided by study medication.

For study medication ratio (AUClast and Cmax), descriptive

statistics will be provided.
For each variable other than AUClast, Cmax, AUCinf, AUCt, tmax, and study medication ratio (AUClast and Cmax), descriptive statistics and CV will be provided by study medication.

7.9.1.3 Assessment of Bioequivalence

Primary Endpoints

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Pharmacokinetic Parameters of TAK-438F and Unchanged Aspirin
AUClast Cmax

Analytical Methods: For Study 1, the following summaries will be provided.

(1) ANOVA for PK Parameters
The difference in the least square means between study medications (TAK-438ASA tablet – concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include a log-transformed (natural log) analysis variable as the dependent variable, and study medication, sequence, and period as independent variables.

(2) ANOVA for PK Parameters
For reference, the difference in the least square means between study medications (TAK-438ASA tablet − concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include an untransformed analysis variable as the dependent variable, and study medication, sequence, and period as independent variables.

Secondary Endpoints

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Pharmacokinetic Parameters of TAK-438F and Unchanged Aspirin

	AUCinf	tmax	MRTinf,ev
	Lambda z		

Analytical Methods: For Study 1, the following summaries will be provided.

(1) ANOVA for PK Parameters
The difference in the least square means between study medications (TAK-438ASA tablet − concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include a log-transformed (natural log) analysis variable as the dependent variable, and study medication, sequence, and period as independent variables.

(2) ANOVA for PK Parameters
The difference in the least square means between study medications (TAK-438ASA tablet − concomitant administration of TAK-438 tablet and aspirin enteric-coated tablet) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include an untransformed analysis variable as the dependent variable, and study medication, sequence, and period as independent variables.

7.9.1.4 Individual Plasma Concentrations

Analysis Set: All Subjects Who Entered the Treatment Period

Analysis Variables: Plasma Concentrations of TAK-438F and Unchanged Aspirin

Visit: TAK-438F
Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours
Unchanged Aspirin
Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, and 12 hours

Analytical Methods: For Study 1, the following case plots will be provided.

(1) Individual Plasma Concentrations for Each Study Medication (Vertical Axis: Normal Scale)

7.9.2 Pharmacokinetic Analysis (Food Effect Study)

7.9.2.1 Plasma Concentrations

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Plasma Concentrations of TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul), Unchanged Aspirin and its Metabolite (Salicylic Acid)

Visit: TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul)
Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours
Unchanged Aspirin and its Metabolite (Salicylic Acid)
Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, and 24 hours

Analytical Methods: For Study 2, the following summaries will be provided.

(1) Summary of Plasma Concentrations by Visit for Each Dosing Condition
(2) Mean and Standard Deviation Plot of Plasma Concentration for Each Dosing Condition (Vertical Axis: Normal Scale)
(3) Mean Plot of Plasma Concentration for Each Dosing Condition (Vertical Axis: Common Logarithmic Scale)

7.9.2.2 Pharmacokinetic Parameters

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Pharmacokinetic Parameters of TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul), Unchanged Aspirin and its Metabolite (Salicylic Acid)

AUCinf	AUCt	AUClast
Cmax	tmax	CL/F (TAK-438F, Unchanged Aspirin only)
Vz/F (TAK-438F, Unchanged Aspirin only)	t1/2z	Lambda z
MRTinf,ev	MRTlast,ev	

Analytical Methods: For Study 2, the following summaries will be provided by dosing condition.

(1) Summary of Pharmacokinetic Parameters
For AUCinf, AUCt, AUClast, and Cmax, descriptive statistics,

geometric mean, and CV will be provided.
For tmax, descriptive statistics will be provided.
For each variable other than AUCinf, AUCt, AUClast, Cmax and tmax, descriptive statistics and CV will be provided.

7.9.2.3 Assessment of Food Effect

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Pharmacokinetic Parameters of TAK-438F, Unchanged Aspirin and its Metabolite (Salicylic Acid)

AUCinf AUCt AUClast
Cmax

Analytical Methods: For Study 2, the following summaries will be provided.

(1) ANOVA for PK Parameters
The difference in the least square means between dosing condition (TAK-438ASA tablet taken in a fed (30 minutes after starting breakfast) − TAK-438ASA tablet taken in a fasted (without breakfast) condition) and the two-sided 90% confidence interval will be provided using a crossover ANOVA model. The ANOVA model will include a log-transformed (natural log) analysis variable as the dependent variable, and dosing condition, sequence, and period as independent variables.

7.9.2.4 Urinary Excretion Ratio

Cumulative Urinary Excretion Ratio

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variables: Aet, fe,t, and CLR of TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul), and fe,t of TAK-438F+M-1+M-II+M-III+M-IV-Sul
Aet, fe,t, and CLR of Unchanged Aspirin and its Metabolites (Salicylic Acid and Salicyluric Acid), and fe,t of Unchanged Aspirin + Salicylic Acid + Salicyluric Acid

Analytical Methods: For Study 2, the following summaries will be provided by dosing condition.

(1) Descriptive Statistics and CV of Cumulative Urinary Excretion

Ratio by Visit

7.9.2.5 Individual Plasma Concentrations

Analysis Set:	All Subjects Who Entered the Treatment Period
Analysis Variables:	Plasma Concentrations of TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul), Unchanged Aspirin and its Metabolite (Salicylic Acid)
Visit:	TAK-438F and its Metabolites (M-I, M-II, M-III, and M-IV-Sul) Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours Unchanged Aspirin and its Metabolite (Salicylic Acid) Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 16, and 24 hours
Analytical Methods:	For Study 2, the following summaries will be provided. (1) Individual Plasma Concentrations for Each Dosing Condition (Vertical Axis: Normal Scale)

7.10 Other Outcomes

Not applicable.

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 Variables:	TEAE	
Categories:	Relationship to Study Drug	[Related, Not Related]
	Intensity	[Mild, Moderate, Severe]

Analytical Methods: The following summaries will be provided by study medication for Study 1 and by dosing condition for Study 2.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
7) Serious Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below. Percentages for each study medication will be based on the number of subjects who were treated by that study medication in the safety analysis set in Study 1. Percentages for each dosing condition will be based on the number of subjects who were treated by that dosing condition in the

safety analysis set in Study 2.

[Number of subjects]

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3), and 6)
  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 Variables:	TEAE
Categories:	Intensity [Mild, Moderate, Severe]
Analytical Methods:	The following summaries will be provided using frequency distribution by study medication for Study 1 and by dosing condition for Study 2.

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) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(2) Treatment-Emergent Adverse Events by System Organ Class
(3) Treatment-Emergent Adverse Events by Preferred Term
(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(7) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(8) Treatment-Emergent Adverse Events of Special Interest by System Organ Class

The frequency distribution will be provided according to the rules below.

[Number of subjects]

- Summary tables other than (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages for each study medication will be based on the number of subjects who were treated by that study medication in the safety analysis set in Study 1. Percentages for each dosing condition will be based on the number of subjects who were treated by that dosing condition in the safety analysis set in Study 2.

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAEs within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages for each study medication will be based on the number of subjects who were treated by that study medication in the safety analysis set in Study 1. Percentages for each dosing condition will be based on the number of subjects who were treated by that dosing condition in the safety analysis set in Study 2.

7.11.1.3 Displays of Pretreatment Events

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variables:	PTE
Analytical Methods:	The following summaries will be provided using frequency distribution. PTEs 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.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

[Number of subjects]

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE 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 Variables: Hematology

Erythrocytes	Leukocytes	
White Blood Cell Fractions (Neutrophils/Leukocytes, Eosinophils/Leukocytes, Basophils/Leukocytes, Monocytes/Leukocytes, Lymphocytes/Leukocytes)		
Hemoglobin	Hematocrit	Platelets

Serum Chemistry

ALT	Albumin	ALP
AST	Bilirubin	Protein
Creatinine	BUN	Creatine Kinase
GGT	Potassium	Sodium
Glucose	Chloride	

Visit: Predose, 48 hours

Analytical Methods: The following summaries will be provided by study medication for Study 1 and by dosing condition for Study 2.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Laboratory Test Results

Plots over time for each subject will be presented.

(3) Summary of Shifts of Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.
For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

7.11.2.2 Urinalysis

Analysis Set: Safety Analysis Set

Analysis Variables: Specific Gravity
pH
Protein
Glucose

Visit: Predose, 48 hours

Analytical Methods: For specific gravity, summaries (1) to (3) will be provided by study medication for Study 1 and by dosing condition for Study 2. For each variable other than specific gravity, summaries (3) will be provided by study medication for Study 1 and by dosing condition for Study 2.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of Urine Laboratory Test Results
Plots over time for each subject will be presented.

(3) Summary of Shifts of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.
For each urine laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range. The shift tables will be based on these classifications.

7.11.3 Vital Signs and Weight

Analysis Set: Safety Analysis Set

Analysis Variables:	Temperature Respiratory Rate Systolic Blood Pressure Diastolic Blood Pressure Pulse Rate Weight
Visit:	Variables other than Weight Predose, 2, 24, and 48 hours Weight Predose, 48 hours
Analytical Methods:	The following summaries will be provided by study medication for Study 1 and by dosing condition for Study 2. (1) Summary of Vital Signs Parameters and Change from Baseline by Visit Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit. (2) Case Plots of Vital Signs Parameters and Weight

7.11.4 12-Lead ECGs

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Heart Rate RR Interval PR Interval QT Interval QRS Interval QTcF Interval 12-Lead ECG Interpretation	[Within Normal Limits, Abnormal, Not Clinically Significant, Abnormal, Clinically Significant]
Visit:	Predose, 2 and 48 hours	
Analytical Methods:	For each variable other than 12-lead resting ECG interpretations, summaries (1) and (2) will be provided by study medication for Study 1 and by dosing condition for Study 2. For 12-lead resting ECG interpretation, summary (3) will be provided by study medication for Study 1 and by dosing condition for Study 2.	

(1) Summary of ECG Parameters and Change from Baseline by Visit

Descriptive statistics for observed values and changes from baseline (each postdose visit - Predose) will be provided by visit.

(2) Case Plots of ECG Parameters

Plots over time for each subject will be presented.

(3) Summary of Shift of 12-lead ECG Interpretation

Shift table showing the number of subjects in each category at Predose and each postdose visit will be provided.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

After the completion of the pilot study, an analysis will be performed on data obtained from the pilot study together with that from Study 2 to determine whether the results may warrant further analysis in the pivotal study. On the basis of bioequivalence evaluation in the pilot study, the Sponsor will determine entry into the pivotal study after discussions with the medical experts, and will promptly notify the investigator. Refer to the following procedures for proceeding to the pivotal study.

<u>In the case that the analysis results from the pilot study satisfy the criteria of bioequivalence:</u>

Study 1 will be completed without implementing the pivotal study.

<u>In the case that the analysis results from the pilot study do not meet the criteria of bioequivalence:</u>

The pivotal study will be implemented after the number of subjects required to conclude the bioequivalence is calculated based on the results from the pilot study. If bioequivalence is verified only for TAK-438F or unchanged aspirin in the pilot study, the pivotal study will be implemented for testing the bioequivalence of only the compound for which bioequivalence has not been verified. Any evidence from the pilot study suggesting difficulties in bioequivalence testing in the pivotal study may lead to the pivotal study not being implemented.

7.13 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

None.