Title: A Single Center, Open-Label, Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of TAK-123 after Intravenous Infusion in Japanese Healthy Adult Male Subjects

NCT Number: NCT04155567

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-123-1001

A Single Center, Open-Label, Phase 1 Study to Evaluate the Pharmacokinetics, Safety andTolerability of TAK-123 after Intravenous Infusion in Japanese Healthy Adult Male Subjects

Version: 1st

Date: 20 December 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 1 Version

Protocol Date: 10 October 2019

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

3.0 LIST OF ABBREVIATIONS

AE	adverse event
Ae	amount of drug excreted in urine
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
AUC	area under the concentration-time curve
BMI	body mass index
CL R	renal clearance
Cmax	maximum observed concentration
ECG	electrocardiogram
fe	fraction of administered dose of drug excreted in urine
GGT	gamma glutamyl transferase
Lambda z	terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
NaBZ	sodium benzoate
NaPA	sodium phenylacetate
PK	pharmacokinetics
PT	prothrombin time
QTc	corrected QT
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
tmax	time of first occurrence of Cmax
t1/2z	half-life period
V_z	volume of distribution during the terminal elimination phase
WBC	white blood cell
WHO Drug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

- The primary objective of the study is to evaluate the PK of phenylacetate and benzoate after intravenous infusion of TAK-123 in Japanese healthy adult male subjects.

4.2 Secondary Objectives

- The secondary objective of the study is to evaluate the safety and tolerability of TAK-123 after intravenous infusion of TAK-123 in Japanese healthy adult male subjects.

4.3 Study Design

This study is a single-center, open-label, uncontrolled study.

In this study, TAK-123 will be administered intravenously as a loading dose over 90 minutes at the dose level of 3.75 g/m^2 of NaPA and 3.75 g/m^2 of NaBZ under the breakfast fasting condition, followed by an equivalent maintenance dose over 24 hours to evaluate the PK, safety and tolerability of TAK-123 in Japanese healthy adult male subjects.

A 4 mg of dose of ondansetron will be administered intravenously 30-40 minutes before the start of TAK-123 infusion.

The dose of TAK-123 to be investigated is shown in Table 4.a. The dose of ondansetron to be administered before the administration of TAK-123 is shown in Table 4.b.

Table 4.a Dosage of TAK-123

Study drug	Dose	Mode of administration
TAK-123	3.75 g/m^2 of NaPA and 3.75 g/m^2 of NaBZ	1) Intravenous infusion (via a peripheral vein) over 90 minutes as a loading dose 2) An equivalent intravenous infusion (via a peripheral vein) over 24 hours as a maintenance dose after the completion of the above 1).

Table 4.b Dosage of ondansetron

Premedication	Dose	Mode of administration
Ondansetron	4 mg	Slow intravenous infusion

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoint

- PK parameters (C_{max}, AUC_{last}, AUC_{∞}) of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate).

5.1.2 Secondary Endpoints

- Number of subjects with treatment-emergent adverse events (TEAEs)

5.1.3 Safety Endpoints

- TEAEs, laboratory tests, vital signs, body weight, and 12-lead ECG

5.1.4 Exploratory Endpoints

- Plasma PK parameters (t_{max}, $t_{1/2z}$, λ_z) of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate)
- Urinary excretion amounts (Ae) and excretion ratios (fe) of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate)

6.0 DETERMINATION OF SAMPLE SIZE

The sample size was determined as 10 subjects that are considered to be sufficient to evaluate the PK and safety of TAK-123.

The sample size is not based on considerations of statistical power.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Treatment-emergent adverse event (TEAE): An adverse event whose date of onset occurs on or after the start of study drug (TAK-123)
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug (TAK-123)
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV) (%): Standard deviation / mean * 100

7.2 Analysis Sets

- Safety analysis set: All subjects who received at least one dose of TAK-123
- Pharmacokinetic analysis set: All subjects who received at least one dose of TAK-123 and provided sufficient PK measurements available to estimate PK parameters, at least 1 estimable PK parameter.

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 of Last Subject's Last Visit/Contact MedDRA Version SAS Version Used for Creating the Datasets
Analytical Method(s) :	(1) Study Information Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:	All Subjects Who Did Not Receive Study Drug (TAK-123)
Analysis Variable(s) :	Age (years)
Analytical Method(s) :	(1) Screen Failures Descriptive statistics will be provided.

7.3.3 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s) :	Study Drug (TAK-123) Administration Status	[Treated, Not Treated]
	Primary Reason for Subject Not Being Treated	[Adverse Event, Death, Lost to Follow-up, Protocol Deviation, Sample Size Sufficient, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]
Analytical Method(s) :	(1) Study Drug (TAK-123) Administration Status	

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being treated, the total number of not treated subjects will be used as the denominator.

7.3.4 Disposition of Subjects

Analysis Set:	All Subjects Who Received Study Drug (TAK-123)	
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, Sample Size Sufficient, Study Terminated by Sponsor, Withdrawal by Subject, Other]

Analytical Method(s) : (1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who did not complete all planned study visits will be used as the denominator.

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Analysis Set:	All Subjects Who Received Study Drug (TAK-123)	
Analysis Variable(s) :	Significant Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s) : (1) Protocol Deviations

Frequency distribution will be provided 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:	All Subjects Who Received Study Drug (TAK-123)	
Analysis Variable(s) :	Handling of Subjects	[Categories are based on the specifications in Subject Evaluability List]
	Analysis Sets	
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]
Analytical Method(s) :	(1) Subjects Excluded from Analysis Sets (2) Analysis Sets Frequency distributions will be provided. 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 Set:	Safety Analysis Set	
Analysis Variable(s) :	Age (years) Height (cm) Weight (kg) BMI (kg/m^2)	
	Smoking Classification	[Never, Current, Former]
	Alcohol Classification	[Daily, A Few Times Per Week, A Few Times Per Month, No]
	Caffeine Classification	[Yes, No]
Analytical Method(s) :	(1) Summary of Demographics and Baseline Characteristics Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.	

7.5 Study Drug Exposure and Compliance

Not applicable.

7.6 Efficacy Analysis

Not applicable.

7.6.1 Primary Efficacy Endpoint(s)

Not applicable.

7.6.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.6.3 Additional Efficacy Endpoint(s)

Not applicable.

7.6.4 Statistical/Analytical Issues

7.6.4.1 Adjustments for Covariates

Not applicable.

7.6.4.2 Handling of Dropouts or Missing Data

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

7.6.4.3 Multicenter Studies

Not applicable.

7.6.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.6.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

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

Not applicable.

7.6.4.7 Examination of Subgroups

Not applicable.

7.7 Pharmacokinetic/Pharmacodynamic Analysis

7.7.1 Pharmacokinetic Analysis

7.7.1.1 Plasma Concentrations

Analysis Set:	Pharmacokinetic Analysis Set
Analysis Variable(s) :	Plasma Concentrations of Phenylacetate, Benzoate and These Metabolites (Phenylacetylglutamine and Hippurate)
Visit:	Predose; 0.25, 0.75, 1.5, 2.5, 4.5, 6.5, 8.5, 10.5, 12.5, 16.5, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29.5, 30.5, 32.5 and 48 Hours Postdose;
Analytical Method(s) :	The following summaries will be provided.

(1) Summary of Plasma Concentrations by Visit
Descriptive statistics and CV will be provided by visit.

(2) Case Plot of Plasma Concentrations
Plots over time for each subject will be presented. The vertical axis will be a normal scale and a common logarithmic scale.

(3) Mean and Standard Deviation Plot of Plasma Concentrations
Mean and standard deviation will be plotted for each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a normal scale.

(4) Mean Plot of Plasma Concentrations
Mean will be plotted for each analysis variable. Visit will be plotted on the horizontal axis and each of the analysis variables will be plotted on the vertical axis. The vertical axis will be a common logarithmic scale.

7.7.1.2 Pharmacokinetic Parameters

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic Parameters of Phenylacetate, Benzoate and These Metabolites (Phenylacetylglutamine and Hippurate)

AUClast	AUCinf	AUC48
Cmax	tmax	t1/2z
Lambda z	Vz (for Phenylacetate and Benzoate)	CL (for Phenylacetate and Benzoate)

Analytical Method(s): The following summary will be provided.

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

7.7.1.3 Urine Pharmacokinetic Parameter

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Urine Pharmacokinetic Parameters of Phenylacetate, Benzoate and These Metabolites (Phenylacetylglutamine and Hippurate)
Urine Pharmacokinetic Parameters of Sum of Phenylacetate and Phenylacetylglutamine, and Sum of Benzoate and Hippurate for fe48

Ae48	fe48	CLR

Analytical Method(s): The following summary will be provided.

(1) Summary of Urine Pharmacokinetic Parameter
Descriptive statistics and CV will be provided.

7.7.2 Pharmacodynamic Analysis

Not applicable.

7.8 Safety Analysis

In this study, safety will be evaluated as the primary endpoint.

7.8.1 Adverse Events

7.8.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Relationship to Study Drug (TAK-123)	[Related, Not Related]
	Intensity	[Mild, Moderate, Severe]
Analytical Method(s) :	The following summaries will be provided.	

(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 (TAK-123) (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 (TAK-123) 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 (TAK-123) (number of events, number and percentage of subjects)
   7) Serious Treatment-Emergent Adverse Events leading to study drug (TAK-123) 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 will be based on the number of subjects in the safety analysis set.

<u>Number of subjects</u>

- 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.

7.8.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
	Period	[Loading Period, Maintenance Period, After Infusion Period]
Analytical Method(s) :	The following summaries will be provided using frequency distribution. 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 System Organ Class 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) Treatment-Emergent Adverse Events Leading to Study Drug (TAK-123) Discontinuation by System Organ Class and Preferred Term
(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Period

The frequency distribution will be provided according to the rules below. Percentages will be based on the number of subjects who were treated in the safety analysis set.

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.
- Summary tables for (5) and (6)
  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.

7.8.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variable(s): PTE

Analytical Method(s): 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.

7.8.2 Clinical Laboratory Evaluations

7.8.2.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Hematology

Red Blood Cell (RBC)	Hemoglobin	Hematocrit
Platelets	White Blood Cell (WBC)	

WBC Differentials (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes)

PT	aPTT	

Serum Chemistry

Total Protein	Albumin	Blood Urea Nitrogen
Creatinine	Total Bilirubin	Direct Bilirubin
Sodium	Potassium	Chloride
Calcium	ALP	Creatine kinase
AST	ALT	GGT
Glucose	Glucose (Self-monitoring)	

Visit: Glucose (Self-monitoring):
Predose; 1 and 1.5 Hours Postdose;
Sodium, Potassium and Chloride:
Predose; 1.5, 25.5, and 48 Hours Postdose; Day 8
Variables other than Glucose (Self-monitoring), Sodium, Potassium and Chloride:
Predose; 25.5, and 48 Hours Postdose; Day 8
(Data obtained at Day -1 will be used as the "Predose" visit)

Analytical Method(s) : The following summaries will be provided.

(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.

7.8.2.2 Urinalysis

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	Specific Gravity	
	pH	[Min<= - <=8.0, 8.0< - <=Max]
	Protein	[-, +-, 1+, 2+, 3+, 4+]
	Glucose	[-, +-, 1+, 2+, 3+, 4+]
	Occult blood	[-, 1+, 2+, 3+]
	Nitrite	[-, 1+, 2+]
	Urobilinogen	[-, +-, 1+, 2+, 3+, 4+]
Visit:	Predose; 25.5, and 48 Hours Postdose; Day 8 (Data obtained at Day -1 will be used as the "Predose" visit)	
Analytical Method(s) :	For specific gravity, summaries (1), (2) and (4) will be provided. For each variable other than specific gravity, summaries (3) and (4) will be provided. (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) Number of Subjects in Categories of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at Predose and each postdose visit will be provided.

(4) 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. The laboratory value for specific gravity will be classified as "Low", "Normal" or "High" relative to the normal reference range. If applicable, the laboratory value for each urine laboratory test other than specific gravity will be classified as "Normal" or "Abnormal" relative to the normal reference range. The shift tables will be based on these classifications.

7.8.2.3 Blood Gas Test

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	pH HCO_3^{-b}
Visit:	Predose; 1.5 and 25.5 Hours Postdose; (Data obtained at Day -1 will be used as the "Predose" visit)
Analytical Method(s) :	The following summaries will be provided. (1) Summary of Blood Gas 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.

7.8.3 Vital Signs and Weight

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Temperature Systolic Blood Pressure Diastolic Blood Pressure Respiration Rate Pulse Rate

	Weight
Visit:	Temperature, Systolic Blood Pressure, Diastolic Blood Pressure, Respiration Rate, Pulse Rate: Predose, 1.5, 4, 25.5, and 48 Hours Postdose; Day 8 Weight: Predose; 48 Hours Postdose; Day 8
Analytical Method(s) :	The following summaries will be provided. (1) Summary of Vital Signs Parameters and Weight 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 Plots over time for each subject will be presented.

7.8.4 12-Lead ECGs

Analysis Set:	Safety Analysis Set
Analysis Variable(s) :	Heart Rate RR Interval PR Interval QRS Interval QT Interval QTcF Interval Interpretation [Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Visit:	Predose, 1.5 and 48 Hours Postdose; Day 8
Analytical Method(s) :	For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided. For 12-lead ECG interpretation, summary (3) will be provided. (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" visit and each postdose visit will be provided.

7.8.5 Other Observations Related to Safety

Not applicable.

7.9 Interim Analysis

Not applicable.

7.10 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

8.0 REFERENCES

No reference.