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
Protocol Approve Date: 10-OCT-2019

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

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TAKEDA PHARMACEUTICALS

PROTOCOL

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

Study Identifier:	TAK-123-1001
Compound:	TAK-123
Date:	10 October 2019 (English translation: 10 October 2019)
Version/Amendment Number:	Amendment 1

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceuticals	**Compound:** TAK-123
Study Identifier: TAK-123-1001	**Phase:** 1
Protocol 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	
Trial 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 sodium phenylacetate and 3.75 g/m^2 of sodium benzoate under the breakfast fasting condition, followed by an equivalent maintenance dose over 24 hours to evaluate the pharmacokinetics (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.	
Trial Primary Objective: To evaluate the PK of phenylacetate and benzoate after intravenous administration of TAK-123 in Japanese healthy adult male subjects. **Secondary Objectives:** To evaluate the safety and tolerability of phenylacetate and benzoate after intravenous infusion of TAK-123 in Japanese healthy adult male subjects.	
Trial Subject Population: Japanese healthy adult male subjects	
Planned Number of Subjects: 10 subjects	**Planned Number of Sites:** 1 site
Dose Levels: TAK-123 will be administered intravenously via a peripheral vein as loading dose over 90 minutes at the dose level of 3.75 g/m^2 of sodium phenylacetate and 3.75 g/m^2 of sodium benzoate under the breakfast fasting condition, followed by maintenance dose over 24 hours at the dose level of 3.75 g/m^2 of sodium phenylacetate and 3.75 g/m^2 of sodium benzoate.	**Route of Administration:** Intravenous infusion via a peripheral vein
Duration of Treatment: Over 90 minutes followed by over 24 hours	**Planned Trial Duration:** Screening: Day -28 to -2 Check-in: Day -1 Treatment Period: Day 1 to 8
Criteria for Inclusion: Subjects to participate in this study should meet all the following criteria. 1. The subject is capable of understanding and complying with protocol requirements in the opinion of the investigator or sub-investigator. 2. The subject signs and dates a written informed consent form prior to the initiation of any study procedures. 3. The subject is a Japanese healthy adult male. 4. The subject is aged 20 to 45 years inclusive at the time of informed consent. 5. The subject weighs at least 50.0 kg, and has a body mass index (BMI) between 18.5 and 25.0 kg/m^2, inclusive, at	

Screening.

6. The subject is sterile, vasectomized or agrees to use an appropriate method of contraception during the predefined period in this study.

Criteria for Exclusion:

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any study drugs within 90 days before screening for this study (including the cases that at least 5 times the elimination half-lives of any study drugs have not yet passed).
2. The subject previously received TAK-123, its ingredients, or related compound before participation in this study except for the cases where benzoic acid is ingested as a food additive.
3. The subject is an employee of the Sponsor or the study site, or immediate family member, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or who may be forced to provide consent.
4. The subject has previous or current history of diseases considered to be inappropriate for participation in this study, including uncontrolled, clinically relevant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, endocrine, hematologic, immune, skin disease or psychiatric disorder.
5. The subject has a history of multiple episodes or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerance to prescription drugs, over-the-counter drugs or foods.
6. The subject has had an anaphylactic reaction to active ingredients or additives of TAK-123, ondansetron or additives of ondansetron, or salicylic acid associated with the intravenous administration of TAK-123.
7. The subject has a positive urine drug test at the time of screening.
8. The subject has a history of drug abuse (defined as any illicit drug use) or has a history of alcohol dependence within 2 years before the start of screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
9. The subject consumes 6 or more servings of caffeinated beverages (containing about 720 mg of caffeine or more) such as coffee, tea, cola, or energy drinks per day.
10. The subject is a smoker who smoked cigarettes or used nicotine-containing products (such as nicotine patch) within 6 months before the study drug administration.
11. The subject has a history of cancer.
12. The subject has a positive test result for any of the following at the time of screening: hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, serological test for syphilis.
13. The subject has poor peripheral venous access.
14. The subject has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of study drug administration.
15. The subject has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of study drug administration.
16. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of study drug administration.
17. The subject has any clinically relevant abnormality in vital signs or 12-lead ECG at screening or predose of Day 1.
18. The subject has abnormal laboratory test values at screening or Day -1 indicating clinically relevant underlying disease, or showing alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5×upper limit of normal (ULN).
19. The subject has been on an abnormal diet (eg, excessive drinking and eating or starvation condition) during the 4 weeks prior to the start of study drug administration in the opinion of the investigator or sub-investigator.
20. The subject who used or plans to use excluded concomitant medications, supplements, or dietary products (see

Table 7.a) during the predefined period in this study.

21. The subject is unlikely to comply with the protocol requirements or is unsuitable as a subject of this study for any other reason in the opinion of the investigator or sub-investigator.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is:

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

The secondary endpoints will be assessed through evaluation of the following parameters:

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

Statistical Considerations:

PK Analysis:

The following analyses will be performed in the PK analysis set.

Plasma concentrations of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate) will be summarized over each scheduled sampling time using descriptive statistics. Plasma and urine PK parameters of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate) will be summarized using descriptive statistics.

Safety Analysis:

The following analyses will be performed in the safety analysis set.

A TEAE refers to an AE that occurs on or after the start of the administration of TAK-123. The frequency of all TEAEs, TEAEs related to TAK-123, all TEAEs by intensity, TEAEs related to TAK-123 by intensity, TEAEs leading to TAK-123 discontinuation and serious TEAEs will be summarized. TEAEs will be coded using Medical Dictionary for Regulatory Activities Terminology (MedDRA) and summarized by system organ class (SOC) and preferred term

For continuous variables, the observed values and changes from baseline will be summarized for each scheduled sampling time using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled sampling time will be provided.

Sample Size Justification:

The sample size of 10 subjects is chosen to evaluate PK, safety and tolerability of TAK-123. The sample size is not based on statistical power considerations.

2.0 STUDY SCHEMATIC

Period	Screening Period		Treatment Period				
Day	-28～-2	-1	1	2	3	…	8
Visit/ Confinement	Visit	Confinement					Visit
Procedure	Informed consent/ Screening tests	Check-in/Examinations	Administration of study drug	Examinations	Examinations/Discharge		Follow-up

3.0 SCHEDULE OF STUDY PROCEDURES

	Screening Period		Treatment Period				
Study Day:	**Day -28~ Day -2 (At Screening)**	**Day -1 (Check in)**	**Day 1**	**Day 2**	**Day 3 (Discharge)**	**Early Termination**	**Day 8 (Follow-up)**
Confinement		X	X	X	X		
Informed Consent	X						
Inclusion/Exclusion Criteria (a)	X		X				
Demographics and medical history	X						
Medication history	X						
Physical examination (b)	X	X	X	X	X	X	X
Vital signs (c)	X		X	X	X	X	X
Weight, height, and BMI (d)	X		X		X	X	X
Concomitant medications	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG) (e)	X		X		X	X	X
Clinical laboratory tests (f)(g)	X	X	X (h)	X	X	X	X
Blood gas tests (i)		X	X	X			
Urine drug screen	X						
Immunology tests	X						
Dosing of the Study Drug (j)			X--------X				
PK blood collection (k)			X	X	X	X (l)	
PK urine collection (m)			X	X	X		
AE assessment (n)	X	X----------X					

(a) Check of the inclusion/exclusion criteria will be done at Screening and predose (Day 1 before the administration of TAK-123).
(b) Physical examination will be performed at Screening (Day -28 to -2), Day -1, predose, 4, 25.5 and 48 hours after the start of TAK-123 infusion and Day 8 or at Early Termination.
(c) The sitting blood pressure (resting more than 5 minutes), sitting pulse rate, respiratory rate, and body temperature (axillary) will be measured at Screening, predose, 1.5, 4, 25.5 and 48 hours after the start of TAK-123 infusion and Day 8 or at Early Termination.
(d) Weight will be measured at Screening, predose, 48 hours after the start of TAK-123 infusion and Day 8 or at Early Termination.
Height will be measured only at Screening.
BMI will be calculated at Screening.
(e) The 12-lead ECG will be measured at Screening, predose, 1.5 and 48 hours after the start of TAK-123 infusion and Day 8 or at Early Termination.
(f) Laboratory tests include hematology, serum chemistry, and urinalysis. Blood samples will be collected at Screening, Day -1, 25.5 and 48 hours after the start of TAK-123 infusion and Day 8 or at Early Termination after fasting for at least 8 hours.
(g) Glucose level will be assessed at Day -1, 1 and 1.5 hours after the start of TAK-123 infusion by a self-monitoring blood glucose meter.
(h) Blood samples for laboratory tests (Na, K, Cl) will be collected at 1.5 hours after the start of TAK-123 infusion in addition to the time points stipulated in (f).
(i) Blood gas tests will be performed at Day -1, 1.5 and 25.5 hours after the start of TAK-123 infusion.
(j) A 4 mg of dose of ondansetron will be administered intravenously 30-40 minutes before the start of TAK-123 infusion.
(k) PK blood samples will be collected at predose (from waking-up to immediately before the administration of TAK-123) and 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 after the start of TAK-123 infusion.
(l) Measured only if the subject discontinues the study within 48 hours after the start of TAK-123 infusion.
(m) PK urine samples will be collected at predose (spot), 0-24 and 24-48 hours after the start of TAK-123 infusion.
(n) The collection of AEs will commence from the time the subject signs the informed consent at Screening and continue until the follow-up examination.

4.0 INTRODUCTION

4.1 Background

Urea cycle disorders (UCD) is an inborn metabolic disorder caused by a deficiency of one of enzymes involved in the urea cycle, leading to hyperammonemia as a result of inhibited conversion of ammonia to urea. As clinical symptoms, non-specific neuropathies, such as vomiting, anorexia, multiple breathing, convulsions, disturbance of consciousness, behavior abnormalities, developmental disorders, etc. are observed in many patients. Especially in neonates with severe deficits, the disease occurs soon after birth or in the first year of life. Neonatal-onset UCD usually has a severe clinical course, possibly resulting in fatal cases. Thus, UCD is a serious disease [1]. The estimated incidence of UCD is one in 8000 to 44,000 births, and 286 patients of those who were registered with inborn error of metabolism (4778 patients in total) had UCD according to the nationwide registry survey conducted by Medical Aid Program for Chronic Pediatric Diseases of Specified Categories in 2011 [2]. The distribution by disease category was as follows: 16 patients with carbamoylphosphate synthetase (CPS) deficiency; 76 patients with ornithine transcarbamylase (OTC) deficiency, 120 patients with argininosuccinate synthetase (ASS) deficiency, 8 patients with argininosuccinate lyase (ASL) deficiency, 6 patients with arginase (ARG) deficiency, and 51 patients with hyperammonemia.

Rapid reduction of blood ammonia levels is given the highest priority for the treatment of hyperammonemia to improve neurological abnormality such as encephalopathy and comatose and avoid fatal cases and irreversible neurologic damage. For the treatment of hyperammonemia in Japan, oral administration of sodium phenylbutyrate (Buphenyl®) and intravenous administration of sodium benzoate (NaBZ) by in-house preparation of reagents are performed as a drug treatment with a nitrogen scavenger. However, oral sodium phenylbutyrate takes time to show its efficacy because it undergoes an absorption process in the gastrointestinal tract. Therefore, a stable and immediate efficacy cannot be expected in a case of an acute attack accompanied by gastrointestinal symptoms. Furthermore, quite a few patients have a difficulty to take oral medication. Also, currently NaBZ is prepared from reagents at hospitals, and thus, it is difficult to assure its quality. Consequently, the current therapeutic environment for acute hyperammonemia is insufficient in Japan.

TAK-123 is a sterile, concentrated, aqueous injectable solution containing 10% sodium phenylacetate (NaPA) and 10% NaBZ that has been marketed in the US for the treatment of acute hyperammonemia and associated encephalopathy in patients with UCD. In Japan, upon the written request for the development of new drugs submitted by the Japanese Society for Inherited Metabolic Diseases, the Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs publicly sought for companies to develop new drugs for UCD in May 2010, and we declared our intent to develop TAK-123 to the MHLW.

The active ingredients of TAK-123 are NaPA and NaBZ. Both compounds are considered nitrogen scavengers; they exert their therapeutic effects by binding waste nitrogen as an alternative pathway to the urea cycle so that it can be excreted in the urine (Figure 4.a). NaPA conjugates with glutamine that is formed by 2 molecules of ammonia, being excreted as phenylacetylglutamine

into the urine. As a result, 2 moles of waste nitrogen are removed per mole of NaPA. NaBZ conjugates with glycine that is formed by one molecule of ammonia, being excreted as hippurate into the urine. As a result, 1 mole of waste nitrogen is removed per mole of NaBZ. TAK-123 with the following characteristics is expected to contribute to the improvement of the prognosis of UCD patients by lowering plasma ammonia concentrations more steadily and more rapidly, compared to the currently available pharmacotherapies for hyperammonemia in patients with UCD.

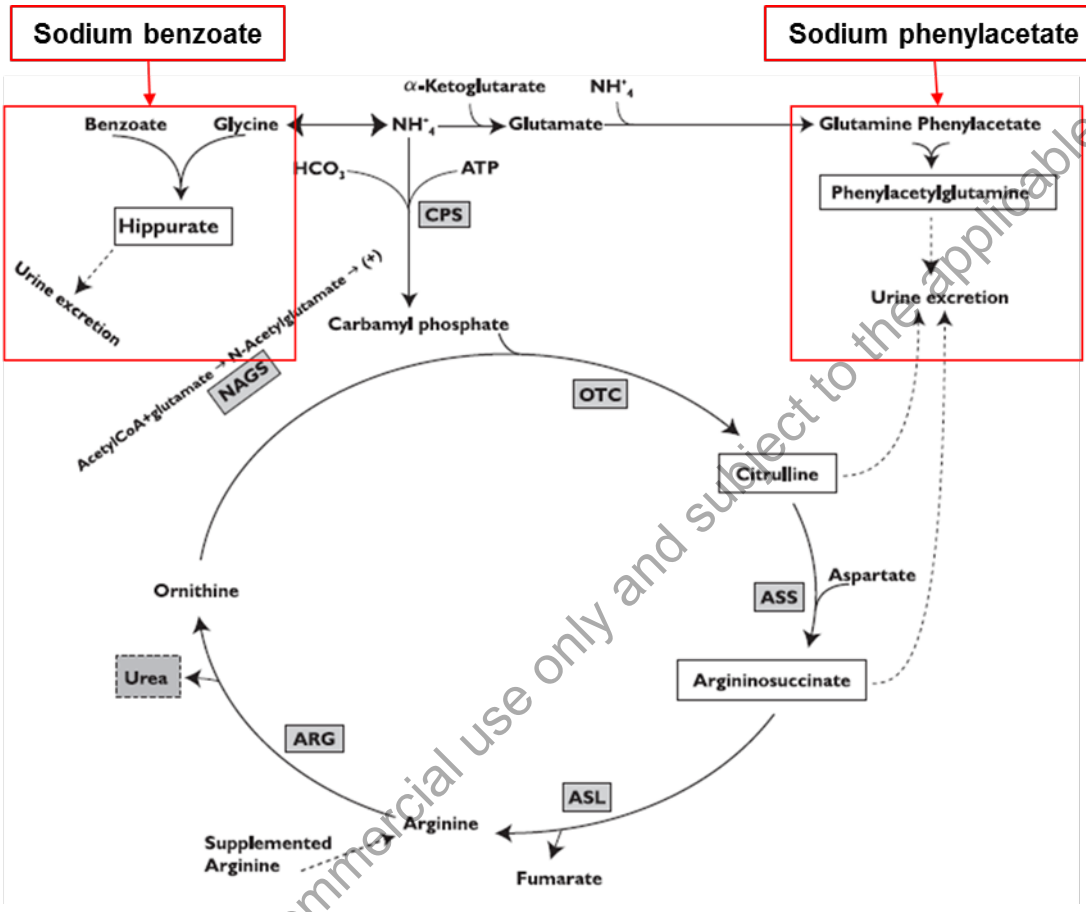
Phenylacetate and benzoate, free-forms of NaPA and NaBZ, are nitrogen scavengers through different routes other than the urea cycle. Consequently, it can be expected that TAK-123 lowers ammonia concentrations in the plasma of UCD patients whose function of urea cycle is not sufficient.

TAK-123, as an injection, can be administered in a case of an acute attack accompanied by gastrointestinal symptoms, and is expected to have faster onset of therapeutic effects than oral medicine.

The PK, safety and tolerability of TAK-123 in non-Japanese healthy subjects after intravenous infusion of TAK-123 have been evaluated in 2 clinical studies (Study 951603 and Study 973600).

In this study, the PK, safety and tolerability of NaPA and NaBZ, and these metabolites (phenylacetylglutamine and hippurate) after the administration of TAK-123 will be evaluated in Japanese healthy adult male subjects.

Figure 4.a Alternative-Pathway Therapy for Nitrogen Disposal by Phenylacetate and Benzoate



ARG: arginase, ASL: argininosuccinate lyase, ASS: argininosuccinate synthetase, ATP: adenosine triphosphate
CPS: carbamoyl phosphate synthetase, NAGS: N-acetylglutamate synthethase, OTC: ornithine transcarbamylase

4.2 Rationale for the Proposed Study

The efficacy and safety of TAK-123 in patients with hyperammonemia were confirmed in a foreign clinical study involving patients with UCD. Also, the PK, safety and tolerability of NaPA and NaBZ (active ingredients of TAK-123) and these metabolites (phenylacetylglutamine and hippurate) have been reported from 2 foreign studies in healthy volunteers (Study 951603 and Study 973600). TAK-123 is currently on the US market for the treatment of acute hyperammonemia and associated encephalopathy in patients with UCD. This study was planned to evaluate the PK, safety and tolerability of NaPA, NaBZ and these metabolites (phenylacetylglutamine and hippurate) following administration of TAK-123 to Japanese healthy adult male subjects.

4.3 Benefit/Risk Profile

There is no benefit to subjects in this clinical study since this is a healthy volunteer study.

Subjects who participate in this study may have adverse events and other risks associated with administration of the study drug. Therefore, subjects will be informed of possible risks before the participation in this study, and will be explained at the time of informed consent that they are free to withdraw from the study at any time without giving a reason.

In a multi-center, open-label, uncontrolled study conducted in overseas for 21 years (1982 to 2003), 316 patients with UCD comprising 1045 hyperammonemia episodes were treated with TAK-123. Adverse events (AEs) were reported for 52% of patients (163/316 patients) and 31% of episodes (319/1045 episodes). AEs with the incidence ≥6% of subjects included vomiting (9% of subjects and 7% of episodes; the same applies below), hypokalaemia (7% and 3%), hyperglycaemia (7% and 2%), seizure (6% and 2%), and mental impairment (6% and 2%). Adverse drug reactions (ADRs) with the incidence ≥6% of subjects included vomiting (8% and 6%) and hypokalaemia (6% and 2%).

For the clinical safety information on TAK-123, please refer to the US package insert of Ammonul [3] and the Investigator's Brochure of TAK-123.

This study will be conducted in the light of the mechanism of action of TAK-123, non-clinical data, clinical data from foreign clinical studies conducted to date, and overseas safety information in order to minimize potential risks. The procedures may be changed during the study period as needed based on emerging safety information.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Trial Objectives

5.1.1 Trial Primary Objective

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.

5.1.2 Trial Secondary Objective

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.

5.2 Endpoints

5.2.1 Primary Endpoint

PK parameters:

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

5.2.2 Secondary Endpoints

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

5.2.3 Safety Endpoints

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

5.2.4 Exploratory Endpoints

PK:

- 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 TRIAL DESIGN AND DESCRIPTION

6.1 Trial 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 6.a. The dose of ondansetron to be administered before the administration of TAK-123 is shown in Table 6.b.

Table 6.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 6.b Dosage of ondansetron

Premedication	Dose	Mode of administration
Ondansetron	4 mg	Slow intravenous infusion

6.2 Rationale for Trial Design, Dose, and Endpoints

6.2.1 Rationale of Trial Design

Japanese healthy adult male subjects will be enrolled in this study in order to appropriately evaluate the PK of TAK-123 in Japanese. An open-label, uncontrolled design is adopted for this study to evaluate the PK profile following intravenous infusion of TAK-123 to Japanese subjects.

In a previous clinical PK study of TAK-123 with healthy adult volunteers conducted in the US (Study 951603), 2 of 3 subjects with a dose of 5.5 g/m^2 experienced severe vomiting, although antiemetic drug, ondansetron, was co-administrated during the first 15 minutes. Therefore, all remaining subjects after the first 3 subjects in the same study and all subject in another clinical study with healthy volunteers had been pretreated with ondansetron. Although several subjects experienced moderate or mild nausea and/or vomiting at a dose levels of 3.75 g/m^2 or 4 g/m^2 under the pretreatment of ondansetron, subjects were generally well tolerated. Consequently, it is considered that pretreatment of ondansetron is needed for this study with healthy volunteers in consideration of ensuring the subject's safety.

6.2.2 Rationale for Dose

The dosage of TAK-123 in this study was set by referring to the approved dosage in the US and results from a PK study of TAK-123 in healthy volunteers conducted in the US (Study 951603).

As for the approved dosage of TAK-123 in the US, for patients whose body weight exceeds 20 kg, TAK-123 is administered through a central intravenous catheter as a loading dose infusion over 90 to 120 minutes at the dose level of 5.5 g/m^2 of NaPA and 5.5 g/m^2 of NaBZ, followed by an equivalent maintenance dose infusion over 24 hours.

On the other hand, in the PK study (Study 951603), TAK-123 was administered intravenously as a loading dose infusion over 90 minutes at the start dose level of 5.5 g/m^2 of NaPA and 5.5 g/m^2 of NaBZ, followed by an equivalent maintenance dose infusion over 24 hours. However, nausea and vomiting were occured in all of the initial 3 subjects at the dose of 5.5 g/m^2. Thus, all of the rest subjects were administered at the decreased dose of 3.75 g/m^2. As a result, PK profiles of phenylacetate and benzoate in healthy volunteers were evaluated at the doses of 3.75 g/m^2 in 17 subjects and 5.5 g/m^2 in 3 subjects. Even though limited PK data were available following the 5.5 g/m^2 dose, this was approved at the dose of TAK-123 in the US.

Considering AEs observed at 5.5 g/m^2 above, administration at the dose of 5.5 g/m^2 to healthy volunteers could be difficult from the tolerability point of view also in this study. In addition, PK of TAK-123 will be compared between Japanese and non-Japanese by using results from this study in the future. Consequently, 3.75 g/m^2 was selected as the dosage to be investigated in this study. The US package insert states that TAK-123 must be administrated through a central intravenous catheter. However, administration through a central line is more invasive than that via a peripheral line, imposing a greater burden on patients. In PK studies conducted outside Japan for healthy volunteers (Study 951603 and Study 973600) where TAK-123 was administered through a peripheral intravenous catheter, no AE related to administration site was observed. In addition, as described above, the healthy volunteers will be entered to this study and the result of this study will be compared with that of studies conducted outside Japan in the future. Thus, the administration route through a peripheral intravenous catheter, was chosen for this study.

The 0.15 mg/kg of the approved dose for Ondansetron which has an indication for nausea and vomiting with treatment of anticancer drug in the US was pre-treated in the PK study conducted outside Japan. The 4 mg of Ondansetron will be pre-treated in this study according to the administration and dosage for Ondansetron in Japan because Ondansetron was approved in the dose of 4 mg.

6.2.3 Rationale for Endpoints

Since the primary objective of this study is to characterize the PK of TAK-123 in Japanese healthy adult male subjects, PK parameters (C_{max}, AUC_{last}, and AUC_{∞}) of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate) were set as primary endpoints.

Endpoints that are generally used in Phase 1 studies involving healthy adult male subjects were chosen as the endpoints for evaluating the safety and tolerability of TAK-123 administered as intravenous infusion in this study.

6.2.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

The objective of this section is to specify the sequence of procedures in the cases where the timing of each procedure overlaps.

- Safety evaluation will be conducted within the predetermined allowance window as far as possible.
- Blood samples for PK assessment will be collected at time points as close to the specified time as possible.
- Other procedures must be completed at time points as close to the specified or planned hours as possible irrespective of before or after the specified times.
- If the timing of blood sampling and ECG or vital signs measurement overlap, blood sampling should be prioritized. ECG or vital signs measurement may be performed before blood sampling within an acceptable time window (Appendix E).

6.3 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The acceptable time windows for each examination/test, observation, and evaluation are defined (Appendix E).

6.4 Trial Beginning and End/Completion

6.4.1 Definition of Beginning of the Trial

The entire study will start when the first subject signs the informed consent form to participate in this study.

6.4.2 Definition of End of the Trial

The entire study will end when the last subject completes the last planned visit or follow-up visit or is withdrawn from the study or lost to follow-up (the status that the subject cannot be reached by the investigator or sub-investigator).

6.4.3 Definition of Trial Discontinuation

The study may be discontinued for reasons other than safety such as the followings:

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

Discontinuation of the clinical study for safety reasons:

- The study is prematurely terminated because other clinical, non-clinical trials, or commercial use in launched regions where the study drug or other drugs of the same class are administered have confirmed unexpected safety concerns based on the methodology used in this study.

6.4.4 Criteria for Premature Termination or Suspension of the Trial

6.4.4.1 Criteria for Premature Termination or Suspension of Trial

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

- New information or other evaluation regarding the safety or efficacy of TAK-123 that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objective or compromises subject safety.

6.4.4.2 Criteria for Premature Termination or Suspension of a Site

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

6.4.4.3 Procedures for Premature Termination or Suspension of a Site

In the event that the Sponsor, an IRB, or a regulatory authority elects to terminate or suspend of the entire study or the study site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by the applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subjects to participate in this study should meet all the following criteria.

1. The subject is capable of understanding and complying with protocol requirements in the opinion of the investigator or sub-investigator.
2. The subject signs and dates a written informed consent form prior to the initiation of any study procedures.
3. The subject is a Japanese healthy adult male.
4. The subject is aged 20 to 45 years inclusive at the time of informed consent.
5. The subject weighs at least 50.0 kg, and has a body mass index (BMI) between 18.5 and 25.0 kg/m^2, inclusive, at Screening.
6. The subject is sterile, vasectomized or agrees to use an appropriate method of contraception during the predefined period in this study.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any study drugs within 90 days before screening for this study (including the cases that at least 5 times the elimination half-lives of any study drugs have not yet passed).
2. The subject previously received TAK-123, its ingredients, or related compound before participation in this study except for the cases where benzoic acid is ingested as a food additive.
3. The subject is an employee of the study site, or immediate family member, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or who may be forced to provide consent.
4. The subjects have previous or current history of diseases that may affect the participation in this study or study results, including uncontrolled, clinically relevant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, endocrine, hematologic, immune, skin disease or psychiatric disorder.
5. The subject has a history of multiple episodes or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerance to prescription drugs, over-the-counter drugs or foods.
6. The subject has had an anaphylactic reaction to active ingredients or additives of TAK-123, ondansetron or additives of ondansetron, or salicylic acid associated with the intravenous administration of TAK-123.
7. The subject has a positive urine drug test at the time of screening.

8. The subject has a history of drug abuse (defined as any illicit drug use) or has a history of alcohol dependence within 2 years before the start of screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
9. The subject consumes 6 or more servings of caffeinated beverages (containing about 720 mg of caffeine or more) such as coffee, tea, cola, or energy drinks per day.
10. The subject is a smoker who smoked cigarettes or used nicotine-containing products (such as nicotine patch) within 6 months before the study drug administration.
11. The subject has a history of cancer.
12. The subject has a positive test result for any of the following at the time of screening: hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen, serological test for syphilis.
13. The subject has poor peripheral venous access.
14. The subject has undergone whole blood collection of at least 200 mL within 4 weeks (28 days) or at least 400 mL within 12 weeks (84 days) prior to the start of the study drug administration.
15. The subject has undergone whole blood collection of at least 800 mL in total within 52 weeks (364 days) prior to the start of the study drug administration.
16. The subject has undergone blood component collection within 2 weeks (14 days) prior to the start of the study drug administration.
17. The subject has any clinically relevant abnormality in vital signs or 12-lead ECG at screening or predose of Day 1.
18. The subject has abnormal laboratory test values at screening or Day -1 indicating clinically relevant underlying disease, or showing alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >1.5 × upper limit of normal (ULN).
19. The subject has been on an abnormal diet (eg, excessive drinking and eating or starvation condition) during the 4 weeks (28 days) prior to the start of the study drug administration in the opinion of the investigator or sub-investigator.
20. The subject who used or plans to use excluded concomitant medications, supplements, or dietary products (see Table 7.a) during the predefined period in this study.
21. The subject is unlikely to comply with the protocol requirements or is unsuitable as a subject of this study for any other reason in the opinion of the investigator or sub-investigator.

7.3 Excluded Medications, Supplements, Dietary Products

Table 7.a shows excluded medications, supplements, and dietary products.

Use of the drugs listed on Table 7.a (prescribed drugs and over-the-counter drugs), vitamins, supplements, and dietary products will be excluded from a specified time point to until discharge or the follow-up visit (Day 8) given the effect on the safety and PK. Use of prohibited concomitant drugs will be allowed when the investigator or sub-investigator deems it necessary to use any of

the concomitant drugs for reasons including treatment of an AE (eg, when nausea and/or vomiting occur as AEs during or after the administration of TAK-123, 4 mg of ondansetron can be used additionally only once for such symptoms if judged as necessary by the investigator or sub-investigator).

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator or sub-investigator.

Table 7.a Excluded Medications, Supplements, and Dietary Products

From 28 days before TAK-123 administration (Day 1) to the follow-up visit (Day 8)	From 7 days before TAK-123 administration (Day 1) to the follow-up visit (Day 8)	From 7 days before TAK-123 administration (Day 1) to the discharge	From 24 hours before TAK-123 administration (Day 1) to the discharge
• Prescription drugs • over-the-counter drugs • Supplements (St. John's wort, ginseng, kava-kava, ginkgoes biloba, and melatonin) • Chinese herbal medicines • Vaccination/vaccine • Nicotine-containing products	• Grapefruit/grapefruit juice • Char-broiled meat	• Vitamins • Alcohol-containing products • Cruciferous vegetables (eg, kale, broccoli, watercress, collard green, kohlrabi, sprout, mustard)	• Caffeine-containing products • Xanthine-containing products

Note: Excludes the drug needs to be administered to treat an AE and if the investigator or sub-investigator considers necessary to use the drug

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Diet and fluid (except water) must be ingested at least 8 hours before performing clinical laboratory tests.

On the day before clinical laboratory tests, evening meal must be ingested by 21:00.

During hospitalization, pre-specified diets must be ingested, and other diets will be prohibited. After discharge, excessive drinking and eating must be avoided until completion of follow-up period (Day 8).

Subjects will be instructed to fast from at least 8 hours before the start of TAK-123 infusion to 4 hours after the start of TAK-123 infusion.

Subjects will take low-fat/high-carbohydrate diets after the start of TAK-123 infusion to the discharge. Subjects will take the first and second meals approximately 4 and 9 hours after the start of TAK-123 infusion, respectively, and at appropriate times thereafter.

Note: For low-fat/high-carbohydrate diet, the energy produced by lipid will account for ≤20% of the total calorie, and the remaining calorie will be supplemented by carbohydrate to compensate for an equivalent total calorie of ordinary diet.

If meals and tests or blood sampling are scheduled at the same time, subjects will take meals after tests or blood sampling are completed.

7.4.2 Activity

Smoking is prohibited during the study.

Excessive exercise is prohibited during the study.

Blood donation is prohibited for at least 12 weeks (84 days) from completion of the last test for the study.

If a subject visits another medical institution during the study period, the investigator or sub-investigator should be informed of the visit in advance whenever possible, and should be reported the circumstances and therapy after visit. The investigator or sub-investigator should communicate that medical institution about the subject's participation in the study.

7.5 Record of Discontinuation or Withdrawal of a Subject Before TAK-123 Administration

The investigator or sub-investigator is responsible for all subjects who signed the informed consent form. If a subject is withdrawn from the study before the start of the administration of TAK-123, the investigator or sub-investigator will complete the electronic case report form (eCRF) to record the details.

The primary reason for the withdrawal before the start of the administration of TAK-123 will be recorded in the eCRF using the following categories:

- Death
- Adverse events (AEs)
- Screen failure (The subject did not meet the inclusion criteria or did meet the exclusion criteria.) <Specify the reason.>
- Protocol deviation
- Lost to follow-up
- Withdrawal by subject <Specify the reason.>
- Study terminated by the Sponsor
- Sample size sufficient
- Other <Specify the reason.>

7.6 Criteria for Discontinuation or Withdrawal of a Subject

Primary reasons for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the eCRF using the following categories. For the subject who is withdrawn from the study before the administration of TAK-123, refer to Section 7.5.

1. Death

A subject died on study.

Note: If the subject dies on study, the event will be considered as a serious adverse event (SAE). See Section 10.2.9.3 for the reporting procedures.

2. AE

The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

TAK-123 will be immediately discontinued if a condition meets any following criteria during the treatment, and appropriate follow-up will be performed (clinical laboratory tests will be repeatedly performed until the clinical laboratory test profiles have normalized or returned to baseline, refer to Section 9.2.8.1):

- Liver Function Test Abnormalities
  - ALT or AST >8 × ULN, or
  - ALT or AST >5 × ULN and persists for more than 2 weeks, or
  - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
  - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
- Hyperglycemia
  - Fasting glucose level after the administration of TAK-123 >500 mg/dL, or
  - The investigator or sub-investigator considered inappropriate to continue the study because of obvious hyperglycemia
- Metabolic acidosis
  - Diagnosed or suspected metabolic acidosis (eg, pH <7.25, or pH <7.35 and HCO_3^- <22 mEq/L persist) and the investigator or sub-investigator considered inappropriate to continue the study

  If metabolic acidosis was suspected, the investigator or sub-investigator should consider to perform a blood gas test with arterial blood or other laboratory tests to confirm the diagnosis and take an appropriate treatment or intervention.
- QT/QTcF interval prolonged

  - If at least one remarkable prolonged QT interval was observed on 12-lead ECG (eg, absolute value of QTcF intervals >500 msec or an increase >60 msec from baseline), and the investigator or sub-investigator considered inappropriate to continue the study.

- Nausea and/or vomiting

  If nausea and/or vomiting occur after the administration of TAK-123 and unacceptable nausea and/or vomiting are continuing after the administration of antiemetics.

3. Protocol deviation

The discovery after the administration of TAK-123 that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. Lost to follow-up

The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documentation.

5. Withdrawal by subject

The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

6. Study terminated by the Sponsor

The Sponsor terminates the study.

7. Other

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator or sub-investigator may discontinue a subject's study participation at any time during the study if the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator or sub-investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

7.8 Subject Replacement

This study can have a few reserve subjects considered eligible for participation in the study based on screening test. If a subject has not received TAK-123 as scheduled during the study owing to any reason occurring before the administration of TAK-123, a reserve subject will be allowed to participate in the study.

If a subject withdraws from the study after initiation of TAK-123, the subject will not be replaced with a reserve subject.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

[Test drug]

Code name: TAK-123

Dosage form and strength:

TAK-123 is an injection containing 5 g NaPA and 5 g of NaBZ per vial (50 mL).

[Premedication (concomitant drug)]

Ondansetron (product name: Ondansetron INJ 4 mg SYRINGE "HK")

Ondansetron will be provided for clinical trial use by the Sponsor. Refer to the package insert for the drug details.

8.1.1 Clinical Study Drug Labeling

Study drug labeling will show name of the study drug, quantity and storage condition of the study drug, manufacture number, expiration date, protocol number, name and address of the Sponsor, and statement the drug is for clinical trial use only.

8.1.2 Clinical Study Drug Inventory and Storage

TAK-123 is stored at 25°C with the permissible range of 15 to 30°C.

Ondansetron is stored at room temperature and protected from light.

Study drug must be kept in an appropriate, limited-access, secure place until it is used, or returned to the Sponsor or its designee. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed.

8.1.3 Clinical Study Drug Blinding

This study was designed as an open-label study since the primary objective is to characterize the PK of TAK-123.

8.1.4 Randomization Code Creation and Storage

The randomization table/schedule will not be created since TAK-123 is to be administered to all the subjects at the same dosage and administration in this study.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

Not applicable since this is an open-label study.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (a site designee) will receive the pharmacy manual created by the Sponsor, and follow the procedures for managing the Sponsor-supplied drug supplies. A copy of these procedures will be provided to the investigator as well. The manual will provide instructions on ensuring appropriate receipt, handling, storage, management, and dispensation of the Sponsor-supplied drug. The manual will also describe procedures for the collection of unused medications from the subject and their return to the Sponsor, or the destruction of any unused supplies.

The on-site pharmacist (a site designee) will immediately return any unused study drugs in a sealed package to the Sponsor after the study is closed at the study site.

9.0 STUDY PROCEDURES

The investigator or sub-investigator should collect data according to the procedures described in the following sections. For each procedure, subjects are to be assessed by the same investigator, sub-investigator or site designee whenever possible. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The requirements of informed consent are described in Section 13.2.

Informed consent must be obtained before the subject enters into the study and before any protocol-directed procedures (including the fasting for laboratory tests) are performed.

9.1.1.1 Assignment of Subject Identification Number

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

9.1.1.2 Study Drug Assignment

No study drug will be assigned in this study.

9.1.2 Inclusion and Exclusion

Each subject will be assessed according to the eligibility criteria provided in Section 7.1 and 7.2.

9.1.3 Medical History/Demography

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

Medical history to be obtained will include determining whether the subject has any clinically significant conditions or diseases that resolved within 1 year prior to the signing of informed consent. Ongoing conditions will be considered concurrent medical conditions. Medication history information to be obtained will include any medication relevant to eligibility criteria and safety evaluations stopped at or within 4 weeks (28 days) prior to the signing of informed consent.

9.1.4 Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Subjects will be asked whether they have taken any medication other than the study drug (used from the signing of informed consent through Day 8), and all medication including vitamin supplements, over-the-counter drugs, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication names, route of administrations, start and end dates, and reasons for use.

Pay attention to using the drugs which stipulated in the Section "Precautions for Co-administration" in the package insert of ondansetron.

9.2 Clinical Procedures and Assessments

Each observation and test/examination item will be performed and evaluated in accordance with the Schedule of Study Procedures in Section 3.0.

9.2.1 Full Physical Exam

A physical examination will consist of the following body systems.

(1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

9.2.2 Height and Weight

Each subject should have a height and weight measured. Height will be recorded in centimeters without decimal places (rounding off the first decimal place). Weight will be collected in kilograms (kg) with the first decimal place (rounding off the second decimal place).

9.2.3 BMI

BMI is calculated using the formula provided below. The values should be calculated to the first decimal place (rounding off the second decimal place). When the BMI is used as entry criteria, then this determination must be made after rounding. BMI will not be described in eCRF.

BMI=weight (kg)/(height [m] ×height [m])

9.2.4 Vital Signs

Vital signs will include body temperature (axilla measurement), respiratory rate, sitting blood pressure (systolic and diastolic, after resting more than 5 minutes), and pulse (beats per minute).

9.2.5 12-Lead ECG

A standard 12-lead ECG will be recorded. Subjects should be resting in a recumbent position for at least 5 minutes before each ECG measurement

The investigator or sub-investigator (or a qualified observer at the study site) will interpret the ECG using one of the following categories: normal or abnormal.

If an ECG is abnormal, the investigator or sub-investigator (or a qualified observer at the study site) will judge clinical significance of the abnormality. The time that the ECG was performed will be recorded.

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

9.2.6 Study Drug Administration

TAK-123 must be diluted with 10% glucose injection to the concentration of 400 mL/m^2 before administration, then, administered intravenously as a loading dose infusion over 90 minutes (peripheral intravenous infusion) at the dose level of 3.75 g/m^2 of NaPA and 3.75 g/m^2 of NaBZ, followed by an equivalent maintenance dose infusion over 24 hours (peripheral intravenous infusion) under the breakfast fasting condition (subjects will be fasted from at least 8 hours before the start of TAK-123 infusion to 4 hours after the start of TAK-123 infusion [see Section 7.4.1]).

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

Subjects should be resting for a period from the start of TAK-123 infusion to 2.5 hours after the start of TAK-123 infusion.

9.2.7 AE Monitoring

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

9.2.8 Laboratory Procedures and Assessments

The following laboratory tests will be conducted in the study site. Samples for laboratory tests will be collected following a minimum 8-hour fast on the days stipulated in the Schedule of Study Procedures in Section 3.0. See Appendix E for the amount of blood samples.

The investigator or sub-investigator will take responsibility for evaluation of the clinical laboratory test results and storage. The investigator will maintain a copy of the reference ranges for the laboratory used.

9.2.8.1 Clinical Laboratory Tests

Hematology

Hematology evaluations will consist of the following tests:

Red blood cell (RBC)
White blood cell (WBC)
WBC and differential (neutrophil, basophil, eosinophil, lymphocyte, and monocyte) (%)
Hemoglobin
Hematocrit
Platelet
PT/INR
aPTT

Serum Chemistry

Serum chemistry evaluations will consist of the following tests:

ALT	BUN
Albumin	Creatine kinase
ALP	GGT
AST	Potassium
Total bilirubin	Sodium
Direct bilirubin	Glucose assessed by a self-monitoring blood glucose meter (under fasting)
Total protein	Chloride
Creatinine	Calcium

Urinalysis

Urinalysis will consist of the following tests:

pH
Specific gravity
Qualitative: (Protein, glucose, occult blood, nitrite, and urobilinogen)
Sediment (RBC, WBC, and Casts)*

*Urine sediment will be performed if urinalysis is abnormal.

Other

Immunological tests	**Urine/blood**
HIV antibody and antigen tests	Blood gas measurement (pH, HCO_3^-) in venous blood
Hepatitis screen (HBs antigen, HCV antibody)	Urine drug screening (phencyclidine, benzodiazepines, cocaines, stimulants, cannabinoids, morphines, barbiturates, and tricyclic antidepressants)
Syphilis test (antibody)	

HIV: Human immunodeficiency virus, HBs: Hepatitis B surface, HCV: Hepatitis C virus
Note: The investigator or sub-investigator will report the results of "immunology" and "urine drug screening" directly to subjects. The Sponsor will confirm the overall test results ("Positive" or "All negative"), rather than detailed results, for subjects (including reserve subjects) to be administered TAK-123.

Consideration for the clinical laboratory tests

- If subjects experience an ALT or AST of >3×ULN (except the tests at Screening) after the administration of TAK-123, follow-up laboratory tests (at a minimum, ALP, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

- Refer to Section 7.6 and Section 10.2.9.5 for the discontinuation or withdrawal criteria of a subject and the appropriate guidance on reporting abnormal liver function tests as SAEs, respectively.
- The glucose test by a self-monitoring blood glucose meter will be performed by the investigator, sub-investigators or study collaborators. If subjects experience an obvious hyperglycemia (eg, fasting blood glucose >300 mg/dL) in the glucose test by a self-monitoring blood glucose meter 1.5 hours or over after the start of the TAK-123 infusion, the subjects should be carefully monitored for clinical signs and symptoms, and glucose test should be repeated after 30 minutes. Follow-up tests should be performed repeatedly until abnormality of fasting blood glucose recovers or improves.
- If subjects experience a pH <7.35 and HCO_3^- <22 mEq/L in the blood gas test after the administration of TAK-123, remeasurement should be performed after 30 minutes.

9.3 PK Sample

Primary specimen collection for PK analysis are provided in Table 9.a.

Samples for PK will be collected according to the Schedule of Study Procedures (Section 3.0). Separated procedures describe the details of sampling, handling, and transferring to central laboratory. See Appendix E for the amount of blood samples. The actual sampling time for PK analyses will be documented in the subject's source documents and eCRF.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Blood	Plasma	Plasma sample for PK analysis	Mandatory
Urine sample for PK	Urine	Urine	Urine sample for PK analysis	Mandatory

9.3.1 PK Measurements

The following PK parameters will be calculated from plasma and urine concentrations of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate), unless otherwise stated:

- AUC_{last}: Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
- AUC_{∞}: Area under the plasma concentration-time curve from time 0 to infinity
- C_{max}: Maximum observed concentration (measured values)
- t_{max}: Time of first occurrence of C_{max}
- $t_{1/2z}$: Terminal elimination half-life
- λ_z: Terminal elimination rate constant

- V_z: Volume of distribution during the terminal elimination phase (only for phenylacetate and benzoate)
- CL: Total clearance after intravenous infusion (only for phenylacetate and benzoate)

The following PK parameters will be calculated from urine concentrations of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate), unless otherwise stated:

- Ae_t: Urinary excretion amount from time 0 to t
- fe_t: Urinary excretion rate from time 0 to t

9.3.1.1 Plasma for PK Measurements

Blood samples for PK analysis of TAK-123 (NaPA and NaBZ) and these metabolites will be collected according to Table 9.b.

Table 9.b Sampling of blood samples for PK analysis

Analyzed substances	Samples	Study date	Blood sampling time (hours) Note
TAK-123 (NaPA and NaBZ) and these metabolites	Plasma	Day 1	Day 1: Predose (from the wake-up time to immediately before the start of TAK-123 infusion), 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 after the start of TAK-123 infusion

Note: If a subject is withdrawn within 48 hours after the start of the TAK-123 infusion, samples should be collected also at the early termination visit.

9.3.1.2 Urine for PK Measurements

Urine samples for measurements of TAK-123 (NaPA and NaBZ) and these metabolites will be collected according to Table 9.c.

Table 9.c Sampling of urine samples for PK analysis

Analyzed substances	Samples	Study date	Time from the start of infusion(hours)
TAK-123 (NaPA and NaBZ) and these metabolites	Urine	Day 1	Day 1: Predose (spot urine), 0 to 24 hours and 24 to 48 hours after the start of infusion

The details of the processing and shipment of samples are described in the separately prepared laboratory manual.

9.3.2 Confinement

4 days (admission on Day -1 and discharge on Day 3)

Subjects will be admitted to the study site during a period from Day -1 to Day 3 and discharged from the study site if no clinically significant abnormalities were found at the physical examinations and tests on Day 3, and confirmed by the investigator or sub-investigator.

10.0 ADVERSE EVENTS

Collection of AEs will commence at the time the subject signs the informed consent and continue until the follow-up visit (Day 8).

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily required to have a causal relationship with the treatment (including the study drug).

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

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator or sub-investigator for any reason.

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters may be considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator or sub-investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline

evaluation (eg, laboratory test, ECG, X-ray, etc.) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators or sub-investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators or sub-investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators or sub-investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study drug (TAK-123) or after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators or sub-investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study drug (TAK-123), the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

- An overdose is defined as a known deliberate or accidental administration of study drug (TAK-123), to or by a study subject, at a dose above that which is assigned to that individual

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

- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.
- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.9.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Acute liver failure
	Anaphylactic shock
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute renal failure
	Pulmonary hypertension
Malignant hypertension	Pulmonary fibrosis
Convulsive seizures (including convulsion and epilepsy)	Neuroleptic malignant syndrome / malignant hyperthermia
Agranulocytosis	Spontaneous abortion / stillbirth and fetal death
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis /Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
Hepatic necrosis	

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Section 10.2.9.3).

10.1.2 Special Interest AEs

Not applicable

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The severity/intensity for AEs are classified and defined as follows:

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

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

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

10.2.2 Assigning Causality of AEs

The relationship of each AE to study drug (TAK-123) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (TAK-123) (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug (TAK-123) and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Assigning Causality of AEs to Study Procedures

The causality of each AE to study procedures (including the ondansetron treatment) will be assessed.The causality should be assessed as Related if the investigator or sub-investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the causality should be assessed as Not Related.

10.2.4 Start Date

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

10.2.5 End Date

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

10.2.6 Pattern of Adverse Event (Frequency)

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

10.2.7 Action Taken with Study Treatment (Administration of TAK-123)

- Drug withdrawn – a study drug (administration of TAK-123) is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug (administration of TAK-123).
- Unknown – only to be used if it has not been possible to determine what action has been taken.

- Not applicable – a study drug (administration of TAK-123) was stopped for a reason other than the particular AE eg; the study has been terminated, the subject died, dosing with study drug (administration of TAK-123) had not yet started or dosing with study drug (administration of TAK-123) was already stopped before the onset of the AE.

10.2.8 Outcome

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

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

10.2.9.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up visit on Day 8. For subjects who discontinue prior to the administration of TAK-123, AEs will be followed until the subject discontinues study participation.

10.2.9.2 Reporting AEs

At each study visit, the investigator or sub-investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may

be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE prior to the first exposure to TAK-123 must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin prior to the first exposure to TAK-123, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of TAK-123 or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the treatment of TAK-123. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Investigators' opinion of the causal relationship between the event and administration of TAK-123.
- Investigators' opinion of the causal relationship between the event and the study procedure(s) (including the ondansetron treatment) (The details of study procedure(s) that may cause the event should also be provided).
- Action taken with TAK-123.
- Outcome of the event.
- Seriousness.
- Timing of occurrence (after administration of TAK-123).

10.2.9.3 Reporting SAEs

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

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

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.

- Investigator's or sub-investigator's name.
- Causality assessment.

The SAE form should be transmitted within 1 business day to the attention of the contact listed in Section 14.1.1.

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

Reporting of SAEs that begin before first administration of TAK-123 will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

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

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.9.4 Reporting Special Interest AEs

Not applicable

10.2.9.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.9.3. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.8 must also be performed.

10.2.10 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of TAK-123 or that would be sufficient to consider changes in the

administration of TAK-123 or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

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

11.1.1 Analysis Sets

In this study, the safety analysis set and the PK analysis set will be used as analysis sets. The detailed definitions of each analysis set will be separately described in the SAP.

The Sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed. If necessary, the SAP will be supplemented with new handling rules that were not discussed at the planning stage. The SAP must be finalized prior to database lock.

11.1.1.1 Safety Analysis Set

The safety analysis set will be defined as all subjects who received at least one dose of TAK-123.

11.1.1.2 PK Analysis Set

The PK analysis set will be defined as 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.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Major demographics and other baseline characteristics will be summarized using the safety analysis set.

11.1.3 PK Analysis

The following analyses will be performed in the PK analysis set.

Plasma concentrations of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate) will be summarized for each scheduled sampling time using descriptive statistics. Furthermore, plasma and urine PK parameters of phenylacetate, benzoate, and these metabolites (phenylacetylglutamine and hippurate) will be summarized using descriptive statistics.

11.1.4 Safety Analysis

The following analyses will be performed in the safety analysis set.

11.1.4.1 AEs

A TEAE is defined as an AE that occurs on or after the start of the administration of TAK-123.

The analyses of TEAEs will be conducted for the followings. TEAEs will be coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) and summarized by the System Organ Class (SOC) and the Preferred Term.

- The frequency of all TEAEs
- The frequency of TEAEs related to TAK-123
- The frequency of all TEAEs by intensity
- The frequency of TEAEs related to TAK-123 by intensity
- The frequency of TEAEs leading to TAK-123 discontinuation
- The frequency of serious TEAEs

11.1.4.2 Clinical Laboratory Evaluation

For continuous variables, the observed values and changes from baseline will be summarized for each scheduled sampling time using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled sampling time will be provided.

11.1.4.3 Vital Signs

The observed values and the changes from baseline will be summarized for each scheduled sampling time using descriptive statistics.

11.1.4.4 Other Safety Parameters

ECG parameters will be summarized as follows: For continuous variables, the observed values and changes from baseline will be summarized for each scheduled sampling time using descriptive statistics. For categorical variables, shift tables showing the number of subjects in each category at baseline and each post-baseline scheduled sampling time will be provided.

The details of statistical methods for other endpoints will be described in the SAP.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

11.3 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.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator or sub-investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator or sub-investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator or sub-investigator should consult with the Sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments [eg, the Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), the Pharmaceuticals and Medical Devices Agency of Japan (PMDA)]. If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB Approval

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

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

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

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

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator or sub-investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the Sponsor prior to use.

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

The subject must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, determines he will participate in the study, then the informed consent form must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or sub-investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator or sub-investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

13.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any

regulatory authority (eg, FDA, MHRA, PMDA), the Sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

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

The Sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it Sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with the facility name, investigator's city, country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The study sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the Sponsor.

Any investigator who objects to the Sponsor providing this information to callers must provide the Sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Trial Results Disclosure

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

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

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

14.1.2 Investigator Agreement

The investigator and Sponsor will sign the protocol or alternative document to confirm the consensus that investigator will conduct the study in compliance with the protocol.

14.1.3 Study-Related Responsibilities

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

14.1.4 List of Abbreviations

Ae_t	amount of drug excreted in urine from time 0 to time t
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ARG	arginase
ASL	argininosuccinate lyase
ASS	argininosuccinate synthetase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measurable concentration
BMI	body mass index
BUN	blood urea nitrogen
CL	total clearance after intravenous infusion
C_{max}	maximum observed concentration
CPS	carbamoylphosphate synthetase
FDA	Food and Drug Administration
fe_t	fraction of administered dose of drug excreted in urine from time 0 to time t
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HBsAg	hepatitis B virus antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus

ICH	International Council for Harmonisation
INR	international normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NaBZ	sodium benzoate
NAGS	N-acetylglutamate synthase
NaPA	sodium phenylacetate
OTC	ornithine transcarbamylase
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PT	prothrombin time
SAE	serious adverse event
SOC	System Organ Class
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment emergent adverse event
t_{max}	time of first occurrence of C_{max}
UCD	Urea Cycle Disorders
V_z	volume of distribution during the terminal elimination phase
λ_z	terminal elimination rate constant

15.0 DATA HANDLING AND RECORDKEEPING

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

15.1 eCRFs

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

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

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded in the eCRF:

- Laboratory results (including blood gas tests and glucose test by a self-monitoring blood glucose meter)
- Drug concentration measurement results

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

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

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all

participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 (Section 4.9.5) requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 (Section 4.9.5) states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the Sponsor before disposing of any such documents.

16.0 REFERENCES

1. Japanese Society for Inherited Metabolic Diseases. Diagnostic criteria for urea cycle disorders. Revised on November 25 2013.
2. Health and Labour Sciences Research Grants in FY 2012 Shared research report of "Research on registration, management, analysis, and information provision of specific pediatric chronic diseases". Registration of research on treatment for specific pediatric chronic diseases in Japan in FY 2011.
3. AMMONUL- sodium phenylacetate and sodium benzoate injection, solution, concentrate [pre scribing information]. USA: Ucyclyd Pharma Inc., 2018 Jan.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

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

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Subjects must use highly effective contraception (as defined in the informed consent) from the beginning of screening throughout the duration of the study and for 91 days after the last dose of TAK-123.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 91 days after last dose of TAK-123, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception. In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:

    - Non-Hormonal Methods:
        - Intrauterine device (IUD).
        - Bilateral tubal occlusion.
        - Vasectomised partner (the vasectomised partner has received medical assessment of the surgical success).
    - Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method.

  - Combined pill (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
  - Contraceptive pill (combined hormonal contraception)

2. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
   - Sexual abstinence is NOT an acceptable method of contraception.
3. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Is there a chance your partner could be pregnant?

Pregnancy

If any pregnancies in the partner of a male subject during the study or for 91days after the last dose of TAK-123, should also be recorded following authorization from the subject's partner.

If the female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies in female partners of male subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after the birth of the child will also be conducted.

Appendix E Acceptable Time Window for Study Procedure

Specified in the protocol		Acceptable window
Variables	Timing of procedures	
Demographics, medical history, and medication history	Screening	Days -28 to -2
Immunology tests and urine drug screen	Screening	Days -28 to -2
Physical examination	Screening	Days -28 to -2
	Day -1	The day before the study drug administration
	Day 1 predose of TAK-123	From awakening to immediately prior to dose
	4 hours postdose of TAK-123	Within ± 60 minutes
	25.5 hours postdose of TAK-123	Within ± 60 minutes
	48 hours postdose of TAK-123	Within ± 60 minutes
	Day 8	± 1 day
Height	Screening	Days -28 to -2
Weight	Screening	Days -28 to -2
	Day 1 predose of TAK-123	From awakening to immediately prior to dose
	48 hours postdose of TAK-123	Within ± 60 minutes
	Day 8	± 1 day
Vital signs (body temperature, sitting blood pressure, respiratory rate, sitting pulse rate)	Screening	Days -28 to -2
	Day 1 predose of TAK-123	From awakening to immediately prior to dose
	1.5 hours postdose of TAK-123	Within ± 15 minutes
	4 hours postdose of TAK-123	Within ± 60 minutes
	25.5 hours postdose of TAK-123	Within ± 60 minutes
	48 hours postdose of TAK-123	Within ± 60 minutes
	Day 8	± 1 day
12-lead ECG	Screening	Days -28 to -2
	Day 1 predose of TAK-123	From awakening to immediately prior to dose
	1.5 hours postdose of TAK-123	Within ± 15 minutes
	48 hours postdose of TAK-123	Within ± 60 minutes
	Day 8	± 1 day

Specified in the protocol		Acceptable window
Variables	Timing of procedures	
Clinical laboratory tests	Screening	Days -28 to -2
	Day -1	The day before the study drug administration
	1 hour postdose of TAK-123 (glucose assessed by a self-monitoring blood glucose meter only)	Within ± 15 minutes
	1.5 hours postdose of TAK-123 (Na, K, Cl, glucose assessed by a self-monitoring blood glucose meter only)	Within ± 15 minutes
	25.5 hours postdose of TAK-123	Within ± 60 minutes
	48 hours postdose of TAK-123	Within ± 60 minutes
	Day 8	± 1 day
Blood gas tests	Day -1	The day before the study drug administration
	1.5 hours postdose of TAK-123	Within ± 5 minutes
	25.5 hours postdose of TAK-123	Within ± 60 minutes
PK blood collection	Day 1 predose of TAK-123	From awakening to immediately prior to dose
	0.25, 0.75, 1.5 ,2.5 hours postdose of TAK-123	Within ± 3 minutes
	4.5, 6.5, 8.5, 10.5, 12.5, 16.5 hours postdose of TAK-123	Within ± 5 minutes
	25.5, 26, 26.5, 27 hours postdose of TAK-123	Within ± 3 minutes
	27.5, 28, 28.5, 29.5, 30.5, 32.5, 48 hours postdose of TAK-123	Within ± 5 minutes
PK urine collection	Day 1 predose of TAK-123 (spot)	From awakening to immediately prior to dose
	0 to 24 hours postdose of TAK-123	Not applicable
	24 to 48 hours postdose of TAK-123	Not applicable

Whole blood volume collected from each subject is indicated below.

Blood Volume Table

Sample Type	Sample Volume (mL)	Number of Samples		Total Volume (mL)
		Screening	Treatment	
Safety laboratory samples (hematology, serum chemistry), Blood gas tests, and Immunology tests	5 - 9.8	1	5	51
PK samples	2	-	22	44
Total Blood Sampling Volume (approximately)				95

In addition, the volume of blood sampling by self-meter for blood glucose: 0.8 µL/time (3 times in total)