Clinical Study Protocol

NCT Number: NCT05543187

Title: An Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of TAK-625 in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis

Study Number: TAK-625-3002

Document Version and Date: Amendment 2 / 08-Dec-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL

An Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of TAK-625 in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis

Short Title

TAK-625 for the Treatment of Progressive Familial Intrahepatic Cholestasis (PFIC)

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan 540-8645		
Study Number:	TAK-625-3002		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-625		
Date:	08 Dec 2022	**Version/Amendment Number:**	Amendment 02

Amendment History:

Date	Amendment Number	Amendment Type	Region
08 Dec 2022	02	Substantial	All sites
15 Jul 2022	01	Nonsubstantial	All sites
19 Apr 2022	Initial version	Not applicable	All sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

A separate contact information list will be provided to each site (see the annexes).

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual subjects in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.
- "Ministerial Ordinance Concerning the Standards for the Conduct of Clinical Trials of Medicinal Products" (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997; hereinafter referred to as "the GCP Ordinance").
- "Ministerial Ordinance that Partially Revises the Ministerial Ordinance Concerning the Standards for the Conduct of Clinical Trials of Medicinal Products" (hereinafter referred to as "the revised GCP Ordinance").
- Pharmaceutical Affairs Law.

After the marketing approval of TAK-625 is obtained in Japan, this study can be continued as a post-marketing clinical study in accordance with Good Post-marketing Study Practice for medical products (MHLW Ordinance No. 171, 20 December 2004) in addition to above.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories, as applicable can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

[redacted] Date

[redacted] Date [redacted] Date

INVESTIGATOR AGREEMENT

I confirm that I have read and understand this protocol, the investigator's brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, life, dignity, integrity, confidentiality of personal information, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator as described in this protocol.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a potential participant to obtain their informed consent to participate.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

_____ _____
Signature of Investigator Date

_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State/Province)

_____
Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes

This section describes the changes in the protocol amendment 02.

The primary reasons for this amendment are to:

- Revise the lower age limit for enrollment in this study from 1 year of age to 1 month of age based on the results of an interim analysis of Study MRX-801.
- Provide the status and results of an interim analysis of Study MRX-801 in subjects <12 months of age with Alagille syndrome (ALGS) or PFIC.
- Provide the detailed information on the administration of concomitant sodium phenylbutyrate.
- Provide the exceptions in procedures of blood sampling for subjects who are too small to collect enough amount of blood.
- Update the table of sample daily exposure.
- Provide the procedures of dilution of study drug for infants with a body weight <5 kg.
- Clarify the fasting time before blood sampling.
- Clarify the procedures of clinical laboratory tests.
- Add vitamin K to clinical symptoms of lipid soluble vitamin (LSV) deficiency.
- Any minor changes (grammatical and editorial changes, correction of inconsistencies, clerical errors, and typographical errors) are included for clarification purposes only.

The following is a summary of the changes made in this amendment.

Protocol Amendment 02		
Summary of Changes		
Sections (on the current version) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
• Section 4.1.3 Key Clinical Experience	Updated the text "one study, MRX-501, completed and the other, MRX-502 is ongoing outside Japan" to "mainly one phase 2 study, MRX-501, has been completed and the other, one phase 3 study, MRX-502, is ongoing outside Japan".	Description adjustment: to clarify the status/situation of clinical experiences.
• Section 4.1.3 Key Clinical Experience	Added the text "In addition, one phase 2 study, MRX-801, is ongoing outside Japan for patients <12 months of age with ALGS or PFIC."	To provide the information on Study MRX-801 for patients <12 months of age with ALGS or PFIC.

Protocol Amendment 02		
Summary of Changes		
Sections (on the current version) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
• Section 4.1.3.1 Pharmacokinetics in Clinical Studies	Added the text "In addition, the mean (standard deviation [SD]) 2.5 hours after dosing TAK-625 concentration was 0.54 (0.62) ng/mL in subjects <12 months of age with ALGS. This low TAK-625 concentraion result is consistent with previous result in subjects ≥12 months of age who were administered TAK-625."	To provide the PK result in subjects <12 months of age with ALGS enrolled in Study MRX-801.
• Section 4.1.3.3 Study MRX-801 (Phase 2 Study)	Added a section to describe the results summary of an interim analysis of Study MRX-801.	To provide the results of an interim analysis of Study MRX-801.
• Section 4.2 Rationale for the Proposed Study	Added descriptions on the rationale for the enrollment of patients ≥1 month of age in this study.	To revise the lower age limit for enrollment (inclusion criteria) based on the results of an interim analysis of Study MRX-801.
• Section 5.2.4 Exploratory Efficacy Endpoints • Section 9.1.7.2 Serum Bile Acids and Other Cholestasis Biomarkers • Section 9.1.11 Procedures for Clinical Laboratory Samples (Table 9.a) (Footnote a) • [redacted] • [redacted]	Added a note "* FGF-19 and autotaxin are not mandatory, if the subjects are too small to collect enough amount of blood."	To clarify the exceptions for laboratory tests in subjects who are too small to collect enough amount of blood.
• Section 6.1 Study Design • Section 2.0 Study Summary (Subject Population)	Revised the age of defined study population of this study from "1 year of age or older" to "1 month of age or older".	To revise the lower age limit for enrollment (inclusion criteria) based on the results of an interim analysis of Study MRX-801.

Protocol Amendment 02		
Summary of Changes		
Sections (on the current version) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
• Section 6.2 Justification for Study Design, Dose, and Endpoints (Justification for Study Population)	Added the text "Although the safety of TAK-625 was confirmed in subjects <12 months of age with ALGS with moderate to severe cholestasis enrolled in Study MRX-801, the lower age limit for enrollment in this study is set to be 1 month of age, in consideration of preventing the patients from being exposed to the amount of PG in TAK-625 over the maximum daily dose limit of PG specified in the guidance by the EMA."	To revise the lower age limit for enrollment (inclusion criteria) based on the results of an interim analysis of Study MRX-801.
• Section 6.2 Justification for Study Design, Dose, and Endpoints (Justification for Dose and Regimen of Study Drug)	Removed the words "(ie, µg/kg)" from the text "TAK-625 is provided as an oral solution that is dosed on a weight basis (ie, µg/kg)".	Description adjustment.
• Section 6.2 Justification for Study Design, Dose, and Endpoints (Justification for Dose and Regimen of Study Drug)	Updated the wording "1 year of age" to "12 months of age" before the words "on treatment for over 5 years".	Description adjustment.
• Section 6.2 Justification for Study Design, Dose, and Endpoints (Justification for Dose and Regimen of Study Drug)	Added the text "Although the efficacy results in infants <12 months of age with PFIC are not yet available, improvements in pruritus and sBA were observed and the safety of TAK-625 was confirmed in infants <12 months of age with ALGS in the ongoing Study MRX-801, in which infants <12 months of age with ALGS or PFIC had been enrolled."	To provide the results of an interim analysis of Study MRX-801 and to clarify that the results in subjects with PFIC in Study MRX-801 are not yet available.
• Section 6.2 Justification for Study Design, Dose, and Endpoints (Justification for Dose and Regimen of Study Drug)	• Updated the weight range from "5 to 70 kg" to "3 to 70 kg" in the text referencing Table 6.a. • Added sample daily exposure for weight of 3 kg in Table 6.a.	To provide the sample daily exposure for weight of 3 kg based on the revision of inclusion criteria #2 of this study.

Protocol Amendment 02		
Summary of Changes		
Sections (on the current version) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
• Section 7.1 Inclusion Criteria (Inclusion Criteria #2) • Section 2.0 Study Summary (Main Criteria for Inclusion)	• Revised the lower weight limit from ≥5 kg to ≥3 kg. • Revised the lower age limit from ≥1 year of age to ≥1 month of age. • Added the text that defined the gestational age and postmenstrual age for subjects <12 months of age.	• To revise the lower weight limit for enrollment in this study from ≥5 kg to ≥3 kg. • To revise the lower age limit for enrollment in this study from ≥1 year of age to ≥1 month of age. • To provide the gestational age and postmenstrual age for subjects <12 months of age.
• Section 7.1 Inclusion Criteria (Inclusion Criteria #4) • Section 2.0 Study Summary (Main Criteria for Inclusion) • Section 9.1.2 Eligibility Assessment • Section 9.3.1 Screening Period	Added the text "Since it is difficult to evaluate pruritus in infants, subjects <12 months of age at screening whose pruritus is unavoidably difficult to be evaluated are not necessarily required to meet the above score."	To revise the lower age limit for enrollment in this study from ≥1 year of age to ≥1 month of age.
• Section 7.1 Inclusion Criteria (Inclusion Criteria #6) • Section 2.0 Study Summary (Main Criteria for Inclusion)	Added the note "(*≤6 months is acceptable for subjects <12 months of age)" to the words "Chronic cholestasis as manifested by persistent (>6 months) pruritus".	To clarify the exception for period of persistence of pruritus for patients <12 months of age.
• Section 7.5.1.2 Permitted Concomitant Medications, Procedures, and Treatments	Added the information on the temporary dose adjustments and dose adaptations of sodium phenylbutyrate.	To provide the detailed information on the administration of concomitant sodium phenylbutyrate.

Protocol Amendment 02		
Summary of Changes		
Sections (on the current version) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
• Section 7.5.2 Diet, Fluid, and Activity Control • Section 8.1.1.1 Study Drug • Section 8.1.3 Dose and Regimen • [redacted]	Added the information on the at-home dilution of study drug for infants with a body weight <5 kg.	To provide the necessity of dilution of study drug for infants with a body weight <5 kg and to provide the procedures of the dilution.
• Section 7.5.2 Diet, Fluid, and Activity Control • Section 9.1.7.2 Serum Bile Acids and Other Cholestasis Biomarkers • [redacted] • [redacted]	Amended the texts that defined the fasting time before blood sampling.	To clarify the fasting time and to add the required fasting time for subjects <12 months of age.
• Section 8.1.1.1 Study Drug	Removed the word "TAK-625" from "(TAK-625; formerly maralixibat, SHP625, LUM001)".	Description adjustment.
• Section 8.1.1.2 Packaging	Removed the words "and bottle adapters (if needed)". Added the text "Bottle adapters and equipment for at-home dilution will also be supplied where required."	To clarify the operating procedure.
• Section 9.1.11 Procedures for Clinical Laboratory Samples (Table 9.a)	• Removed footnote "a" from "Lipid Panel", "Cholestasis Biomarkers", "and Lipid Soluble Vitamins". • Added footnote "b" for RBP.	To move the footnote for "Lipid Panel", "Cholestasis Biomarkers", "and Lipid Soluble Vitamins" to Appendix B, and to provide the explanation on the measurement of RBP for subjects <12 months of age.

Protocol Amendment 02		
Summary of Changes		
Sections (on the current version) Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
• Section 9.1.20.1 Collection of Blood for PK Sampling • [redacted] • [redacted]	Added the text "Postdose PK samples should be collected in preference to predose PK samples, if the subjects are too small to collect enough amount of blood."	To clarify the operating procedure.
• Section 10.4.5 Safety Monitoring for LSVs	Added the words "(refer to Appendix B)" after the text "blood samples will be obtained at the study visit before the daily dose of vitamins is administered".	To clarify the operating procedure.
• Section 10.4.5 Safety Monitoring for LSVs	Added "vitamin K" to the clinical symptoms of LSV deficiency.	To clarify the clinical symptoms of LSV deficiency.
[redacted]		

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Pharmaceutical Company Limited	**Compound:** TAK-625	
Title of Protocol: An Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of TAK-625 in the Treatment of Subjects with Progressive Familial Intrahepatic Cholestasis	**IND No.:** Not Applicable.	**EudraCT No.:** Not Applicable.
Study Number: TAK-625-3002	**Phase:** 3	

Study Design:

This is a phase 3, multicenter, open-label, uncontrolled study to evaluate the efficacy and safety of TAK-625 in the treatment of Japanese subjects with progressive familial intrahepatic cholestasis (PFIC).

- Screening Period (up to 6 weeks prior to the Study Administration):

In the screening period, for subjects who do not have documentation of mutation related with PFIC, a blood sample will be obtained for genotyping. Subjects diagnosed with PFIC2 (non-truncating PFIC2 [nt-PFIC2]) will be enrolled in the primary cohort and those with other types of PFIC will be enrolled in the supplemental cohort. The electronic Diary (eDiary) for assessing pruritus with the Itch Reported Outcome (ItchRO) instrument will be dispensed and subjects and caregivers will undergo training during the screening visit.

- Dose Escalation Period: (4 weeks [up to 6 weeks]: Week 0 to 4 [6]):

In the dose escalation period, at the baseline visit (Week 0/Visit 2), subjects will be assessed to confirm continued study eligibility and undergo a physical examination including body weight, height, body mass index (BMI), and vital signs, and have urine and blood samples taken for hematology, chemistry, fasting lipid panel, baseline levels of serum bile acid (sBA) and other cholestasis biochemical markers. Compliance with ItchRO will be assessed. Study drug will be supplied at each visit (Week 0/Visit 2, Week 2/Visit 3, and Week 4/Visit 4). The subject contacts (phone calls) will be conducted at Weeks 1 and 3. The dose is increased weekly, 150 µg/kg, 300 µg/kg, 450 µg/kg, and 600 µg/kg, twice daily (BID).

Dose escalation should occur in the absence of major safety (eg, liver parameters and lipid soluble vitamin [LSV] deficiency) or tolerability concerns (eg, gastrointestinal [GI]-related TEAEs) related or possibly related to study drug. Subjects with such safety concerns can be down-titrated to a lower, previously tolerated dose level for 1 week before continuing dose escalation. The minimum dose to continue in the study will be 150 µg/kg, BID; subjects who cannot tolerate this dose will be discontinued from the study. The dose escalation period is allowed to be extended up to 6 weeks depending on the safety or tolerability concerns.

- Stable Dosing Period (44 weeks: Week 5 to 48):

After the dose escalation period, each subject will continue dosing with study drug at the Week 4 or Week 6 dose level (the maximum tolerated dose [MTD] level) in the stable dosing period. Subjects will return to the study site at Weeks 6, 10, 14, 18, 22, 26, 28, 32, 36, 40, 44, and 48 and undergo physical examinations. Subject contacts (phone calls) will be conducted as appropriate throughout the stable dosing period. Subjects and caregivers will continue twice daily completion of their ItchRO throughout the period.

- Follow-up Dosing Period (after Week 48):

Additionally, in the follow-up dosing period, each subject will continue dosing with study drug. The safety evaluation will be performed in all the subjects every 12 weeks from Week 48 visit until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication. Bile acids and ItchRO will be measured to evaluate the long-term effectiveness of TAK-625. For subjects discontinuing early, safety follow-up will be conducted.

- Safety Follow-up (after Final Visit/Early Termination [ET]):

Subjects/caregivers will have a final safety follow-up subject contact (phone call) 7 days after the final study visit or ET visit (except for screen failure).

Primary Objectives:

- To evaluate the efficacy of TAK-625 in the primary cohort.
- To evaluate the safety of TAK-625 in subjects with PFIC.

Secondary Objectives:

- To evaluate the efficacy of TAK-625 in subjects with PFIC.
- To evaluate the pharmacokinetics (PK) of TAK-625 in subjects with PFIC.

Subject Population: Japanese subjects with PFIC who are 1 month of age or older. Subjects diagnosed with PFIC2 due to adenosine triphosphate (ATP) Binding Cassette Subfamily B Member 11 (ABCB11) mutation that predicts residual bile salt excretion pump (BSEP) function (nt-PFIC2) will be enrolled in the primary cohort. Subjects with other PFIC subtypes (eg, truncating PFIC2 [t-PFIC2], PFIC1/3/4, or other PFIC mutation variants) or postsurgical subjects (eg, internal or external biliary diversion surgery) will be enrolled in the supplemental cohort.

Number of Subjects:	**Number of Sites:**
The primary cohort (nt-PFIC2): up to approximately 3 subjects. The supplemental cohort (other types of PFIC): up to approximately 6 subjects.	Estimated total: approximately 10 sites in Japan.
Dose Levels: • Dose Escalation period: The dose escalation period will consist of the following weekly steps: – Dose level 1: 150 µg/kg TAK-625, BID for 1 week – Dose level 2: 300 µg/kg TAK-625, BID for 1week – Dose level 3: 450 µg/kg TAK-625, BID for 1 week – Dose level 4: 600 µg/kg TAK-625, BID for the remaining duration of the study • Stable Dosing Period: After the dose escalation period, each subject will continue dosing with study drug at the Week 4 or Week 6 dose level (the MTD level) in the stable dosing period. • Follow-up Dosing Period: After the stable dosing period, each subject will continue dosing with study drug at the Week 4 or Week 6 dose level (the MTD level).	**Route of Administration:** Oral

Duration of Treatment:	**Period of Evaluation:**
• Dose Escalation Period: 4 weeks (up to 6 weeks). The dose escalation period is allowed to be extended up to 6 weeks depending on the safety or tolerability concerns. • Stable Dosing Period: 44 weeks. • Follow-up Dosing Period: until TAK 625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication.	• Screening Period: up to 6 weeks. • Dose Escalation Period: 4 weeks (up to 6 weeks). • Stable Dosing Period: 44 weeks. • Follow-up Dosing Period: every 12 weeks after the stable dosing period until TAK 625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication. • Safety Follow-up (phone call): 7 days after the final study visit or ET visit (except for screen failure).

Main Criteria for Inclusion:

The main criteria for inclusion in this study are as follows:

- The subject is Japanese male or female with a body weight ≥3.0 kg and who is ≥1 month of age at the time of informed consent.
  For subjects <12 months of age, gestational age ≥36 weeks at birth. For subjects born with gestational age between 32 and 36 weeks, a postmenstrual age of ≥36 weeks is required. Postmenstrual age is defined as the time elapsed between the first day of the last menstrual period and birth plus the time elapsed after birth.
- The subject has a cholestasis as manifested by total sBA ≥3× upper limit of the normal range (ULN) (applies to the primary cohort only).
- The subject has an average morning observer-reported Itch Reported Outcome (ItchRO [Obs]) score ≥1.5 during 4 consecutive weeks of the screening period, leading to the baseline visit (Week 0/Visit 2). Since it is difficult to evaluate pruritus in infants, subjects <12 months of age at screening whose pruritus is unavoidably difficult to be evaluated are not necessarily required to meet the above score.
- The caregiver has completed at least 21 valid* morning ItchRO (Obs) entries during 4 consecutive weeks of the screening period, leading to the baseline visit (Week 0/Visit 2) (*valid=completed and not answered as "I don't know"; the maximum allowed invalid reports=7, no more than 2 invalid reports during the last 7 days before the baseline visit [Week 0/Visit 2]).
- The subject has a diagnosis of PFIC based on:
  Chronic cholestasis as manifested by persistent (>6 months*) pruritus in addition to biochemical abnormalities and/or pathological evidence of progressive liver disease (*≤6 months is acceptable for subjects <12 months of age).
  And
  Primary cohort:
  - The subject has a genetic testing result consistent with disease-causing variation in ABCB11 (PFIC2), based on a genotyping.

  Supplemental cohort:
  - The subject has a genetic testing results consistent with disease causing variation in ATPase Phospholipid Transporting 8B1 (ATP8B1) (PFIC1), ATP Binding Cassette Subfamily B Member 4 (ABCB4) (PFIC3), or tight junction protein 2 gene (TJP2) (PFIC4), based on a genotyping.
  - The subject has a PFIC phenotype without a known mutation or with another known mutation not described above.
  - The PFIC subject has internal or external biliary diversion surgery history, and the internal or external biliary diversion surgery was reversed.

Main Criteria for Exclusion:

The main criteria for exclusion in this study are as follows:

- The diagnosed with PFIC2 due to ABCB11 mutation that predicts complete absence of BSEP function due to the type of ABCB11 mutation (t-PFIC2), based on a genotyping (applies to the primary cohort only). The subject may enter the study in the supplemental cohort.
- The subject has a diagnosis of benign recurrent intrahepatic cholestasis indicated by a history of intermittent cholestasis with no disease progression.
- The subject has a current or recent history (<1 year) of atopic dermatitis or other non-cholestatic diseases associated with pruritus.
- The subject has a previous history of surgical interruption of the enterohepatic circulation (applies to the primary cohort only).
- The subject with chronic diarrhea requiring intravenous (IV) fluid or nutritional intervention and/or its sequelae at screening or during the 6 months prior to screening.
- The subject has a history of liver transplant or currently requires imminent liver transplant.
- The subject with decompensated cirrhosis (international normalized ratio [INR] >1.5, and/or albumin <30 g/L, history, or presence of clinically significant ascites, and/or variceal hemorrhage, and/or encephalopathy).
- The subject has an alanine aminotransferase (ALT) or total serum bilirubin (TSB) level >15× ULN at screening.
- The subject has other liver disease.
- The subject has any other disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs, including bile salt metabolism in the intestine (eg, inflammatory bowel disease), per investigator discretion.
- The subject has received bile acid, lipid binding resins or ileal bile acid transporter (IBAT) inhibitors within 28 days prior to screening and throughout the trial.
- The subject who has received sodium phenylbutyrate for less than 6 months at the initiation of screening.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is change in the average morning ItchRO (Obs) severity score between baseline and average of Week 15 through Week 26. Key secondary endpoints for this study are change in the average morning ItchRO (Obs) frequency score between baseline and average of Week 15 through Week 26, and change in total sBA between baseline and Week 26. Secondary endpoints for this study are proportion of subjects who experience an sBA control (defined as a reduction to <102 µmol/L, or a reduction of >75%, or normalization) from baseline through Week 26, and change in the ItchRO (Obs) weekly average severity (based on daily maximum of morning and evening severity scores) between baseline and average of Week 15 through Week 26.

Statistical Considerations:

The primary, key secondary and other secondary endpoints will be mainly evaluated in the primary cohort.

Analytical Methods for Primary Endpoint

Primary Analysis: Descriptive statistics and two-sided 95% confidence interval (CI) of mean will be provided on the primary cohort in the intention-to-treat set (ITT).

Secondary Analysis: For supportive analysis, the same analysis as the primary analysis will be performed on the primary cohort in the per protocol analysis set (PPS) to confirm robustness of the results.

Other Analysis: The same analysis as the primary analysis will also be performed in the ITT population separately on the overall supplemental cohort, all cohorts combined, and in the PFIC1 and PFIC3 sub-cohorts (separately) given sufficient sample size.

Analytical Methods for Key Secondary Endpoints

Descriptive statistics and two-sided 95% CI of mean will be provided on the primary cohort in the ITT. For supportive analysis, the same analysis as the above analysis will be performed on the primary cohort using the PPS to confirm robustness of the results.

The same analysis as the above analysis will also be performed in the ITT population separately on the overall supplemental cohort, all cohorts combined, and in the PFIC1 and PFIC3 sub-cohorts (separately) given sufficient sample size.

Analytical Methods for Secondary Endpoints

For continuous endpoints, descriptive statistics and two-sided 95% CI of mean will be provided on the primary cohort in the ITT. For binary endpoints, frequency distribution will be provided on the primary cohort in the ITT with proportion and the two-sided 95% CI.

The same analysis as the above analysis will also be performed in the ITT population separately on the overall supplemental cohort, all cohorts combined, and in the PFIC1 and PFIC3 sub-cohorts (separately) given sufficient sample size.

Sample Size Justification:

PFIC is a rare disease. The targeted sample size of the primary cohort is approximately 3 subjects, and that of the supplemental cohort is approximately 6 subjects, based on enrollment feasibility of this population in Japan, rather than power calculation.

3.0 LIST OF ABBREVIATIONS

ABCB4	ATP Binding Cassette Subfamily B Member 4
ABCB11	ATP Binding Cassette Subfamily B Member 11
AE	adverse event
AECI	adverse event of clinical interest
AFP	α-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ALGS	Alagille syndrome
ANA	antinuclear antibody
APRI	AST to platelet ratio index
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
ATP8B1	ATPase Phospholipid Transporting 8B1
AUC	area under the curve
7αC4	7α-hydroxy-4-cholesten-3-one
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BSEP	bile salt excretion pump
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
C_{max}	maximum drug concentration
CMV IgM	cytomegalo virus immunoglobulin M
COA	clinical outcomes assessment
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRO	contract research organization
CSR	clinical study report
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced livery injury
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary

EMA	European Medicines Agency
EOT	end of treatment
ET	early termination
EU	European Union
fBA	fecal bile acid
FDA	Food and Drug Administration
FGF-19	fibroblast growth factor 19
FIB-4	fibrosis-4
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HAV IgM	hepatitis A virus immunoglobulin M
HBs Ag	hepatitis B virus surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL-C	high density lipoprotein-cholesterol
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IB	investigator's brochure
IBAT	ileal bile acid transporter
IC_{50}	half maximal (50%) inhibitory concentration
ICH	International Council for Harmonisation
ID	identification
INR	international normalized ratio
IRB	institutional review board
IRT	Interactive Response Technology
ItchRO	Itch Reported Outcome
ItchRO (Obs)	Observer-reported Itch Reported Outcome Itch Reported Outcome (Observer) (Observer-reported outcome, observer rated Itch Reported Outcome)
ItchRO (Pt)	Patient-reported Itch Reported Outcome Itch Reported Outcome (Patient) (Patient-reported outcome, patient rated Itch Reported Outcome)
ITT	intention-to-treat set
IUD	intrauterine device
IV	intravenous
LC-MS	liquid chromatography-mass spectrometry
LC-MS/MS	liquid chromatograph-tandem mass spectrometer
LDH	lactate dehydrogenase
LDL-C	low density lipoprotein-cholesterol

LOQ	lower limit of quantification
LSV	lipid soluble vitamin
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MYO5B	myosin VB
NR1H4	nuclear receptor subfamily 1 group H member 4
nt-PFIC2	non-truncating PFIC2
PEBD	partial external biliary diversion
[redacted]	[redacted]
PET	polyethylene terephthalate
PFIC	progressive familial intrahepatic cholestasis
PG	propylene glycol
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per protocol analysis set
PRO	patient reported outcome
PT	prothrombin time
q12h	every 12 hours
QD	once a day
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RBP	retinol binding protein
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TG	triglycerides
TJP2	tight junction protein 2 gene

t-PFIC2	truncating PFIC2
TSB	total serum bilirubin
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

3.1 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

3.2 Study Definitions

Terms	**Definitions**
Duration of Treatment and Duration of Follow-up	The study will be continued until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication.
End-of-Trial	The study completion date is defined as the date when the final subject, across all sites, completes their final protocol-defined assessment.
Primary cohort	Subjects diagnosed with progressive familial intrahepatic cholestasis 2 (PFIC2) due to adenosine triphosphate (ATP) Binding Cassette Subfamily B Member 11 (ABCB11) mutation that predicts residual bile salt excretion pump (BSEP) function (non-truncating PFIC2 [nt-PFIC2]) will be enrolled in the primary cohort. (Subjects diagnosed with PFIC2 due to ABCB11 mutation that predicts complete absence of BSEP function [truncating PFIC2; t-PFIC2] are excluded from the primary cohort and can be enrolled only in the supplemental cohort.)
Supplemental cohort	Subjects diagnosed with other PFIC subtypes (eg, t-PFIC2, PFIC1/3/4, or other PFIC mutation variants) or postsurgical subjects (eg, internal or external biliary diversion surgery) will be enrolled in the supplemental cohort.

4.0 INTRODUCTION

4.1 Background

4.1.1 Drug Overview

Ileal bile acid transporter (IBAT) is a transmembrane protein localized on the luminal surface of enterocytes in the terminal ileum and plays a key role in the enterohepatic circulation of bile acids by reabsorbing bile acids. TAK-625 (maralixibat) was designed to be minimally absorbed, therefore maximizing the local exposure of the molecule to the receptor and minimizing systemic exposure of the drug and limiting drug-drug interactions and systemic toxicity. These characteristics include a high molecular weight of 710 Da and the addition of a positively charged quaternary amino moiety that can interact with the negatively charged surface of the enterocyte cell membrane and prevent absorption. TAK-625, a highly potent and selective IBAT inhibitor (half maximal (50%) inhibitory concentration [IC_{50}]=0.3 nmol/L), inhibits intestinal bile acids reabsorption, thereby increasing fecal bile acid (fBA) excretion and lowering serum bile acid (sBA) levels without systemic exposure.

By virtue of its ability to interrupt enterohepatic circulation by inhibiting bile acid absorption, TAK-625 is being developed as a therapeutic agent for signs and symptoms of cholestatic liver disease. In September 2021, TAK-625 was approved in the United States (US) for the treatment of pruritus associated with Alagille syndrome (ALGS). Clinical studies for progressive familial intrahepatic cholestasis (PFIC) and biliary atresia are currently ongoing outside Japan.

TAK-625 is provided as an oral solution and will be prescribed to a given subject based on body weight (µg/kg). This is the standard dosing regimen for pediatric patients and is supported by clinical experience in development programs for pediatric cholestatic liver disease.

4.1.2 Disease Background

PFIC is an autosomal recessive liver disorder characterized by intrahepatic cholestasis due to defects in bile transportation from hepatocytes to bile canaliculi. Its estimated prevalence is between 1/50,000 and 1/100,000 births [1]. In Japan, only about 5 patients are newly enrolled for PFIC in the Medical Aid Program for Chronic Pediatric Diseases of Specified Categories each year [2].

PFIC is categorized into several subtypes, including the main subtypes PFIC1, PFIC2, and PFIC3, caused by mutations in the genes adenosine triphosphatease (ATPase) Phospholipid Transporting 8B1 (ATP8B1), ATP Binding Cassette Subfamily B Member 11 (ABCB11), and ATP Binding Cassette Subfamily B Member 4 (ABCB4), respectively [3]. Five/ten-year native liver survival was 73/51% in PFIC1 and 61/45% in PFIC2 patients. Also, in patients with PFIC2, native liver survival is only 33% at 18 years, overall [4].

PFIC2 is further categorized into non-truncating PFIC2 (nt-PFIC2) with residual bile salt excretion pump (BSEP; protein encoded by ABCB11) function and truncating PFIC2 (t-PFIC2) with no residual BSEP function. In a previous study, MRX-501, TAK-625 was effective in subjects with nt-PFIC2.

Among clinical symptoms of PFIC, pruritus can be severe, even in the absence of jaundice. Elevation of sBA is frequently accompanied by pruritus, and a causal association between pruritus and bile acids is suggested by the following: (1) pruritus can be induced in volunteers by applying topical unconjugated bile acids, deoxycholate and chenodeoxycholate to the skin; and (2) pruritus can be relieved by surgical interruption of the enterohepatic circulation, which dramatically lowers sBA.

Intractable and pharmacologically recalcitrant pruritus is one of the major morbidities afflicting children with PFIC. Treatment with anti-pruritics and bile salt resins may provide partial relief of pruritus for children with PFIC, but currently available pharmacologic approaches are of limited value. Interruption of the entero-hepatic circulation of bile acids through partial external biliary diversion (PEBD) surgery can lead to promising results with respect to pruritus, jaundice, and histology, both in patients with PFIC1 and PFIC2. Schukfeh, et al. reported a dramatic improvement in 1-year outcome in patients undergoing PEBD with 13/21 (62%) of patients normalizing sBAs and liver function [5].

In July 2021, odevixibat (IBAT inhibitor) was approved in the European Union (EU) and the US for the treatment of pruritus in patients with PFIC. There is no other drug approved for PFIC at this time in the EU or the US. Importantly, there are no approved drugs for PFIC in Japan. Since reduction in bile acid concentrations with PEBD has been shown to be associated with improvement in cholestatic pruritus in PFIC, pharmacological diversion of bile acids with an IBAT inhibitor could be an attractive alternative to surgical intervention in PFIC without surgical complications. TAK-625 potentially reduces cholestasis due to PFIC and the related effects of cholestatic pruritus, xanthomas, and growth deficiency by above mechanism.

4.1.3 Key Clinical Experience

For subjects with PFIC, mainly one phase 2 study, MRX-501, has been completed and the other, one phase 3 study, MRX-502, is ongoing outside Japan. In addition, one phase 2 study, MRX-801, is ongoing outside Japan for patients <12 months of age with ALGS or PFIC.

4.1.3.1 Pharmacokinetics in Clinical Studies

In clinical studies evaluating pharmacokinetics (PK), TAK-625 is minimally absorbed, with little detectable unchanged TAK-625 in plasma (lower limit of quantification [LOQ] 0.25 ng/mL) after multiple dosing with TAK-625 at doses ≤ 20 mg. In addition, the mean (standard deviation [SD]) 2.5 hours after dosing TAK-625 concentration was 0.54 (0.62) ng/mL in subjects <12 months of age with ALGS. This low TAK-625 concentraion result is consistent with previous result in subjects ≥12 months of age who were administered TAK-625.

Concomitant administration of a high-fat meal with a single oral dose of TAK-625 decreased both the rate and extent of absorption. Area under the curve (AUC) and maximum drug concentration (C_{max}) of TAK-625 values in the fed state were 64.8% to 85.8% lower relative to oral administration of 30 or 45 mg in fasted conditions.

Fecal excretion was found to be the major route of elimination. Following a single oral dose of 5 mg [^{14}C] TAK-625, the majority was recovered in feces, with recovery in whole blood, plasma,

or urine accounting for <1%. Three metabolites were detected in feces, but these accounted for <3% of total fecal radioactivity. The remainder of the fecal radioactivity (>94%) was associated with unchanged TAK-625.

4.1.3.2 Study MRX-501 (Phase 2 Study)

The efficacy of TAK-625 was assessed in Study MRX-501, which was an open-label phase 2 study in pediatric subjects (aged 12 months to 18 years) with PFIC1 or PFIC2 designed to evaluate the safety and efficacy of TAK-625. Subjects were initially treated with doses up to 280 µg/kg, once a day (QD) until Protocol Amendment 4 (after Week 72), which allowed partial responders and nonresponders (n=10) to be treated with doses up to 280 µg/kg, twice daily (BID). The primary efficacy evaluation for this study was the change from baseline to Week 48 in fasting sBA level.

The following is a summary of Study MRX-501 results through Week 72:

Efficacy Results:

In the primary endpoint of change from baseline to Week 13/early termination (ET) in sBA, numerical improvement was observed in subjects with PFIC2 (mean [SD] change from baseline, -38 [177.7] µmol/L) but not in subjects with PFIC1. In the overall study population, the mean (SD) change from baseline was -23 (161.0) µmol/L.

In the secondary endpoints of change from baseline to endpoint (Week 13/ET), numerical improvements were observed in the overall study population in mean (SD) the observer-reported Itch Reported Outcome (ItchRO [Obs]) 4-week average morning score (-0.7 [0.65]), the patient-reported Itch Reported Outcome (ItchRO [Pt]) 4-week average morning score (- 0.6 [0.57]), alanine aminotransferase (ALT) (-9 [61.8] U/L), total bilirubin (TBili) (- 0.2 [1.65] mg/dL), and direct bilirubin (-0.1 [1.12] mg/dL). Numerical improvements in each of the parameters listed above were noted in subjects with PFIC2 and PFIC1.

In the endpoints of change from baseline to endpoint (Week 72/ET), numerical improvements were observed in the overall study population in mean (SD) sBA (-2 [146.0] µmol/L) and ALT (- 12 [59.6] µmol/L). Numerical improvements were noted in sBA (Mean [SD], - 10 [162.8] µmol/L) and ALT (mean [SD], -19 [65.0] U/L) in subjects with PFIC2, but not subjects with PFIC1.

In the endpoints of change from baseline to endpoint (Week 48/ET), numerical improvements were observed in the overall study population in ItchRO (Obs) 4-week average morning score (mean [SD], -0.9 [0.94]) and ItchRO (Pt) 4-week average morning score (mean [SD], - 1.0 [0.69]). Numerical improvements were noted in ItchRO (Obs) 4-week average morning score (mean [SD], -1.0 [0.96]) and ItchRO (Pt) 4-week average morning score (mean [SD], - 1.0 [0.80]) in subjects with PFIC2. Numerical improvements in ItchRO (Obs) and ItchRO (Pt) were also observed in subjects with PFIC1.

Safety Results:

Treatment-emergent adverse events (TEAEs) related to study drug were experienced by 23 subjects (69.7%) overall, with a lower incidence in subjects with PFIC1 (3 subjects [37.5%]) compared with subjects with PFIC2 (20 subjects [80.0%]). Gastrointestinal events (from the Gastrointestinal [GI] disorders system organ class [SOC]) were the most frequently reported treatment-related TEAEs (18 subjects [54.5%]).

Serious adverse events (SAEs) were experienced by 14 subjects (42.4%) overall, including 4 subjects (50.0%) with PFIC1 and 10 subjects (40.0%) with PFIC2. Gastrointestinal events (from the GI disorders SOC) were the most frequently reported SAEs (6 subjects [18.2%]). The only SAEs reported for more than 1 subject were abdominal pain and diarrhea, each experienced by 2 subjects (6.1%). SAEs potentially related to study drug were experienced by 5 subjects (15.2%) overall, with a similar incidence in subjects with PFIC1 (1 subject [12.5%]) and PFIC2 (4 subjects [16.0%]). The treatment-related SAEs were reported for 1 subject each and included abdominal pain, abdominal pain upper, diarrhea, pancreatitis, blood bilirubin increased, and international normalized ratio (INR) increased.

A total of 5 subjects (15.2%) experienced TEAEs that led to permanent treatment discontinuation, including disease progression (2 subjects [6.1%]), blood bilirubin increased (2 subjects [6.1%]), and pancreatitis (1 subject [3.0%]). Of the TEAEs that led to permanent treatment discontinuation, only the TEAE of pancreatitis was considered potentially related to study drug. All of the TEAEs that led to permanent treatment discontinuation were experienced by subjects with PFIC2. No deaths were reported during the conduct of the study.

4.1.3.3 Study MRX-801 (Phase 2 Study)

Currently, Study MRX-801, which is an open-label, multicenter, phase 2 study in pediatric subjects (<12 months of age) with ALGS or PFIC designed to evaluate the safety and tolerability of TAK-625, is ongoing. ALGS or PFIC subjects receive TAK-625 over a 13-week treatment period (core study period) that includes dose escalation and stable dosing. Stable dosing occurs at 400 µg/kg once daily (QD; for ALGS) and at 600 µg/kg twice daily (BID; for PFIC), or at the highest tolerated dose. For subjects <1 month of age, the dose for both ALGS and PFIC is 75 µg/kg QD for the duration of treatment below this age boundary.

The interim analyses were planned when at least 6 subjects had completed the 13-week core study period for each study cohort (ALGS and PFIC).

The following is a summary of the results for the ALGS cohort as of 4 May 2022:

A total of 8 subjects (<12 months of age [2-10 months]) with ALGS were enrolled in the study. All subjects successfully escalated to the proposed label dose of 400 µg/kg/day with the proposed single drug-escalation step. Overall, 7 subjects completed the 13-week core study period, and 1 subject discontinued during the 13-week core study period.

Efficacy Results:

Improvements in pruritus and sBA were observed, as indicated by decreases in Clinician Scratch Scale (CSS) scores and sBA levels over time with treatment with TAK-625.

The mean (SD) change in sBA from baseline at Week 13 was -88.91 (113.35) µmol/L. There were decreases in sBA from baseline to Week 3, 10, and 13.

The mean (SD) change from baseline to Week 13 for CSS score was -0.2 (1.91) and ranged from -3 to 3. The mean change from baseline for CSS score decreased from baseline to Week 6 and Week 13.

Safety Results:

TAK-625 was well tolerated. A total of 7 subjects (87.5%) experienced at least 1 TEAE, 2 subjects (25.0%) had a TEAE related to the study drug (both events were Grade 1 diarrhea), and 4 subjects (50.0%) had a Grade ≥3 TEAE, none of which were considered to be related to the study drug. The most frequent TEAEs were nasopharyngitis, abdominal pain, diarrhea, teething, and pyrexia. These events were in all cases self-limiting and resolved with no drug interruption or change in dose. Most TEAEs were Grade 1 in severity. Four subjects (50.0%) had 7 SAEs, none of which were considered to be related to the study drug. No TEAE led to study discontinuation or death.

Most subjects had fluctuations in liver chemistry (ALT, aspartate aminotransferase [AST]), and total bilirubin) from baseline to each time point; however, 4 subjects (50.0%) had a decrease from baseline in total bilirubin, indicating improvement over time. Most subjects maintained or had mild increases in lipid soluble vitamin (LSV) levels from baseline to each time point, consistent with standard-of-care vitamin supplementation administered to subjects with ALGS.

4.1.3.4 Study MRX-502 (Phase 3 Study)

Currently, Study MRX-502, which is a 6-month, international, multicenter, randomized, double-blind, placebo-controlled phase 3 study in subjects with PFIC, is ongoing. The study will be followed by the long-term extension study MRX-503, during which all subjects who complete Study MRX-502 will have the opportunity to be treated continuously with TAK-625. Subjects will be randomized in a 1:1 ratio to the TAK-625 or placebo treatment groups, respectively, stratified by cohort (Primary cohort: up to 30 subjects with nt-PFIC2, Supplemental cohort: up to 60 subjects with other PFIC subtypes). Subjects are treated with doses up to 600 µg/kg, BID with 4-step dose escalation. The primary efficacy evaluation for this study is the mean change in the average morning ItchRO (Obs) severity score between baseline and Week 15 through Week 26. The secondary endpoints are 1) the mean change in the average morning ItchRO (Obs) frequency score between baseline and Week 15 through Week 26; 2) the mean change in total sBA between baseline and Week 26; 3) Proportion of subjects who experience an sBA control (defined as a reduction to <102 µmol/L or a reduction of >75%, or normalization) from baseline through Week 26.

4.2 Rationale for the Proposed Study

TAK-625 has never been used in Japan, although Study MRX-501 suggested that TAK-625 was safe and effective for nt-PFIC2 and the effect sustained in long-term period in subjects with nt-PFIC2. In this study, efficacy, safety, and PK profile of TAK-625 will be evaluated in Japanese subjects with PFIC. Because all treatment responders in Study MRX-501 were subjects with PFIC2, the primary cohort will include subjects with PFIC2, and the supplemental cohort will include subjects with PFIC other than PFIC2. This protocol was developed to confirm the similarity to Study MRX-502 by comparing the results between Japanese data and overseas data. TAK-625 was well tolerated in subjects <12 months of age with ALGS with moderate to severe cholestasis in Study MRX-801. Given the clinical outcomes associated with PFIC and ALGS, including the negative impact on patients' and caregivers' quality of life and the fact that there are currently no or limited approved treatments for patients <12 months of age, there is a high unmet medical need for a novel treatment for these diseases. Thus, patients <12 months of age will be enrolled as well as patients ≥12 months of age in this study. Study MRX-801 was designed to enroll patients ≥0 days of age with PFIC; however, from the age of onset of PFIC, it is assumed that the administration of TAK-625 would not be started before 1 month after birth. Therefore, patients ≥1 month of age was planned to be enrolled in this study, in consideration of preventing the patients from being exposed to the amount of propylene glycol (PG) in TAK-625 over the maximum daily dose limit of PG specified in the guidance by the European Medicines Agency (EMA).

In Japan, a diagnosis of PFIC is made comprehensively with symptoms such as jaundice and intense pruritus, as well as characteristic findings in liver biopsy (cholestasis in the bile canaliculus and giant cell hepatitis), immunostaining of BSEP. The gene analysis is also considered when the diagnosis is difficult [6], like in overseas. Regarding the current treatments for patients with PFIC, there are only symptomatic medicines. Also, the overall process from diagnosis to treatment is not different in Japan and overseas. These support the rationale for comparison between data in Japanese subjects and data in non-Japanese subjects. However, since it is not feasible to include a placebo arm considering the extreme rarity of PFIC, the randomized, double-blind, placebo-controlled drug withdrawal period will not be used in this study. LSV deficiency will be monitored regularly for a long-term as a potential adverse event (AE) based on the mechanism of action.

4.3 Benefit/Risk Profile

The proposed study is designed to evaluate the efficacy, safety, and PK profile of TAK-625 in Japanese patients with PFIC.

As previously stated in Section 4.1.3, the safety and efficacy profile of TAK-625 in non-Japanese subjects with nt-PFIC2 has been confirmed in Study MRX-501, though TAK-625 has never been used in Japan. The long-term efficacy has been also confirmed in Study MRX-501.

Based on clinical study data, diarrhoea and abdominal pain have been classified as identified risk and transaminases increased has been classified as potential risk of TAK-625. The majority of reported severities of diarrhoea and abdominal pain in clinical studies were mild or moderate.

Therefore, TAK-625 has a positive benefit-risk profile in the treatment to PFIC.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

- To evaluate the efficacy of TAK-625 in the primary cohort.
- To evaluate the safety of TAK-625 in subjects with PFIC.

5.1.2 Secondary Objectives

- To evaluate the efficacy of TAK-625 in subjects with PFIC.
- To evaluate the PK of TAK-625 in subjects with PFIC.

5.1.3 Additional Objectives

- To evaluate primary, secondary, and exploratory endpoints in the supplemental cohort.

5.2 Endpoints

5.2.1 Primary Endpoint

- Change in the average morning ItchRO (Obs) severity score between baseline and average of Week 15 through Week 26.

5.2.2 Secondary Endpoints

5.2.2.1 Key Secondary Endpoints

- Change in the average morning ItchRO (Obs) frequency score between baseline and average of Week 15 through Week 26.
- Change in total sBA between baseline and Week 26.

5.2.2.2 Secondary Endpoints

- Proportion of subjects who experience an sBA control (defined as a reduction to <102 μmol/L, or a reduction of >75%, or normalization) from baseline through Week 26.
- Change in the ItchRO (Obs) weekly average severity (based on daily maximum of morning and evening severity scores) between baseline and average of Week 15 through Week 26.

5.2.3 Safety Endpoints

- Incidence of AEs including SAEs, related to study drug, leading to study drug discontinuation, and AEs of clinical interest (AECIs).

  AECIs include the following:

  – LSV deficiency events.

  – Liver parameter disruption.

- Change from baseline in clinical laboratory values (hematology, chemistry, urinalysis, and others), physical examination findings (including body weight, height, and body mass index [BMI]), vital signs, and electrocardiogram (ECG) parameters.

[redacted]

5.2.5 PK Endpoint

- Plasma levels of TAK-625 at predose and approximately 2.5 hours after the morning dose at Week 10.
- Plasma levels of TAK-625 at predose (optional) and approximately 30 minutes after the morning dose at Week 14 (or any visit up to Week 26).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3, multicenter, open-label, uncontrolled study to evaluate the efficacy and safety of TAK-625 in the treatment of Japanese subjects with PFIC.

Study Population:

The study population is defined as "Japanese patients with PFIC who are 1 month of age or older". Subjects diagnosed with PFIC2 due to ABCB11 mutation that predicts residual BSEP function (nt-PFIC2) will be enrolled in the primary cohort. Subjects with other PFIC subtypes (eg, t-PFIC2, PFIC1/3/4, or other PFIC mutation variants) or postsurgical subjects (eg, internal or external biliary diversion surgery) will be enrolled in the supplemental cohort. (Subjects diagnosed with PFIC2 due to ABCB11 mutation that predicts complete absence of BSEP function [t-PFIC2] are excluded from the primary cohort and can be enrolled only in the supplemental cohort. PFIC subtypes should be determined by a genotyping [refer to Section 7.1]).

Study Period (Screening, Treatment [Dose Escalation, Stable Dosing, and Follow-Up Dosing], and Safety Follow-Up Period):

This study consists of the screening period (up to 6 weeks prior to the study administration), 4-week (up to 6-week) dose escalation period (doses up to 600 µg/kg, BID, as tolerated), 44-week stable dosing period, and follow-up dosing period (until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication).

1. Screening Period (up to 6 Weeks prior to the Study Administration):

In the screening period, for subjects who do not have documentation of mutation related with PFIC, a blood sample will be obtained for genotyping. Subjects diagnosed with PFIC2 (nt-PFIC2) will be enrolled in the primary cohort and those with other types of PFIC will be enrolled in the supplemental cohort. The electronic Diary (eDiary) for assessing pruritus with the Itch Reported Outcome (ItchRO) instrument will be dispensed and subjects and caregivers will undergo training during the screening visit.

2. Dose Escalation Period (4 weeks [up to 6 weeks]: Week 0 to 4 [6]):

In the dose escalation period, at the baseline visit (Week 0/Visit 2), subjects will be assessed to confirm continued study eligibility and undergo a physical examination including body weight, height, BMI, and vital signs, and have urine and blood samples taken for hematology, chemistry, fasting lipid panel, baseline levels of sBA and other cholestasis biochemical markers. Compliance with ItchRO will be assessed. Study drug will be supplied at each visit (Week 0/Visit 2, Week 2/Visit 3, and Week 4/Visit 4). The subject contacts (phone calls) will be conducted at Weeks 1 and 3. The dose is increased weekly, 150 µg/kg, 300 µg/kg, 450 µg/kg, and 600 µg/kg, BID.

Dose escalation should occur in the absence of major safety (eg, liver parameters and LSV deficiency) or tolerability concerns (eg, GI-related TEAEs) related or possibly related to study drug. Subjects with such safety concerns can be down-titrated to a lower, previously tolerated dose level for 1 week before continuing dose escalation. The minimum dose to continue in the study will be 150 µg/kg, BID; subjects who cannot tolerate this dose will be discontinued from the study. The dose escalation period is allowed to be extended up to 6 weeks depending on the safety or tolerability concerns (refer to Section 8.1.3).

3. Stable Dosing Period (44 weeks: Week 5 to 48):

After the dose escalation period, each subject will continue dosing with study drug at the Week 4 or Week 6 dose level (the maximum tolerated dose [MTD] level) in the stable dosing period. Subjects will return to the study site at Weeks 6, 10, 14, 18, 22, 26, 28, 32, 36, 40, 44, and 48 and undergo physical examinations. Subject contacts (phone calls) will be conducted as appropriate throughout the stable dosing period. Subjects and caregivers will continue twice daily completion of their ItchRO throughout the period.

4. Follow-up Dosing Period (after Week 48):

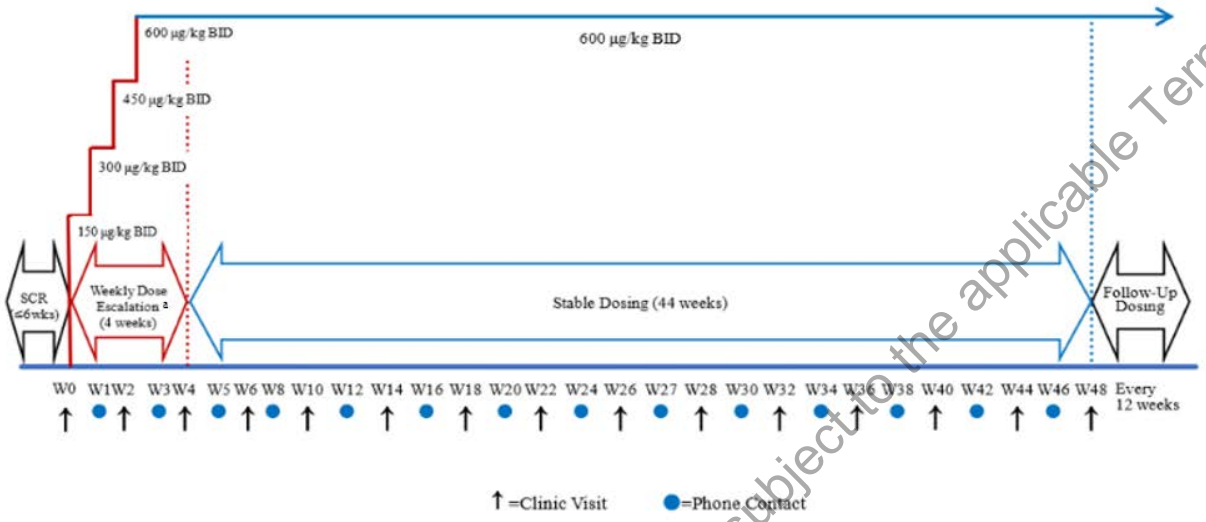
Additionally, in the follow-up dosing period, each subject will continue dosing with study drug. The safety evaluation will be performed in all the subjects every 12 weeks from Week 48 visit until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication. Bile acids and ItchRO will be measured to evaluate the long-term effectiveness of TAK-625. For subjects discontinuing early, safety follow-up will be conducted.

5. Safety Follow-up (after Final Visit/ET):

Subjects/caregivers will have a final safety follow-up subject contact (phone call) 7 days after the final study visit or ET visit (except for screen failure).

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



BID=twice daily; SCR=screening; W=Week; wks=weeks.
a The dose escalation period is allowed to be extended up to 6 weeks depending on the safety or tolerability concerns.

Endpoint:

Primary endpoint is change in the average morning ItchRO (Obs) severity score between baseline and the average of Week 15 through Week 26. Key secondary endpoints are change in the average morning ItchRO (Obs) frequency score between baseline and the average of Week 15 through Week 26, and change in total sBA between baseline and Week 26.

Sample Size:

The primary cohort (nt-PFIC2): up to approximately 3 subjects. The supplemental cohort (other types of PFIC): up to approximately 6 subjects.

Sites and Regions:

The study will be conducted in approximately 10 sites in Japan.

Duration of Treatment:

The study will be continued until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the end of treatment (EOT) visit.

If TAK-625 is approved for marketing by authorities during the study, the study can be shifted to a post-marketing study after the approval. In that case this protocol will continuously be used.

"Clinical Study" mentioned in the protocol will be read as "Post-marketing Study" as appropriate.

6.2 Justification for Study Design, Dose, and Endpoints

TAK-625 has never been used in Japan, although Study MRX-501 suggested that TAK-625 was safe and effective for nt-PFIC2 and the effect sustained in long-term period in subjects with nt-PFIC2. In this study, efficacy, safety, and PK profile of TAK-625 will be evaluated. This protocol was developed to confirm the similarity to Study MRX-502 by comparing the results between Japanese data and overseas data.

Justification for Study Population:

Limiting the analysis to subjects with PFIC2 (primary cohort) is based on the following:(1) All responders in Study MRX-501 are subjects with PFIC2; (2) PFIC2 patients most commonly lack extrahepatic abnormalities; and (3) PFIC2 represents the most prevalent subgroup of PFIC patients and, therefore, constitutes the biggest unmet need. Although the safety of TAK-625 was confirmed in subjects <12 months of age with ALGS with moderate to severe cholestasis enrolled in Study MRX-801, the lower age limit for enrollment in this study is set to be 1 month of age, in consideration of preventing the patients from being exposed to the amount of PG in TAK-625 over the maximum daily dose limit of PG specified in the guidance by the EMA.

Justification for Dose and Regimen of Study Drug:

The TAK-625 up to 600 µg/kg, orally BID dosing regimen was selected based on international phase 2 and phase 3 clinical trials of TAK-625 (Study MRX-501 and Study MRX-502).

TAK-625 is provided as an oral solution that is dosed on a weight basis. In phase 2 studies, TAK-625 has been administered to 119 pediatric subjects with cholestatic liver disease (33 with PFIC and 86 with ALGS; >12 months of age) at doses up to a maximum daily dose of 800 µg/kg/day. Dosing of 400 and 800 µg/kg/day (Study LUM001-304) and 280 and 560 µg/kg/day (Study MRX-501) demonstrated a consistent safety profile. No MTD has been determined at single doses up to 7000 µg/kg and multiple doses up to 1400 µg/kg/day. Furthermore, no dose-related safety findings have been identified to date.

Effective and clinically relevant inhibition of the IBAT using TAK-625 has been demonstrated by durable reductions in sBA and pruritus levels in children with PFIC and ALGS ≥12 months of age on treatment for over 5 years. Although the efficacy results in infants <12 months of age with PFIC are not yet available, improvements in pruritus and sBA were observed and the safety of TAK-625 was confirmed in infants <12 months of age with ALGS in the ongoing Study MRX-801, in which infants <12 months of age with ALGS or PFIC had been enrolled. Evidence from Study MRX-501 indicates that higher doses and BID regimens may improve the responder rate to TAK-625 treatment in PFIC. These data led to the dose selection for Study MRX-502, an ongoing Phase 3 randomized double blinded, placebo-controlled study, investigating the safety and efficacy of higher doses up to 600 µg/kg BID in subjects with PFIC. The 600 µg/kg BID dosing regimen is further supported by documentation of dose-dependent increase in fBA excretion, the direct pharmacodynamic marker of IBAT inhibition, up to total daily doses of

TAK-625 100 mg (weight-based equivalent of 1400 µg/kg/day). In a dose-finding phase 1 study (SHP625-101) conducted in overweight and obese adults, BID dosing (50 mg BID; 700 µg/kg BID equivalent) led to higher fBA excretion compared to 100 mg QD (1400 µg/kg QD equivalent). The safety profile was comparable across the tested dose range, except for increased stool frequency at higher doses.

Doses of TAK-625 up to 1200 µg/kg/day (600 µg/kg BID) are expected to be safe in children with cholestatic liver disease and will be evaluated in Japanese subjects with PFIC for efficacy and safety in this study with the same dose escalation step as that in Study MRX-502.

Sample daily exposure (mg-day) across proposed dose levels for subjects ranging in weight from 3 to 70 kg is provided in Table 6.a.

Table 6.a Sample Daily Exposure (mg/day) in Subjects

Weight (kg)	Daily Exposure of TAK-625 (mg)			
	Dose Level 1 (150 µg/kg, BID)	Dose Level 2 (300 µg/kg, BID)	Dose Level 3 (450 µg/kg, BID)	Dose Level 4 (600 µg/kg, BID)
3	0.9	1.8	2.7	3.6
5	1.5	3.0	4.5	6.0
10	3.0	6.0	9.0	12.0
20	6.0	12.0	18.0	24.0
30	9.0	18.0	27.0	36.0
40	12.0	24.0	36.0	48.0
50	15.0	30.0	45.0	60.0
60	18.0	36.0	54.0	72.0
70	21.0	42.0	63.0	84.0

BID=twice daily.

Justification for Endpoint:

The primary and secondary endpoints in this study are similar those in the previous clinical studies with TAK-625 in PFIC subjects (Study MRX-502) to compare the results between Japanese data and overseas data.

The primary endpoint is the change in the average morning ItchRO (Obs) severity score between baseline and the average of Week 15 through Week 26. The selection of ItchRO (Obs) as the primary endpoint of therapeutic response to TAK-625 treatment was based on the clinically significant improvements observed in Study MRX-501.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the TAK-625, 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 objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

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

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for ET or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

6.3.4 Duration of an Individual Subject's Study Participation

Subjects, including those who achieve a clinical response, may receive TAK-625 until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication. Subjects will discontinue treatment if they have an unacceptable TAK-625-related toxicity.

Subjects will be followed for 7 days after the final study visit or ET visit to permit the detection of any delayed treatment-related AEs.

6.3.5 End of Study/Study Completion Definition and Planned Reporting

End of Study:

The study will be continued until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the EOT visit.

If TAK-625 is approved for marketing by authorities during the study, the study can be shifted to a post-marketing study after the approval.

Study Completion:

The study completion date is defined as the date the final subject, across all sites, completes his or her final protocol-defined assessment. Note that this includes the follow-up visit or contact, whichever comes later (refer to Section 9.3.6 for the defined follow-up period for this protocol) but not the long-term clinical follow-up of persistent safety findings.

Subjects who discontinue at any time during the treatment period will have a final safety follow-up subject contact (phone call) 7 days after the ET visit (see Section 9.3.6). Subjects who discontinue from the study for safety reasons are followed as long as clinically indicated or until no further improvement with an adverse outcome is expected.

Analysis Points:

Interim analysis will be performed at Week 26 and Week 48. Final clinical study report (CSR) will be prepared at the end of the study.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before study entry:

1. The subject signs and dates an informed consent form/assent (as applicable) and any required privacy authorization prior to the initiation of any study procedures.

   If the subjects are under 18 years of age, the investigator is responsible for obtaining written informed consent not only from the under-aged subjects, but also from their legally acceptable representatives.

2. The subject is Japanese male or female with a body weight ≥3.0 kg and who is ≥1 month of age at the time of informed consent.

   For subjects <12 months of age, gestational age ≥36 weeks at birth. For subjects born with gestational age between 32 and 36 weeks, a postmenstrual age of ≥36 weeks is required. Postmenstrual age is defined as the time elapsed between the first day of the last menstrual period and birth plus the time elapsed after birth.

3. The subject has a cholestasis as manifested by total sBA ≥3× upper limit of the normal range (ULN) (applies to the primary cohort only).

4. The subject has an average morning ItchRO (Obs) score ≥1.5 during 4 consecutive weeks of the screening period, leading to the baseline visit (Week 0/Visit 2). Since it is difficult to evaluate pruritus in infants, subjects <12 months of age at screening whose pruritus is unavoidably difficult to be evaluated are not necessarily required to meet the above score.

5. The caregiver has completed at least 21 valid* morning ItchRO (Obs) entries during 4 consecutive weeks of the screening period, leading to the baseline visit (Week 0/Visit 2) (*valid=completed and not answered as "I don't know"; the maximum allowed invalid reports=7, no more than 2 invalid reports during the last 7 days before the baseline visit [Week 0/Visit 2]).
6. The subject has a diagnosis of PFIC based on:

   Chronic cholestasis as manifested by persistent (>6 months*) pruritus in addition to biochemical abnormalities and/or pathological evidence of progressive liver disease (* ≤6 months is acceptable for subjects <12 months of age).

   And

   Primary cohort:

   a) The subject has a genetic testing result consistent with disease-causing variation in ABCB11 (PFIC2), based on a genotyping.

   Supplemental cohort:

   a) The subject has a genetic testing results consistent with disease causing variation in ATP8B1 (PFIC1), ABCB4 (PFIC3), or tight junction protein 2 gene (TJP2) (PFIC4), based on a genotyping.
   b) The subject has a PFIC phenotype without a known mutation or with another known mutation not described above.
   c) The PFIC subject has internal or external biliary diversion surgery history, and the internal or external biliary diversion surgery was reversed.
7. The subject is a male or female of non-childbearing potential. A male and non-pregnant, non-lactating female of childbearing potential who is sexually active must agree to use acceptable methods of contraception during the study and 30 days following the last dose of the study drug. A female of childbearing potential must have a negative pregnancy test result.

Definitions and highly effective methods of contraception are defined in Section 9.1.13 and reporting responsibilities are defined in Section 9.1.14.

8. The subject (whenever possible) and caregiver are able to be contacted by phone for scheduled remote visits (subject contacts [phone calls]).
9. Both a caregiver and subject above the age of assent are capable of reading and understanding the questionnaires.
10. The same caregiver should be contacted during this study.
    The ItchRO (Obs) should be completed by the same caregiver for consistency during this study, even if the subject is an adult (over 18 years old).

7.2 Exclusion Criteria

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

1. The diagnosed with PFIC2 due to ABCB11 mutation that predicts complete absence of BSEP function due to the type of ABCB11 mutation (t-PFIC2), based on a genotyping (applies to the primary cohort only). The subject may enter the study in the supplemental cohort (based on inclusion criteria 6.b) or 6.c) (refer to Section 7.1 for details).
2. The subject has a diagnosis of benign recurrent intrahepatic cholestasis indicated by a history of intermittent cholestasis with no disease progression.
3. The subject has a current or recent history (<1 year) of atopic dermatitis or other non-cholestatic diseases associated with pruritus.
4. The subject has a previous history of surgical interruption of the enterohepatic circulation (applies to the primary cohort only).
5. The subject with chronic diarrhea requiring intravenous (IV) fluid or nutritional intervention and/or its sequelae at screening or during the 6 months prior to screening.
6. The subject has a history of liver transplant or currently requires imminent liver transplant.
7. The subject with decompensated cirrhosis (INR >1.5, and/or albumin <30 g/L, history, or presence of clinically significant ascites, and/or variceal hemorrhage, and/or encephalopathy).
8. The subject has an ALT or total serum bilirubin (TSB) level >15× ULN at screening.
9. The subject has other liver disease.
10. The subject has any other disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs, including bile salt metabolism in the intestine (eg, inflammatory bowel disease), per investigator discretion.
11. The subject has a possible malignant liver mass in imaging, including screening ultrasound.
12. The subject has a history of human immunodeficiency virus (HIV) infection.
13. The subject has been diagnosed with any cancer (except for in situ carcinoma) within 5 years before the screening visit (Visit 1).
14. The subject has a history of drug abuse (substance abuse) or a history of alcohol abuse.
15. The subject has received bile acid, lipid binding resins or IBAT inhibitors within 28 days prior to screening and throughout the trial (refer to Section 7.3).
16. The subject who has received sodium phenylbutyrate for less than 6 months at the initiation of screening (refer to Section 7.3 and Section 7.5.1.2).
17. The subject participated in another clinical study within 28 days or 5 half-lives (whichever is longer) prior to screening.

18. The subject is judged by the investigator or sponsor medical monitor, as being ineligible for any other reason (eg, history of nonadherence to medical regimens, unreliability, medical condition, mental instability, or cognitive impairment) that could compromise the validity of informed consent, compromise the safety of the subject, or lead to nonadherence with the study protocol or inability to conduct the study procedures.
19. The subject has a history of hypersensitivity to TAK-625 or any of its components.

7.3 Excluded Medications

The following medications are prohibited during TAK-625 treatment and within the provided timeframe prior to screening.

Prior Therapy	Time Restriction
Bile acid/Lipid binding resins	Within 28 days prior to screening and throughout the trial.
IBAT inhibitors	Within 28 days prior to screening and throughout the trial.
Sodium phenylbutyrate	If the subject has received sodium phenylbutyrate for less than 6 months at the initiation of screening, the subject cannot be enrolled. (If the subject has received sodium phenylbutyrate for 6 months or more at the initiation of screening, the medication is permitted; however, the dose of sodium phenylbutyrate should not be changed during the study [refer to Section 7.5.1.2].)

IBAT=ileal bile acid transporter.

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

7.3.1 Justification of Excluded Medications

- Bile acids/Lipid binding resins: Since bile acids/lipid binding resins have been used for treatment of pruritus, these medications are excluded to avoid any influence on the efficacy results of TAK-625.
- IBAT inhibitors: Since the mechanism of action of IBAT inhibitors is similar to that of TAK-625, these medications are excluded to avoid any influence on the safety and efficacy results of TAK-625.
- Sodium phenylbutyrate: If the subject has received sodium phenylbutyrate for less than 6 months at the initiation of screening, the subject cannot be enrolled; since sodium phenylbutyrate has been shown to influence pruritus due to cholestatic diseases, the medication is excluded to avoid any influence on efficacy results of TAK-625. Meanwhile, if the subject has received sodium phenylbutyrate for 6 months or more at the initiation of screening, the medication is permitted, because the drug's effect is considered to have reached a plateau.

7.4 Excluded Procedures and Treatments

The subject with a history of surgical interruption of the enterohepatic circulation or liver transplant should not be included in the study.

7.4.1 Justification of Excluded Procedures and Treatments

- Surgical interruption of the enterohepatic circulation: The surgical interruption of the enterohepatic circulation is excluded from the study due to its significant impact on bile acid homeostasis.
- Liver transplant: The liver transplant is excluded from the study since this is considered as a curable treatment for PFIC.

7.5 On Study Restrictions

7.5.1 Concomitant Medications, Procedures, and Treatments

A subject should not be instructed to discontinue use of any medication or treatment to participate in this study until informed consent (or assent as applicable) has been obtained.

Concomitant treatment refers to all treatment, including concomitant therapies, as well as herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, taken between the dates of the first dose of study drug and the end of the subject's participation in the study. Concomitant treatment information must be recorded in the subject's source document.

7.5.1.1 Prohibited Concomitant Medications, Procedures, and Treatments

The prohibited concomitant medications, procedures and treatment are described in Section 7.3 and Section 7.4.

7.5.1.2 Permitted Concomitant Medications, Procedures, and Treatments

The following medications to treat cholestasis/pruritus are allowed during the study if the subject has been on a stable dosing regimen (ie, same dose and frequency in the 30 days prior to the screening visit [Visit 1]) and will continue this dosing regimen throughout study participation. The investigator must contact the medical monitor to discuss any changes to and introduction of concomitant treatments to treat cholestasis/pruritus not listed here that could impact the outcome of the study. Dose adaptations to body weight changes are allowed.

- Ursodeoxycholic, cholic acid, chenodeoxycholic acid or dehydrocholic acid.
- Antihistamines.
- Nalfurafine.
- Phenobarbital.
- Rifampicin.

- Naloxone.

Administration of sodium phenylbutyrate is permitted only under the conditions below. However, the dose of sodium phenylbutyrate should not be changed during the study; temporary dose adjustments for safety concerns or dose adaptations to body weight changes are permitted at the discretion of the investigator.

1. Stable dosing for 6 months or more at the initiation of screening; temporary dose adjustments for safety concerns or dose adaptations to body weight changes are permitted at the discretion of the investigator.
2. Assessed to be in a stable condition (no more improvement will be expected) by the investigator.

7.5.1.3 LSVs

The investigators must ensure that subjects receive LSV supplements, as needed, for the duration of the study.

7.5.2 Diet, Fluid, and Activity Control

- The morning dose should be administered approximately 30 minutes before breakfast and the evening dose approximately 30 minutes before the main evening meal. The doses will be administered prior to meals rather than every 12 hours (q12h) in order to better cover the luminal bile acid release associated with meals. The last meal time prior to blood sampling will be recorded on the source document and electronic case report form (eCRF) at each visit.

  For infants with a body weight <5 kg, at-home dilution will be required (refer to Section 8.1.3).

  For PK plasma samples at approximately 30 minutes (±15 minutes) after morning dose at Week 14 (or any visit up to Week 26), the PK sampling should be conducted before breakfast. Study drug should be administered approximately at the same time each day throughout the study.

- Blood samples for the analysis of cholestasis biomarkers, lipid panel, and LSV should be drawn prior to administration of vitamin supplementation and as much as possible after 6 hours or more of the last food or formula (water intake is permitted if necessary but not recommended). For subjects <12 months of age, samples should be taken before feeding, after 2 hours or more of the last food or formula, and before administration of vitamin supplementation, when possible (water intake, excluding milk, is allowed when required) (refer to Appendix A).

7.6 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.21.

1. AEs.
2. Protocol deviation. The discovery after the first dose of study drug that the subject did not meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not attend visits and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Withdrawal by subject. The subject (or subject's legally acceptable representative) 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. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.14.
7. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and continued participation would pose an unacceptable risk to the subject.
8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF. (eg, "The minimum dose to continue in the study will be 150 µg/kg TAK-625, BID; subjects who cannot tolerate this dose will be discontinued from the study" or "Over 56 days [both morning and evening dose] of cumulative dose interruption during the stable dosing period (to Week 26); administration of the study drug will continue unless the subject meets this discontinuation criteria").

   If subjects discontinue from the study due to disease progression and require rescue therapy with either surgical interruption of the enterohepatic circulation or listing for liver transplant, both the reason for discontinuation and outcome (ie, PEBD, cholecystostomy tube, ileal exclusion, liver transplant, or listed for liver transplant) should be recorded in the subject's source document. If known, the date of the future scheduled procedure should also be recorded. The information regarding surgical interruption of the enterohepatic circulation, liver transplant, or listing for transplant will be collected in the eCRF at the time the subject

completes/early terminates from the study (EOT/ET) until the completion of the safety follow-up period.

7.7 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.6. In addition, a subject may discontinue his 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. In addition, efforts should be made to perform all procedures scheduled for the ET visit.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to any of the drugs defined in Section 8.1.1.1.

For details and the handling of the study drug, refer to the "Investigator's Brochure (IB)" and "Pharmacy Manual".

8.1.1.1 Study Drug

The doses described in this study protocol are for maralixibat chloride (not free base) but are written as "TAK-625". For example, 400 µg/kg of maralixibat chloride is equivalent to 380 µg/kg of TAK-625 free base but is referred to as 400 µg/kg of TAK-625 in this study protocol (the latest TAK-625 IB).

The study drug of this study is TAK-625 (formerly maralixibat, SHP625, LUM001), which will be provided as an oral solution form (eg, 5, 10, 15, and 20 mg/mL) along with either 0.5, 1.0, or 3.0-mL sized oral dosing dispensers. Equipment for at-home dilution will also be supplied where required.

TAK-625 are presented in 30-mL volumes packaged in an amber colored polyethylene terephthalate (PET) bottles equipped with a child resistant cap and require refrigerated storage conditions (2°C to 8°C).

One of the excipients in the TAK-625 oral solution is PG; in order to limit subject exposure to PG, a specific strength of oral solution will be prescribed to a given subject based on body weight and target dose. The dosing plan will limit PG exposure to ≤26 mg/kg/day and, at the same time, will provide reasonable (not too high or too low) dosing volumes to ensure accurate dosing.

Further details are described separately in a "Pharmacy Manual".

8.1.1.2 Packaging

Study drug will be provided with primary packaging and labelling only (no secondary packaging/secondary labeling). Study drug is packaged in the following labeled containers:

- Ready-to-use oral solution of TAK-625 5 mg/mL.
- Ready-to-use oral solution of TAK-625 10 mg/mL.
- Ready-to-use oral solution of TAK-625 15 mg/mL.
- Ready-to-use oral solution of TAK-625 20 mg/mL.

The sponsor or designee will provide 0.5, 1.0, and 3.0 mL sized oral dosing dispensers to study sites. Bottle adapters and equipment for at-home dilution will also be supplied where required. Changes to sponsor-supplied packaging may not occur without full agreement in advance by the sponsor.

8.1.1.3 Labeling

All study drug is labeled according to Japan requirements.

Japanese label is used for TAK-625 oral solution in Japan. Further details are described separately in a "Pharmacy Manual".

8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. TAK-625 must be stored at refrigerated storage conditions (2ºC to 8ºC). A daily temperature log of the drug storage area must be maintained every working day. Further details are described separately in a "Pharmacy Manual".

8.1.3 Dose and Regimen

Route of Administration: oral

Subjects will be administered (or will self-administer) varying volumes of ready-to-use oral solution study drug at each dosing visit, starting with the baseline visit (Week 0/Visit 2). The dosing volume is determined based on the individual body weight, the dose level according to the dose escalation plan (150, 300, 450 or 600 µg/kg), and the strength of solution being administered (5, 10, 15, or 20 mg/mL). For infants with a body weight <5 kg, at-home dilution will be required. This will include a 5-fold dilution of assigned TAK-625 with a predefined quantity of water. Refer to the "Pharmacy Manual" for a dosing table with the dilution scheme.

Dose Regimen:

Study drug administration will take place during the dose escalation, stable dosing, and follow-up dosing periods of the study based on a BID regimen (up to 1200 µg/kg/day).

Subjects will take the first dose of study drug at the baseline visit (Week 0/Visit 2) after all of the exam procedures were performed under the supervision of the investigator or trained staff.

The morning dose should be administered approximately 30 minutes before breakfast and the evening dose approximately 30 minutes before the main evening meal. The doses will be administered prior to meals rather than q12h in order to better cover the luminal bile acid release associated with meals. Study drug should be administered approximately at the same time each day throughout the study.

The interval between administration of study drug and any concomitant treatment should not change during the study.

The dose may be down-titrated throughout the study, at the investigator's discretion and in consultation with the medical monitor, for subjects experiencing intolerance (eg, GI symptoms such as diarrhea, abdominal pain, cramping) to a given dose. Subjects who were down-titrated after the stable dosing period may be rechallenged after discussion with the medical monitor. However, it is preferable to administer the study drug at a stable dose as much as possible until Week 26.

1. Dose Escalation period (4 weeks [up to 6 weeks]: Week 0 to 4 [6]):

The dose escalation period will consist of the following weekly steps:

Dose level 1	150 µg/kg TAK-625, BID for 1 week
Dose level 2	300 µg/kg TAK-625, BID for 1week
Dose level 3	450 µg/kg TAK-625, BID for 1 week
Dose level 4	600 µg/kg TAK-625, BID for the remaining duration of the study

BID= twice daily.

Dose escalation should occur in the absence of major safety (eg, liver parameters and LSV deficiency) or tolerability concerns (eg, GI-related TEAEs) related or possibly related to study drug. Subjects with such safety concerns can be down-titrated to a lower, previously tolerated dose level for 1 week before continuing dose escalation. The minimum dose to continue in the study will be 150 µg/kg, BID; subjects who cannot tolerate this dose will be discontinued from the study. The dose escalation period is allowed to be extended up to 6 weeks depending on the safety or tolerability concerns.

The investigators should also review study drug compliance during the dose escalation period to ensure that subjects have adequate exposure to study drug to assess safety and tolerability. Any compliance concerns should be discussed with the medical monitor.

2. Stable Dosing Period (44 weeks: Week 5 to 48):

After the dose escalation period, each subject will continue dosing with study drug at the Week 4 or Week 6 dose level (the MTD level) in the stable dosing period.

The investigators have until Week 6 to determine the MTD; if re-challenges or further dose escalations fail, the subject will remain on the MTD level for the remainder of the stable dosing period to complete up to 44 weeks of stable dosing.

Dose reductions are allowed for the above-mentioned safety or tolerability reasons down to a minimum level of 150 µg/kg, BID. Subjects who cannot tolerate this dose will be discontinued from the study.

During the stable dosing period (to Week 26), subjects will be allowed a maximum of 28 days (both morning and evening dose missed) of cumulative dose interruption. During the 12 weeks of the stable dosing period (Weeks 15 to 26), subjects will be allowed a maximum of 17 days (both morning and evening dose) of cumulative dose interruption but not more than 7 consecutive days. Subjects may remain on study during dose interruptions and should continue to complete all regularly scheduled subject study visits and assessments. After dose interruption, subjects will reinitiate dosing at their MTD. Any dose interruptions longer than the maximum allowed will be documented as protocol deviations.

Any subject who has over 56 days (both morning and evening dose) of cumulative dose interruption during the stable dosing period (to Week 26) should be discontinued from the study.

3. Follow-up Dosing Period (after Week 48):

Additionally, in the follow-up dosing period, each subject will continue dosing with study drug at the Week 4 or Week 6 dose level (the MTD level) from Week 48 visit until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication.

Dose reductions are allowed for the above-mentioned safety or tolerability reasons down to a minimum level of 150 µg/kg, BID. Subjects who cannot tolerate this dose will be discontinued from the study.

8.1.4 Stopping Criteria of Dosing

Subject dosing must be suspended until the retest results are available. Refer to Sections 10.4.3, 10.4.5, 10.4.6, and 10.4.7.

8.1.5 Overdose and Medication Error

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

A medication error is defined as an error made in prescribing, dispensing, administration, and/or use of a study medication. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the study medication are not considered reportable as medication errors. The administration and/or use of the unassigned or expired study medication is/are always reportable as a medication error.

All cases of overdose or medication error (with or without associated AEs) will be documented. Cases of overdose or medication error without manifested signs or symptoms are not considered AEs. AEs associated with an overdose or a medication error will be documented on AE eCRFs according to Section 10.0.

SAEs associated with overdose or medication error should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose or medication error, the subject should be treated by the investigator based on symptoms.

8.2 Study Compliance

Subject compliance with study procedures and treatment compliance will be assessed at each treatment visit by the site staff.

Dose Escalation Period:

During the dose escalation period, subject compliance will be reviewed as part of the dose escalation assessment. Any concerns with compliance should be discussed with the medical monitor.

Stable Dosing Period:

During the stable dosing period (to Week 26), subjects will be allowed a maximum of 28 days (both morning and evening dose missed) of cumulative dose interruption. During the 12 weeks of the stable dosing period (Weeks 15 to 26), subjects will be allowed a maximum of 17 days (both morning and evening dose) of cumulative dose interruption but not more than 7 consecutive days. Subjects may remain on study during dose interruptions and should continue to complete all regularly scheduled subject study visits and assessments. After dose interruption, subjects will reinitiate dosing at their MTD. Any dose interruptions longer than the maximum allowed will be documented as protocol deviations.

Any subject who has over 56 days (both morning and evening dose) of cumulative dose interruption during the stable dosing period (to Week 26) should be discontinued from the study.

Procedures outlined in Section 9.3.4 should be followed for any subject who is discontinued early from the study.

8.3 Study Drug Assignment and Dispensing Procedures

Subjects will receive treatment according to the study schedule.

The investigator or designee will utilize Interactive Response Technology (IRT) at screening to register the subject into the study and obtain an enrollment number/subject number to identify the subject throughout the study. During this contact, the investigator or designee will provide

the necessary subject-identifying information, including the subject identification (ID) number. The medication ID number of the study drug to be dispensed will then be provided by the IRT as well as at subsequent visits. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IRT. Refer to IRT manual provided separately. The medication ID number will be entered onto the eCRF.

A study manual/user manual with specific functions and instructions for the IRT will be provided to the site, and site personnel will receive training. Please refer to the study manual/user manual for additional details regarding the IRT.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The on-site pharmacist (site designee) will receive the pharmacy manual created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of medications from the subject as well as return of them to the sponsor or destruction of them.

The on-site pharmacist (site designee) will immediately return unused study drugs to the sponsor after the study is closed at the study site.

Refer to “Pharmacy Manual” for detailed and additional instructions.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

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

A unique subject ID number (subject number) will be assigned to each subject at the time that informed consent is obtained. This subject number will be used throughout the study.

If the subjects are under 18 years of age, the investigator is responsible for obtaining written informed consent not only from the under-aged subjects, but also from their legally acceptable representatives.

9.1.2 Eligibility Assessment

The investigator should confirm the subject's eligibility at the screening and prior the first administration (Visit 1 and Visit 2). Subjects who meet eligibility criteria after completion of all screening assessments will enter the dose escalation period.

The screening period will last at a minimum 4 weeks to confirm the average morning ItchRO (Obs) score ≥1.5 and completion of at least 21 valid morning ItchRO (Obs) and will allow for the evaluation of each subject's eligibility for inclusion into the study. Since it is difficult to evaluate pruritus in infants, subjects <12 months of age at screening whose pruritus is unavoidably difficult to be evaluated are not necessarily required to meet the above score. The requirements of Itch Reported Outcome (ItchRO™) are described in Section 9.1.7.1.1.

9.1.3 Demographics, Medical History, Disease History, and Medication History/Prior Treatment Procedure

Demographics:

Subject demographic information including sex, date of birth, and race will be collected at the screening visit (Visit 1). Variance in pediatric age-related reference ranges is significant, and the date of birth is required to ensure correct interpretation of the laboratory report.

Medical History:

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved within 1 year prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.10).

Disease History:

During the screening, the investigator will record PFIC disease history.

Medication History/Prior Treatment:

Medication history/prior treatment information to be obtained includes any medication/treatment relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 3 months prior to signing of informed consent.

9.1.4 Physical Examination Procedure

Abnormalities identified at the screening visit (Visit 1) and the baseline (Week 0/Visit 2) will be documented in the subject's source documents. Significant changes after the screening visit (Visit 1) or the baseline (Week 0/Visit 2) should be assessed as pretreatment events. Refer to Section 10.0 for additional details.

Physical examination assessments should also include specific assessments for signs of hepatomegaly, splenomegaly, edema, ascites, jaundice, and scleral icterus.

9.1.5 Weight, Height, and BMI

Weight will be assessed at the screening visit (Visit 1), the baseline (Week 0/Visit 2), and at the site visits during the treatment period, and recorded to the nearest 0.1 kg, using a balance or electronic scale (children who can stand on their own, generally ≥ 2 years of age) or infant scale (generally <2 years of age).

Height will be collected at the screening visit (Visit 1), the baseline (Week 0/Visit 2), and at all site visits during the treatment period. Height will be measured by trained site staff in children who can stand on their own (generally ≥ 2 years of age) or not (generally < 2 years of age) using a stadiometer or headboard, respectively, via 2 independent measurements, recorded to the nearest 0.1 cm (and a third measurement if values differ by > 0.5 cm). The same stadiometer should be used for all study visit measurements. The detailed procedure will be provided in the "Height and Weight Guidance".

BMI is calculated using metric units with the formula provided below: Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

$BMI = \text{weight (kg)}/\text{height (m)}^2$

9.1.6 Vital Sign Procedure

Vital signs include blood pressure, heart rate, temperature, and respiration rate. Blood pressure should be determined by cuff using the same method, the same arm, and the same position, following 5 minutes of rest throughout the study. Any deviations of vital signs from the screening visit (Visit 1) or the baseline (Week 0/Visit 2) vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.7 Primary Efficacy Measurement

9.1.7.1 eDiary

Subjects and caregivers will be trained on the use of the eDiary during the screening visit (Visit 1). Pruritus will be assessed and recorded twice daily, via ItchRO™, beginning with the day after the screening visit (Visit 1) and every day throughout the duration of the study, as described in Appendix A.

Throughout the duration of the study, subjects/caregivers will be required to submit twice daily (morning and evening) assessments using the eDiary.

9.1.7.1.1 *Itch Reported Outcome (ItchRO™)*

Pruritus will be assessed using the Itch caregiver/patient reported outcome (PRO) measure (ItchRO™) administered as a twice daily eDiary as described in Appendix D. Caregivers for all subjects will complete the Observer instrument: ItchRO (Obs). The ItchRO (Obs) should be

completed by the same caregiver for consistency, whenever possible. The caregivers should assess subject's pruritus and record it, even if the subject is an adult (over 18 years old).

The ItchRO (Obs) eligibility must be determined after a minimum of 4 weeks of ItchRO (Obs) twice daily diary entry. If the subject does not meet eligibility after 4 weeks, ItchRO (Obs) eligibility should be re-assessed at Week 5, and also at Week 6 if eligibility is not met at Week 5. A maximum of 3 attempts can be made to determine ItchRO (Obs) eligibility during the screening period.

Only subjects ≥ 9 years of age at the screening visit (Visit 1) will complete the patient instrument: ItchRO (Pt). If a subject turns 9 years of age at any point after the screening visit (Visit 1), they will not complete the ItchRO (Pt). Due to the expected low number of subjects old enough to rate ItchRO (Pt), this measure will only be analyzed as an exploratory outcome.

ItchRO (Obs)™

The severity of pruritus will be measured by the completion of the first question in the ItchRO (Obs) (how severe were your child's itch-related symptoms). The frequency of pruritus will be measured by completion of the third question in the ItchRO (Obs) (how much of the time was your child rubbing or scratching). Caregivers will rate the severity and frequency of pruritus using 5 choices to describe their pruritus condition. The sixth choice, "I don't know" will not count toward their severity or frequency score (categorized as missing data) and is included to account for rare occasions that the designated caregiver cannot observe the child, or the child could not communicate the severity or frequency of their pruritus condition. Capturing "I don't know" should be kept at an absolute minimum, as this will lead to missing data.

ItchRO (Pt)™

The severity of pruritus will be measured by the completion of the first question in the ItchRO (Pt) (how itchy did you feel). The frequency of pruritus will be measured by completion of the third question in the ItchRO (Pt) (how much of last night/today did feeling itchy make you rub or scratch). Subjects will rate the severity and frequency of pruritus using 5 choices to describe their pruritus condition.

9.1.7.2 Serum Bile Acids and Other Cholestasis Biomarkers

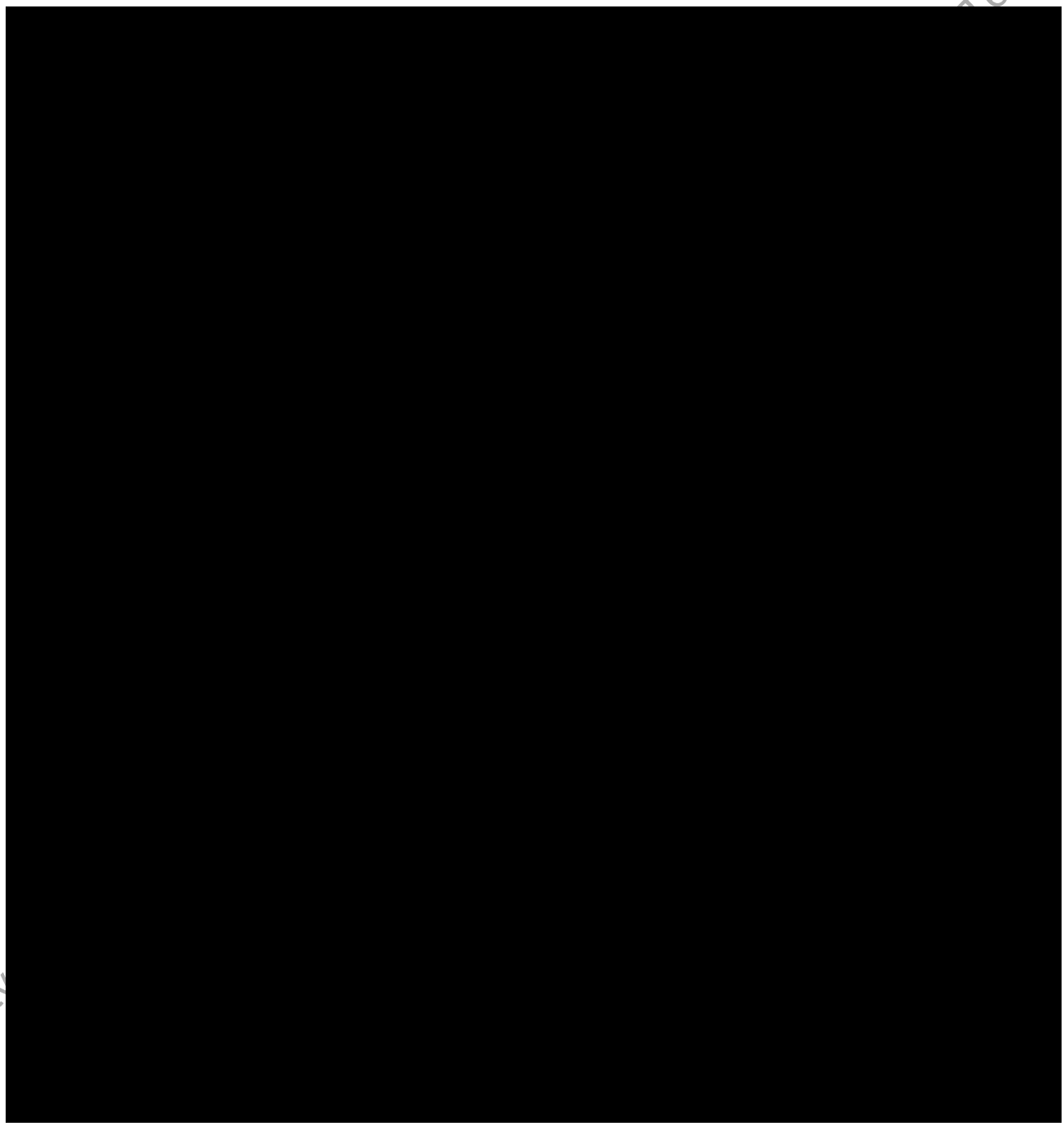
Blood samples will be collected as described in Appendix A and to measure levels of cholestasis biomarkers including total sBA, sBA subspecies, 7αC4, FGF-19*, and autotaxin* as well as liver-related parameters. Subjects ≥12 months of age are encouraged to fast at least 6 hours prior to collection (water intake is permitted if necessary but not recommended). Subjects <12 months of age are encouraged to fast at least 2 hours prior to collection (water intake, excluding milk, is allowed when required).

* FGF-19 and autotaxin are not mandatory, if the subjects are too small to collect enough amount of blood.

Total sBA and sBA subspecies will be quantified with liquid chromatography-mass spectrometry (LC-MS) methodology for assessments. In addition, screening total sBA will be

assessed with an enzymatic assay for inclusion criteria evaluation. 7αC4, a key intermediate in the pathway for bile acid synthesis from cholesterol, will be determined by a validated liquid chromatograph-tandem mass spectrometer (LC-MS/MS) method.

9.1.8 Other Efficacy Measurement



9.1.9 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

The investigators must ensure that subjects receive LSV supplements, as needed, for the duration of the study.

9.1.10 Documentation of Concurrent Medical Conditions (Complication)

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening/baseline examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.11 Procedures for Clinical Laboratory Samples

Clinical laboratory evaluations will be performed according to the central laboratory manual. If possible, reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator must assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Clinical laboratory assessments will be performed as listed in Table 9.a.

The sBA (LC-MS) and PK samples must be examined at central laboratory, in all subjects. In addition, screening total sBA (enzymatic assay) for inclusion criteria evaluation must be examined at central laboratory, in all subjects. The samples for chemistry panel, LSV, cholestasis biomarkers, lipid panel, complete blood count (CBC), coagulation, α-fetoprotein (AFP), and serum storage samples could be examined at study sites, if the subjects are too small to collect enough amount of blood for the central laboratory, depending on the investigator's decision. For each subject, the blood samples should be examined at the same laboratory throughout the study once the laboratory is determined by the investigator, as much as possible.

A serum storage sample will be collected as a back-up sample in case re-analysis is needed.

According to the Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population, the volume of blood drawn from a subject should not exceed 3% of the total blood volume during a period of four weeks and should not exceed 1% at any single time [8]. Should the volume of blood required for a single visit or a 30-day period exceed the maximum allowable amount, the investigator will draw blood in the priority order listed in

Appendix B until the maximum amount has been reached. Laboratory draws missing due to the maximum allowable amount being reached will not be considered protocol deviations. Further instructions will be provided in the "Guidance on Maximum Volume of Blood Draws".

When the laboratory data has not been collected electronically, the investigator or designee is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Unscheduled assessments (eg, laboratory values) are not required to be collected in the eCRF except for those that are directly relevant to the monitoring of an AE/SAE; collection of other values may be requested by the sponsor.

Anion gap and osmolar gap as well as corrected sodium, α-Tocopherol/Total Lipids Ratio, Retinol/retinol binding protein (RBP) Molar Ratio, FIB-4 and APRI will be calculated.

Table 9.a Clinical Laboratory Tests

Hematology (CBC with Differential)	Chemistry	Urinalysis
Hematocrit	Albumin	pH
Hemoglobin	ALP	Specific gravity
MCV, MCH, MCHC	Amylase	Protein
Red blood cells	ALT (SGPT)	Glucose
Platelets	AST (SGOT)	Ketones
White blood cells	Bicarbonate	Bilirubin
WBC Differential (% and absolute)	Bilirubin, direct (conjugated)	Occult blood and cells
Neutrophils	TSB	Nitrite
Eosinophils	BUN	Urobilinogen
Basophils	Calcium	Leukocyte esterase
Lymphocytes	Chloride	Microscopic examination
Monocytes	Creatinine	Oxalate
	GGT	Urinary creatinine
	Glucose	
	Lipase	
	Phosphate	
	Potassium	
	Sodium	
	Total protein	
	Total sBA (enzymatic assay)	
	Uric Acid	
	Measured serum Osmolality	

Other:

Coagulation	Lipid Panel	TAK-625 Levels
aPTT (sec)	Total cholesterol	TAK-625 in plasma
INR	LDL-C (direct)	
PT (sec)	HDL-C	**Marker of HCC**
	TG	AFP
	Cholestasis Biomarkers	
	sBA (LC-MS)	
	sBA subspecies	
	7αC4	
	FGF-19 [a]	
	Autotaxin [a]	
	Lipid Soluble Vitamins	
	25-hydroxy vitamin D	
	Retinol	
	RBP [b]	
	α-Tocopherol	

Urine
β-hCG (for pregnancy)

AFP=α-fetoprotein; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; 7αC4=7α-hydroxy-4-cholesten-3-one; β-hCG=β-human chorionic gonadotropin; CBC=complete blood count; FGF-19=fibroblast growth factor 19; GGT=gamma-glutamyl transferase; HCC=hepatocellular carcinoma; HDL-C=high density lipoprotein-cholesterol; INR=international normalized ratio; LC-MS=liquid chromatography-mass spectrometry; LDL-C=low density lipoprotein-cholesterol; LSV=lipid soluble vitamin; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time; RBP=retinol binding protein; sBA=serum bile acid; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; TG=Triglycerides; TSB=total serum bilirubin; WBC=white blood cell.

a) FGF-19 and autotaxin are not mandatory, if the subjects are too small to collect enough amount of blood.
b) Performed when clinically indicated or in case of low retinol levels for subjects <12 months of age.

The central/local laboratory will perform laboratory tests for hematology, chemistry, urinalysis, and others. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

9.1.12 Pregnancy Test

A urine pregnancy test is performed on all female subjects of childbearing potential prior to dispensing study drug at study visits as outlined in Appendix A, or if pregnancy is suspected or on withdrawal of the subject from the study.

9.1.13 Contraception and Pregnancy Avoidance Procedure

9.1.13.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 30 days after the last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). 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 (from the list in Section 9.1.13.3).

9.1.13.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list in Section 9.1.13.3).

In addition, they must be advised not to donate ova during this period.

9.1.13.3 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 postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, 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 postmenopausal 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. Acceptable and available methods of contraception in Japan are shown in this section. A male subject who is non-sterilized and sexually active with a female partner of childbearing potential must use male condom. Females of childbearing potential who are partners of male subjects are also advised to, or a female subject of childbearing potential who is sexually active with a nonsterilized male partner must use the method of contraception below.
   - Intrauterine devices (IUDs).
   - Bilateral tubal interruption/tubal ligation.
   - A Male partner who is the only partner of the subject and was postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.
   - Progestin/Estrogen mixed preparation for 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.
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.

   † These contraception methods and pregnancy avoidance procedures are not approved or certificated in Japan.
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.
4. During the course of the study, regular urine β-human chorionic gonadotropin (β-hCG) pregnancy tests will be performed only for females of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.

b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners.

c) Assessment of subject compliance through questions such as:

i. Have you used the contraception consistently and correctly since the last visit?

ii. Have you forgotten to use contraception since the last visit?

iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes").

iv. Is there a chance you could be pregnant?

5. In addition to a negative urine β-hCG pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative urine β-hCG pregnancy test at Visit 1 and Visit 2.

9.1.13.4 General Guidance with Respect to the Avoidance of Pregnancy

From signing of informed consent and throughout the duration of the study and for 30 days after the last dose, female subjects of childbearing potential (ie, nonsterilized, premenopausal female subjects) who are sexually active must use acceptable methods of contraception. Also from signing of informed consent, throughout the duration of the study, and for 30 days after last dose, nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use contraception. Such subjects will be provided with information on acceptable 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 during the course of the study. During the course of the study, regular urine β-hCG pregnancy tests will be performed, and subjects will receive continued guidance with respect to avoiding pregnancy as part of the study procedures (Appendix A).

In addition to a negative urine β-hCG pregnancy test at screening period, subjects also must have a negative urine β-hCG pregnancy test on the day of the first dose of study drug (predose), before to receiving any dose of study drug.

In addition, male subjects must be advised not to donate sperm from signing of informed consent to 30 days after the last dose of study drug.

9.1.14 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 30 days after the last dose, should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of study drug or within 30 days of the last dose of study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in the annex.

If the female subject and/or 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 subject/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.

All pregnancies, including female partners of male subjects, in subjects on 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.

9.1.15 ECG Procedure

The following parameters will be collected: heart rate, RR interval, PR interval, QRS duration, uncorrected QT interval, rhythm (sinus or specify other rhythm), ECG normal or abnormal (if abnormal specify abnormality).

QT interval corrected using both Bazett's and Fridericia's formula (QTcB and QTcF) will be derived from data collected in the eCRF.

ECGs should be recorded in the supine position, if possible after at least 10 minutes rest to ensure a stable baseline. A standard 12-lead ECG will be performed at the screening (Visit 1) and other visits as outlined in Appendix A. ECGs will be recorded locally in source documents and results captured in the eCRF.

9.1.16 Ultrasound Liver Imaging

An abdominal ultrasound will be performed at the screening (Visit 1) and other visits as outlined in Appendix A to determine the presence of any liver mass. A screening ultrasound is not required if the results of an ultrasound or liver magnetic resonance imaging (MRI) completed in the last 6 months are available, and the clinical status of the subject has not changed significantly since the time of the test.

9.1.17 AE Collection

At each study visit and subject contact, subjects or their caregivers will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). AEs will be collected from the time informed consent is signed (refer to Section 10.0).

9.1.18 Other Safety Evaluation

Safety will be evaluated based on the occurrence of all AEs, SAEs, AECIs, physical examination findings, vital signs (blood pressure, heart rate, temperature, and respiration rate), clinical laboratory parameters (hematology, chemistry, urinalysis, and others).

AECIs include the following:

- LSV deficiency events.

- Liver parameter disruption.

Safety laboratory tests to be performed at site visits and processed by a central laboratory. However, these could be processed at sites, if the subjects are too small to collect enough amount of blood for the central laboratory, depending on the investigator's decision. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Additional evaluations may be performed at the discretion of the investigator in consultation with the medical monitor or designee.

Stopping Rule Guidance: Subject dosing must be suspended until the retest results are available. If any of the stopping criteria described in Section 10.4.3 and Section 10.4.6 is confirmed, the investigator in consultation with the medical monitor (or appropriately qualified designee) will permanently discontinue the subject from further treatment with study drug.

9.1.19 Genetic Testing (PFIC Genotype)

ATP8B1 (PFIC1), ABCB11 (PFIC2), ABCB4 (PFIC3), TJP2 (PFIC4), nuclear receptor subfamily 1 group H member 4 (NR1H4) (PFIC5) and other genes such as myosin VB (MYO5B) are reported to be predictive of PFIC. The cohort assignment will be determined by the investigator with the genotyping results. If there are only genotyping results obtained as a clinical research, additional genotyping analysis by a registered clinical laboratory or a hospital (e.g., Kazusa DNA Research Institute) should be performed. For the confirmation, the genotype expert reviews the genotyping results for cohort assignment during screening period. If the investigator's determination and the expert's confirmation does not match, the investigator, the expert and the sponsor will discuss the appropriateness of the cohort assignment. The details of the confirmation procedure are described in the genotype confirmation manual.

9.1.20 PK Sample Collection and Analysis

9.1.20.1 Collection of Blood for PK Sampling

Blood samples (one sample per scheduled time) for serum TAK-625 concentration will be collected according to the Schedule of Study Procedures (Appendix A).

Plasma PK samples at predose and approximately 2.5 hours (±30 minutes) after morning dose at Week 10 and at predose and approximately 30 minutes (±15 minutes) after morning dose at Week 14 will be collected. If sample collections at Week 14 are difficult, PK samples can be collected at any visit up to Week 26. Additionally, predose at Week 14 is optional. Postdose PK samples should be collected in preference to predose PK samples, if the subjects are too small to collect enough amount of blood.

The actual dates and times of PK sample collection, the last dose of study drug before the predose PK sample collection and the postdose PK sample collection, and the last meal of each PK sample collection will be recorded on the source document and eCRF.

Instructions for collecting, processing, and shipping of PK samples are provided in the laboratory manual.

9.1.21 Documentation of Screen Failure

The investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the screening visit, the investigator should complete the eCRF. The IRT should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- AE.
- Screen failure (Did not meet inclusion criteria or did meet exclusion criteria <specify reason>).
- Protocol deviation.
- Lost to follow-up.
- Pregnancy.
- Withdrawal by subject <specify reason>.
- Study termination.
- Other <specify reason>.

Subject ID numbers assigned to subjects who fail screening should not be reused.

9.1.22 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the dose escalation period.

If the subject is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

The study drug administration will be recorded in the eCRF/eDiary.

When administration of a study drug was inappropriately conducted, the dosage and the reasons will be recorded in the eCRF/eDiary.

Subjects will be required to bring study drug containers/unused study drugs to each dispensing site visit. All study drugs administered to the subject will be recorded on the eCRFs.

During the dose escalation period, subject compliance will be reviewed as part of the dose escalation assessment. Any concerns with compliance should be discussed with the medical monitor.

During the stable dosing period (to Week 26), subjects will be allowed a maximum of 28 days (both morning and evening dose missed) of cumulative dose interruption. During the 12 weeks of the stable dosing period (Weeks 15 to 26), subjects will be allowed a maximum of 17 days (both morning and evening dose) of cumulative dose interruption but not more than 7 consecutive days. Subjects may remain on study during dose interruptions and should continue to complete all regularly scheduled subject study visits and assessments. After dose interruption, subjects will reinitiate dosing at their MTD. Any dose interruptions longer than the maximum allowed will be documented as protocol deviations.

Any subject who has over 56 days (both morning and evening dose) of cumulative dose interruption during the stable dosing period (to Week 26) should be discontinued from the study.

Procedures outlined in Section 9.3.4 should be followed for any subject who is discontinued early from the study.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

Prior to performing any study-related procedures (including those related to screening), the investigator or designee must obtain written informed consent (or assent as applicable) from the subject (as per local requirements). For information about informed consent process see Section 15.2.

Enrollment numbers /subject numbers are assigned to all subjects as they consent to take part in the study.

Within each site, the subject number is assigned to subjects according to the sequence of presentation for study participation.

The investigator will utilize IRT at screening to register the subject into the study and obtain an enrollment number/subject number to identify the subject throughout the study.

9.3.1 Screening Period

The screening period starts when informed consent (or assent as applicable) is signed. The duration of the screening period is up to 6 weeks during which all procedures listed for the screening visit (Visit 1) in Appendix A must be completed.

The screening period will last at a minimum 4 weeks to confirm the average morning ItchRO (Obs) score ≥1.5 and with completion of at least 21 valid morning ItchRO (Obs) and will allow for the evaluation of each subject's eligibility for inclusion into the study. Since it is difficult to evaluate pruritus in infants, subjects <12 months of age at screening whose pruritus is unavoidably difficult to be evaluated are not necessarily required to meet the above score. If the subject does not meet eligibility after 4 weeks, ItchRO (Obs) eligibility should be re-assessed at Week 5, and also at Week 6 if eligibility is not met at Week 5. A maximum of 3 attempts can be made to determine ItchRO (Obs) eligibility during the screening period and will allow for the

evaluation of each subject's eligibility for inclusion into the study. The requirements of ItchRO™ are described in Section 9.1.7.1.1.

Subjects who meet eligibility criteria after completion of all screening assessments will enter the dose escalation period. This period should not commence until all screening assessments required to confirm eligibility for administering of study drug and the PFIC genotype results have been confirmed by sponsor or designee.

If the subject does not meet eligibility criteria following completion of screening assessments, the investigator or designee will document the subject as a screen failure in the IRT. A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been administered study drug.

In exceptional cases, subjects who initially fail to meet all eligibility criteria may be re-screened at a later timepoint, after consultation with the medical monitor.

Screen failure subject numbers cannot be reassigned to other subjects.

A 5-day visit window will be permitted in the case the 42-day screening period needs to be extended. This window will allow for blood sample retesting at the investigator's discretion.

Procedures to be completed at the screening visit include:

- Informed consent/assent.
- Eligibility assessment based on inclusion/exclusion criteria.
- Demographics, medical history, disease history (including complication), and medication/treatment history.
- Physical examination, vital signs, weight, height, and BMI.
- 12-lead ECG.
- Liver ultrasound.
- Pregnancy test (urine, for females of childbearing potential).
- Confirming PFIC genotype based on a genotyping (for subjects who do not have documentation of mutation related with PFIC).
- eDiary supply and instructions.
- [redacted]
- [redacted]
- Screening clinical laboratory tests (blood).
- AE assessment.
- Concomitant medications (including confirmation of the need to administer LSV supplements).

- Access IRT to obtain subject number.

9.3.2 Dose Escalation Period

Subjects who continue to meet all eligibility criteria will receive TAK-625 as described in Appendix A at the baseline visit (Week 0/Visit 2).

The dose escalation period will comprise of 4 weeks. All assessments and procedures listed for visits and subject contacts (phone calls) from Week 0 to Week 4 (Visits 2 to Visit 4) in Appendix A should be completed during this period.

The dose escalation period is allowed to be extended up to 6 weeks depending on the safety or tolerability concerns (refer to Section 8.1.3).

9.3.2.1 Visits in the Dose Escalation Period

During the dose escalation period, a ±2-day visit window will be permitted, unless otherwise specified. Visit dates and acceptable windows are calculated from the baseline visit (Week 0/Visit 2).

Procedures to be completed in the dose escalation visit include:

- Eligibility assessment based on inclusion/exclusion criteria (only at Week 0).
- Physical examination, vital signs, weight, height, and BMI.
- 12-lead ECG (only at Week 0).
- Pregnancy test (urine, for females of childbearing potential) (at Weeks 0 and 4).
- [redacted]
- [redacted]
- [redacted]
- Clinical laboratory tests (blood) (at Weeks 0 and 2).
- Clinical laboratory tests (urine) (only at Week 0).
- Blood collection for serum storage (at Weeks 0 and 2).
- eDiary review.
- Study drug compliance review.
- Study drug supply and return.
- AE assessment.
- Concomitant medications (including confirmation of the need to administer LSV supplements).

9.3.2.2 Phone Calls in the Dose Escalation Period

During the dose escalation period, subjects/caregivers will receive subject contacts (phone calls) on Weeks 1 and 3 to review the use of concomitant treatments, study drug compliances, and AEs as outlined in Appendix A.

For subject contacts (phone calls) of Weeks 1 and 3, a ±2-day window will be permitted. Contact dates and acceptable windows are calculated from the baseline visit (Week 0/Visit 2).

Procedures to be completed in the subject contacts (phone calls) include:

- Study drug compliance review.
- AE assessment.
- Concomitant medications (including confirmation of the need to administer LSV supplements).

9.3.3 Stable Dosing Period

After the dose escalation period, each subject will continue dosing with study drug at the Week 4 or Week 6 dose level (the MTD level) in the stable dosing period.

The stable dosing period will comprise of 44 weeks. All assessments and procedures listed for visits and subject contacts (phone calls) from Week 5 to Week 48 in Appendix A should be completed during this period.

9.3.3.1 Visits in the Stable Dosing Period

During the stable dosing period, for Weeks 6 and 28, a ±2-day visit window will be permitted. From Week 10 to 26 and Week 32 to 48, a ±5-day visit window will be permitted. Visit dates and acceptable windows are calculated from the baseline visit (Week 0/Visit 2).

Procedures to be completed in the stable dosing visit include:

- Physical examination, vital signs, weight, height, and BMI.
- 12-lead ECG (at Weeks 10, 26 and 48).
- Liver ultrasound (at Weeks 26 and 48).
- Pregnancy test (urine, for females of childbearing potential) (at Weeks 10, 18, 26 and 48).
- [redacted]
- [redacted]
- [redacted]
- Clinical laboratory tests (blood).
- Clinical laboratory tests (urine) (at Weeks 6, 10, 18, 26, 32, 40, and 48).
- Blood collection for PK (at Weeks 10 and 14).

- Blood collection for serum storage.
- eDiary review.
- Study drug compliance review.
- Study drug supply and return.
- AE assessment.
- Concomitant medications (including confirmation of the need to administer LSV supplements).

9.3.3.2 Phone Calls the Stable Dosing Period

During the stable dosing period, subjects/caregivers will receive subject contacts (phone calls) on Weeks 5, 8, 12, 16, 20, 24, 27, 30, 34, 38, 42, and 46 to review the use of concomitant treatments, study drug compliances, and AEs as outlined in Appendix A.

For subject contacts (phone calls) at Weeks 5 and 27, a ±2-day window will be permitted. From Week 8 to 24 and Week 30 to 46, a ±5-day visit window will be permitted. Contact dates and acceptable windows are calculated from the baseline visit (Week 0/Visit 2).

Procedures to be completed in the subject contacts (phone calls) include:

- Study drug compliance review.
- AE assessment.
- Concomitant medications (including confirmation of the need to administer LSV supplements).

9.3.4 ET

Subjects will return to the study site for ET and the procedures and assessments outlined in Appendix A will be performed.

If study drug is permanently discontinued early, regardless of the reason, the subject will be discontinued from the study (refer to Section 7.6), and the evaluations listed for the ET are to be performed. The subject should undergo the ET assessments at the visit during which study drug was discontinued, or the subject should be scheduled for an additional ET visit as soon as possible, if study drug was discontinued between visits.

Subjects who discontinue prematurely at any time during the treatment period will have a final safety follow-up subject contact (phone call) 7 days after the ET visit.

- Physical examination, vital signs, weight, height, and BMI.
- 12-lead ECG.
- Liver ultrasound.
- Pregnancy test (urine, for females of childbearing potential).

- [redacted]
- [redacted]
- [redacted]
- Clinical laboratory tests (blood).
- Clinical laboratory tests (urine).
- Blood collection for serum storage.
- eDiary review.
- Study drug compliance review.
- AE assessment.
- Concomitant medications (including confirmation of the need to administer LSV supplements).

9.3.5 Follow-up Dosing Period

Additionally, in the follow-up dosing period, each subject will continue dosing with study drug. The safety evaluation will be performed every 12 weeks from Week 48 visit until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication.

Procedures to be completed in the follow-up dosing visit include:

- Physical examination, vital signs, weight, height, and BMI.
- 12-lead ECG.
- Liver ultrasound.
- Pregnancy test (urine, for females of childbearing potential).
- [redacted]
- [redacted]
- [redacted]
- Clinical laboratory tests (blood).
- Clinical laboratory tests (urine).
- Blood collection for serum storage.
- eDiary review.
- Study drug compliance review.

- Study drug supply and return.
- AE assessment.
- Concomitant medications (including confirmation of the need to administer LSV supplements).

9.3.6 Safety Follow-up

The safety follow-up period for this protocol is 7 days from the final study visit or ET visit. Subjects/caregivers will have a final safety follow-up subject contact (phone call) 7 days after the final study visit or ET visit (except for screen failure).

Subjects who discontinue at any time during the treatment period will have a final safety follow-up subject contact (phone call) 7 days after the ET visit.

Subjects who discontinue from the study for safety reasons are also followed-up as long as clinically indicated or until no further improvement with an adverse outcome is expected. All AEs and SAEs that are not resolved at the time of this contact will be followed to closure by the site (see Section 10.0).

9.3.7 Post Study Care

The study will be continued until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if the investigator determines the subject's discontinuation, or if the sponsor stops the program or development in this indication. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the EOT visit.

If TAK-625 is approved for marketing by authorities during the study, the study can be shifted to a post-marketing study after the approval.

9.3.8 Alternative Approaches to Study Procedures and Data Collection Due to Coronavirus Disease 2019

In unavoidable circumstances that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures (Appendix A), in particular during the coronavirus disease 2019 (COVID-19) pandemic, contingency measures may be implemented. The following information provides guidance regarding changes to the study procedures that could be implemented for study subjects or study sites that are affected by the COVID-19 public health emergency. This guidance is aligned with the current guidance from global health authorities on the conduct of clinical studies during the COVID-19 pandemic.

As the COVID-19 pandemic may peak in different regions at different times, and as restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the sponsor or designee, while maintaining subject safety and confidentiality as the priority.

The principal investigator should also notify the local IRB, as appropriate, of any deviation for temporary use of alternative methods for conducting subject visits (eg, video conferencing, telephone visits) in the event of restrictive measures due to the COVID-19 pandemic, per local requirements.

Procedural changes due to COVID-19 may include the following:

- No routine COVID-19 testing is required during the study unless the subject has signs or symptoms of COVID-19-related disease or COVID-19 pneumonia in the opinion of the investigator, or the subject has been identified by national or local public health authority as a close contact of a probable or confirmed case of COVID-19. The decision to have the subject tested for COVID-19 is left to the subject and the investigator unless required by the health authority.
- Subjects who discontinued from screening due to COVID-19-related factors but were otherwise qualified to participate in the study may be re-screened if the sponsor or designee agrees.
- All attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:
  - Sites impacted by the COVID-19 pandemic must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection.
  - Sites may seek approval from the medical monitor to continue subjects in the study despite departure from the Schedule of Study Procedures. Principal investigators are expected to evaluate the impact to the safety of the study subjects and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.
- Informed Consent Procedure: If necessary, informed consent from a potential or current study subject's parent or guardian may be obtained via verbal consent when these individuals are unable to travel to the site. Informed consent forms will be signed once the subject and his/her parent, or guardian can return in person to the study site.
- Visits: All visits must be done with the subject present at the study site.
  - Protocol Deviations: Any deviations from the protocol-specified procedures due to COVID-19 will be recorded as related to COVID-19.
  - Visit Window Extension: Sites may seek approval from the sponsor or designee to extend a visit window in order to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window will be recorded as a protocol deviation, and such deviations will be recorded in the study records as related to COVID-19.

  - Local laboratory test may be appliable for assessing clinical chemistry and hematology

- EOT/ET visit: The EOT/ET visit should be performed with the subject present at the study site. Sites may seek approval from the sponsor or designee to extend a visit window in order to conduct an on-site visit. If the visit cannot be conducted on-site within the visit window granted by the sponsor or designee, sites may conduct EOT/ET visit procedures remotely as is feasible, including using local laboratories for assessment of biochemistry, hematology, and urinalysis (as specified in Appendix A). Assessments that cannot be completed during the protocol-specified window will be recorded as a protocol deviation, and such deviations will be recorded in the study records as related to COVID 19.
- When a physical examination or other in-person procedure is needed in response to an AE, the subject should be evaluated in-person at the site per protocol if possible. If the subject cannot visit the site due to COVID-19, the site should contact the Medical Monitor.
- Discontinuation or Withdrawal from the Study or Study Medication: If a subject chooses to withdraw from the study or study medication due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this must be specified as the reason for subject withdrawal in the eCRF.
- Allow transfer of study subjects to study sites away from risk zones or closer to their home to sites already participating in the study or new ones.
- For subjects who are impacted by certain factors, any alternative approaches to study procedures (ie, procedures not conducted per the Schedule of Study Procedures) due to the COVID-19 pandemic must be documented in the study records as related to COVID 19. Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the statistical analysis plan (SAP).

9.4 Biological Sample Retention and Destruction

The additional blood samples collected for this study will be stored at its affiliated companies for up to 15 years from when the study results are reported or if less, the maximum period permitted under applicable law or until consent is withdrawn.

10.0 AEs

10.1 Definitions

10.1.1 Pretreatment Events

A pretreatment event is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but before administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

10.1.3 Additional Points to Consider for AEs

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 for any reason.

Diagnoses vs 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 findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding 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:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations

(eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE. The 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 concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious, or severe in nature. The investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. The 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 any change in study drug, the worsening or complication should be recorded as a new AE. The investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- 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 recorded 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.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose and medication error:

- Cases of overdose or medication error with any medication without manifested side effects are NOT considered AEs, but instead will be documented as overdose or medication error separately. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.4 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. Leads to 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.

10.1.5 AECIs

An AECI (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them.

In this study AECIs include the following:

- LSV deficiency events.
- Liver parameter disruption.

10.1.6 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

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

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

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

The start date of AEs will be determined using the following criteria:

AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings, or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment	The date that a worsening or complication of the condition was noted first by the subject and/or the investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings.	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms.	The date of examination when apparent elevation, reduction, increase, or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; 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 got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- 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 – the AEs that are 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 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time that the subject signs the informed consent and will continue until the end of safety follow-up.

10.2.1.2 AE Reporting

At each study visit, the 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 a serious AE 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.

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

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

Patient eDiary/equestionnaire will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with these instruments, then proper follow-up with the subject for medical evaluation should be

undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.2 Collection and Reporting of SAEs

All AEs spontaneously reported by the subject or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.2.1 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

An SAE should be reported by the investigator to the sponsor within 24 hours/1 business day of the SAE occurrence, along with any relevant information. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible within 24 hours/1 business day of the SAE occurrence, the completed Takeda paper-based SAE form should be submitted to the sponsor/the Emergency Reception Center for Safety Information appropriate personnel (see annexes) 24 hours/1 business day of the SAE occurrence. 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 ID number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

If paper-based SAEs are submitted, EDC/RAVE must be updated as soon as possible with the appropriate information.

- When reporting SAEs or pregnancy, SAE report form or pregnancy report form those are provided by the sponsor or by the institutions must be used.
- After the initial information of SAEs is reported to the sponsor, the initial SAE report form (original wet-ink) must be submitted to the sponsor in Japan. Also, if applicable, copy of related documents should be submitted to the sponsor as soon as possible, once they are available. The investigator should report detailed information without delay after notification of initial information. Additional detailed follow-up data surrounding the SAEs that becomes available following the initial report should be communicated through the same channels as outlined above.

- An operator of the Emergency Center for Safety Information is available for contact 24 hours a day and 365 days a year.

Emergency Center for Safety Information (available 24 hours 365 days) BELLSYSTEM24, Inc. [redacted]

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator will transmit a follow-up EDC SAE report or a paper-based SAE form in an EDC SAE report is not feasible (copy) or provide other written documentation and transmit it immediately. 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.

10.3.1 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, IRBs, and the head of the study site, 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 to the regulatory authorities as expedited report 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 a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

10.4 Safety Monitoring Rules

10.4.1 General Guidelines

The following guidelines are provided for the monitoring of selected laboratory parameters.

Confirmation Guidance: At any time during the study, the initial clinical laboratory results meeting the safety monitoring criteria presented below must be confirmed by performing measurements on new specimens (retest).

Retests should be conducted by the central laboratory. Retests at a local laboratory are acceptable on an as-needed basis. Local laboratory results are sent to the investigator and medical monitor of the sponsor for review (these should include the normal range of the local laboratory).

Retest collection should take place within 48 to 72 hours of the availability of the initial findings of potential concern. The results from the retest must be available prior to the next scheduled study visit or subject contact.

The baseline values for the purpose of the safety monitoring are the average between the value obtained during the screening visit (Visit 1) and the baseline visit (Week 0/Visit 2), unless a confounder (eg, intercurrent illness) causes variability outside what is expected for the underlying disease based on the investigator's judgment (in which case a third value will need to be obtained).

If the confirmed laboratory results or the symptom meets the criteria written in Sections 10.4.3, 10.4.5, 10.4.6 and 10.4.7, administration of study drug should be interrupted. Once the symptom is improved, administration of study drug may be restarted at the MTD after consultation with the medical monitor. Unless otherwise specified, there is no maximum number of restart. If the investigator has concerns about restarting at the MTD, dose reduction is allowed after discussion with the medical monitor.

10.4.2 Close Monitoring Criteria for Liver Parameters

Table 10.a provides the criteria for close monitoring of liver parameters.

Table 10.a Close Monitoring Criteria for Treatment-Emergent Elevated ALT and TSB

Parameter	Baseline Value	Close Monitoring Criteria
ALT	≤30 U/L	≥100 U/L
	>30 to ≤150 U/L	>3× BL or ≥250 U/L whichever comes first
	>150 to ≤450 U/L	≥(BL + 100 U/L)
TSB	Any	≥(BL + 3 mg/dL)

ALT=alanine aminotransferase; BL=baseline; TSB=total serum bilirubin.

Frequency of Repeat Measurements: Subjects with a confirmed ALT or TSB level that is continuing to rise after meeting the close monitoring criteria should have their liver chemistry retested as clinically indicated, until levels stabilize or begin to recover.

Further Investigation into Liver Chemistry Elevations: For subjects with a confirmed increase in ALT or TSB level, meeting the close monitoring criteria, the following investigations should be considered, as clinically indicated:

- Close and frequent monitoring of liver enzyme and serum bilirubin tests as clinically indicated. Frequency of retesting can decrease if abnormalities stabilize, recover, or the study drug has been interrupted or discontinued and the subject has no symptomatic manifestations of hepatitis or immunological reaction.
- Symptoms as well as prior, current, and intercurrent diseases/illnesses.
- Use of or recent change in use of concomitant treatment (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- History for exposure to environmental chemical agents and travel.
- Serology for viral hepatitis (hepatitis A virus immunoglobulin M [HAV IgM], hepatitis B virus surface antigen [HBs Ag], hepatitis C virus [HCV] antibody, HCV ribonucleic acid [RNA], cytomegalo virus immunoglobulin M [CMV IgM], and Epstein-Barr virus [EBV] antibody panel).
- Serology for autoimmune hepatitis (eg, antinuclear antibody [ANA]).
- AST, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH).
- CBC with differential blood count (eosinophils).
- Reticulocyte count, prothrombin time (PT)/INR.

Additional investigations of liver parameters, including gastroenterology/hepatology consultations, and/or hepatic imaging, may be performed at the discretion of the investigator, in consultation with the medical monitor.

10.4.3 Guidelines for Interruption of Study Drug for Specific Liver Parameters

If the confirmed laboratory results meet any of the criteria below and the event is without an alternative explanation (ie, intercurrent illness, disease progression, natural history of the disease), interruption of study drug should be considered:

1. The close monitoring criteria of both ALT and TSB are met simultaneously

   OR
2. An increase of ALT or TSB is accompanied by signs and symptoms (eg, nausea/vomiting, right upper quadrant pain) or an immunological reaction (eg, rash, >5% eosinophilia, fever).
3. The following thresholds are met for either ALT or TSB (see Table 10.b).

Table 10.b Guidelines for Interruption of Study Drug for Specific Liver Parameters

Parameter	Baseline value	Observed change threshold
ALT	≤30 U/L	≥300 U/L
	>30 to ≤150 U/L	>(5× BL AND 300 U/L) OR ≥450 U/L whichever comes first
	>150 to ≤450 U/L	≥(BL + 300 U/L)
TSB	Any	≥(BL + 5 mg/dL)

ALT=alanine aminotransferase; BL=baseline; TSB=total serum bilirubin.

Frequency of Repeat Measurements: Subjects with a confirmed ALT or TSB level meeting interruption criteria should have their liver chemistry tests retested every 72 hours or as clinically indicated, until levels stabilize or begin to recover.

Further Investigation for Increased Liver Chemistry Results: For subjects with a confirmed increase in ALT or TSB level above the threshold, the investigations outlined in Section 10.4.2 should be considered, as clinically indicated.

Study drug may be re-started as long as the subject does not meet the dosing interruption criteria based on retest, does not meet criteria outlined in Section 10.4.4, liver parameters have returned to or near baseline, and an alternative explanation was found for the increased liver parameter (ie, intercurrent illness, disease progression, or natural history of the underlying disease). The investigator and the medical monitor or qualified designee should confer as to whether additional close monitoring is needed.

10.4.4 Rules for Study Drug Discontinuation Following Abnormalities of Liver Parameters

Study drug **should not** be restarted:

- If the subject had a probable Drug-induced Livery Injury (DILI) in the opinion of the investigator and medical monitor.
- If the subject reports signs/symptoms of acute hepatitis, liver decompensation (ie, variceal hemorrhage, ascites, hepatic encephalopathy) or hypersensitivity reaction.
- If the subject had liver parameters elevations meeting criteria in Section 10.4.3 without alternative explanations or that are inconsistent with the natural history of the disease.
- After meeting stopping criteria subsequent to a re-challenge (ie, meeting stopping criteria after re-introduction of study drug) that is likely related to study drug.
- After two previous interruptions for safety reasons, unless there is a compelling reason why the subject should continue with dosing (ie, interruptions were due to disease progression,

natural history, intercurrent illness) and provided that the subject is still compliant with the study protocol as per Section 8.2.

If study drug is permanently discontinued, the subject will be discontinued from the study and will be expected to complete the ET study procedures.

10.4.5 Safety Monitoring for LSVs

The LSV status will be assessed at every study visit per the schedule of assessments (refer to Appendix A); blood samples will be obtained at the study visit before the daily dose of vitamins is administered (refer to Appendix B).

In subjects with LSV deficiency, study drug must be interrupted if clinical symptoms of deficiency occur. Clinical symptoms include, but are not limited to:

- Vitamin A: Night blindness, degeneration of the retina, xerophthalmia, follicular hyperkeratosis, keratomalacia, or Bitot's spots.
- Vitamin D: Rickets, osteomalacia, costochondral beading, epiphyseal enlargement, cranial bossing, bowed legs.
- Vitamin E: Numbness/tingling, decreased deep tendon reflexes, hemolytic anemia, limited extraocular movements, especially upward gaze.
- Vitamin K: Easy bruising, excessive bleeding (eg, epistaxis), blood in the urine or stool, anemia.

Subjects may restart dosing once clinical symptoms resolve and LSV levels begin to improve unless the subject has been previously discontinued for the same symptomatic LSV deficiency. Each subject may be re-challenged after symptomatic LSV deficiency only twice.

In the event of a confirmed level that falls either below the subject's baseline or below the lower limit of normal (refer to central laboratory manual), whichever is lower, for a vitamin (25-hydroxy vitamin D, retinol, retinol binding protein, α-tocopherol), or INR (as a proxy for vitamin K status), without clinical symptoms of deficiency, the investigator should make the appropriate modification to the subject's vitamin supplementation regimen (see also Section 10.4.6 for INR monitoring).

Doses should be increased, as clinically indicated, to optimize the LSV levels. Parenteral formulations should be used (where available) if enteral supplements are unsuccessful at improving LSV deficiency.

The response to the change in regimen will be assessed at the next scheduled on-site study visit. LSV supplements are escalated in monthly intervals over a 3-month period. If during this period the LSV levels are persistently below the subject's baseline value or the lower limit of normal, whichever is lower, and there is an absence of clinical symptoms, the investigator will be given the option of permanent withdrawal of the subject from the study.

10.4.6 Safety Monitoring for Coagulation Panel Results

In the event of a confirmed laboratory result for INR >1.5 despite adequate vitamin K supplementation, the investigator and the medical monitor may consider a temporary interruption of study drug. Dosing may resume when the INR falls below 1.5 or returns to the subject's baseline level.

10.4.7 Study Medication Discontinuation Rules for Diarrhea

Study drug should be discontinued if a subject has severe diarrhea that requires hospitalization and/or an IV or nutritional supplementation or leads to severe electrolyte disturbances.

10.5 Product Complaints

Product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided in the "Pharmacy Manual".

11.0 STUDY-SPECIFIC COMMITTEES

Because it is an unblinded, small-scale, and late phase clinical study conducted with thorough safety information available in advance, Data Safety Monitoring Board (DSMB)/Data Monitoring Committee (DMC) and other review committees will not be established for this study.

12.0 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 medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary/ Japanese Drug Dictionary.

12.1 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.

Corrections are recorded in an audit trail that captures the old information, the new information, ID of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

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

The following data will not be recorded into the eCRFs:

1. BMI.
2. Laboratory test values (except urine pregnancy test).

   These samples could be examined at sites, if the subjects are too small to collect enough amount of blood for the central laboratory, depending on the investigator's decision (refer to Appendix B).
3. Serum concentrations of TAK-625.
4. Itch Reported Outcome.
5. Drug Compliance.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs/eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. 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.

Unscheduled assessments (eg, laboratory values) are not required to be collected in the eCRF except for those that are directly relevant to the monitoring of an AE/SAE; collection of other values may be requested by the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the ID log of all participating subjects, medical records, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. After the marketing approval of TAK-625 in Japan, the term of record retention shall expire on the day when a reexamination or reevaluation of TAK-625 is completed, instead of the day specified as of 1) and 2), if the study is shifted to a post-marketing study. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of ET or completion of the study.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A SAP will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis endpoints and analysis methodology to address all study objectives.

Statistical analyses will be performed using all subjects' data at Week 26 after the data are locked for marketing application. Additionally, statistical analyses will also be performed for marketing application at the time when the data are locked after all subjects complete Week 48, using all subjects' data at Week 48. Furthermore, statistical analyses will also be performed using all subjects' data at the end of the study after the data are locked.

A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

Three kinds of analysis sets are defined in this study. The intention-to-treat set (ITT), the main analysis set used for primary efficacy endpoint, will be defined as below.

- ITT: all subjects who received at least one dose of study drug.
- Per protocol analysis set (PPS): all ITT subjects who did not have any of the major protocol deviations and whose primary endpoint was evaluable.
- Safety analysis set: all subjects who received at least one dose of study drug.

The primary and supplemental cohort are defined in Section 7.1.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized in the ITT population separately on the primary cohort, the overall supplemental cohort, and all cohorts combined.

13.1.3 Efficacy Analysis

The primary, key secondary and other secondary endpoints will be mainly evaluated in the primary cohort.

13.1.3.1 Primary Endpoint

Primary Analysis:

Descriptive statistics and two-sided 95% confidence interval (CI) of mean will be provided on the primary cohort in the ITT.

Secondary Analysis:

For supportive analysis, the same analysis as the primary analysis will be performed on the primary cohort in the PPS to confirm robustness of the results.

Other Analysis:

The same analysis as the primary analysis will also be performed in the ITT population separately on the overall supplemental cohort, all cohorts combined, and in the PFIC1 and PFIC3 sub-cohorts (separately) given sufficient sample size.

13.1.3.2 Key Secondary Endpoints

Descriptive statistics and two-sided 95% CI of mean will be provided on the primary cohort in the ITT. For supportive analysis, the same analysis as the above analysis will be performed on the primary cohort using the PPS to confirm robustness of the results.

The same analysis as the above analysis will also be performed in the ITT population separately on the overall supplemental cohort, all cohorts combined, and in the PFIC1 and PFIC3 sub-cohorts (separately) given sufficient sample size.

13.1.3.3 Secondary Endpoint

For continuous endpoints, descriptive statistics and two-sided 95% CI of mean will be provided on the primary cohort in the ITT. For binary endpoints, frequency distribution will be provided on the primary cohort in the ITT with proportion and the two-sided 95% CI.

The same analysis as the above analysis will also be performed in the ITT population separately on the overall supplemental cohort, all cohorts combined, and in the PFIC1 and PFIC3 sub-cohorts (separately) given sufficient sample size.

[redacted]

13.1.3.5 Methods of Data Transformation and Handling of Missing Data

The derivation method for the primary endpoint will be described below.

- Baseline average morning ItchRO (Obs) severity score is defined as the 4-week (28 days) average morning ItchRO (Obs) severity score prior to the first dose of study medication. Average morning ItchRO (Obs) severity score will be calculated as the sum of the morning severity scores divided by the number of non-missing morning severity scores.

- For Weeks 18 (Weeks 15-18), Week 22 (Weeks 19-22), and Week 26 (Weeks 23-26), post-baseline average morning ItchRO (Obs) severity scores will be calculated as the sum of the morning ItchRO (Obs) severity scores divided by the number of morning ItchRO (Obs) severity scores for the 4-week (28 days) time periods (i.e., Weeks 15-18, 19-22, and 23-26).
- After the above derivations, each subject will have a baseline average morning ItchRO (Obs) severity score and have post-baseline average morning ItchRO (Obs) severity scores at Weeks 18, Week 22, and Week 26. For each subject, change in the average morning ItchRO (Obs) severity score between baseline and post-baseline visit can be calculated at Weeks 18, Week 22, and Week 26. Hence, the primary efficacy endpoint for each subject can be calculated as an average of the changes in the average morning ItchRO (Obs) severity score from Week 15 through Week 26.
- If 25% or more morning ItchRO (Obs) severity scores for the 4-week treatment period before a given study visit are missing, the average morning ItchRO (Obs) severity score at that visit will be treated as missing. The restriction is not set for the baseline average morning ItchRO (Obs) severity score.

13.1.3.6 Significance Level and Confidence Coefficient

- Significance Level: 5% (two-sided test).
- Confidence coefficient: 95% (two-sided).

13.1.4 PK Analysis

The following analysis will be performed in the safety analysis set separately on the primary cohort, the overall supplemental cohort, and all cohorts combined.

Plasma concentrations of TAK-625 will be summarized by each scheduled sampling time and visit using descriptive statistics.

13.1.5 Safety Analysis

The following analysis will be performed in the safety analysis set separately on the primary cohort, the overall supplemental cohort, and all cohorts combined.

13.1.5.1 TEAEs

A TEAE is defined as an AE whose date of onset occurs on or after the start of study drug.

TEAEs will be coded using the MedDRA dictionary. The frequency distribution will be provided using the SOC and the preferred term as follows:

- The frequency of all TEAEs.
- The frequency of drug-related TEAEs.
- The frequency of TEAEs by intensity.

- The frequency of drug-related TEAEs by intensity.
- The frequency of TEAEs leading to study drug discontinuation.
- The frequency of serious TEAEs.
- The frequency of TEAEs of clinical interest.

13.1.5.2 Clinical Laboratory Results, Vital Signs, ECGs, and Physical Examination Findings (Including Body Weight, Height, and BMI)

For continuous endpoints, the observed values and the changes from baseline will be summarized for each visit using descriptive statistics. Case plots will also be presented for the observed values.

For categorical endpoints, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

13.2 Interim Analysis

This study has no criteria for ET (i.e., neither efficacy nor futility stop).

Statistical analyses will be performed using all subjects' data at Week 26 and at Week 48 after the completion of the planned enrollment period (approximately 10 months) and the database lock for marketing application. Additionally, statistical analyses will also be performed using all subjects' data at the end of the study after the data are locked. All enrolled subjects at the completion of the enrollment period will be included in each of the interim / final analysis (1 or more subjects for the primary cohort to be necessary).

13.3 Determination of Sample Size

PFIC is a rare disease. The targeted sample size of the primary cohort (nt-PFIC2) is approximately 3 subjects, and that of the supplemental cohort (other types of PFIC) is approximately 6 subjects, based on enrollment feasibility of this population in Japan, rather than power calculation.

13.4 Other Statistical Considerations

Other details (eg, methods of data transformation, handling of missing data, and so on) will be described in the SAP.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records.

The investigator and the study site/head of the study site guarantee access to source documents by the sponsor or its designee (Contract Research Organization [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 (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Alternative approaches may be used to ensure data quality, data integrity, and subject safety (eg, remote source data review/source data verification via phone or video) as permitted by regional and local regulations. Additional details are in the monitoring plan.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change and its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 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 US Food and Drug Administration [FDA], the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA] of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site/head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonisation (ICH) Harmonised Tripartite

Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix H. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

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/signing a contract for the clinical study). 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. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives drug/notification no protocol activities, including screening may occur.

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

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

15.2 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, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies (if applicable). The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The informed consent form will detail the requirements

of the subject and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor before use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

If the subjects are under 18 years of age, the investigator is responsible for obtaining written informed consent not only from the under-aged subjects, but also from their legally acceptable representatives. If the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, 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, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) 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 a ballpoint pen with either blue or black ink in the case of written informed consent. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent or after receipt of subject signature and before the subject enters the study.

Once signed, the original informed consent form, or certified copy (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) will be maintained by the study site. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be provided to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative 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.

15.3 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 trial database or documentation via a subject ID 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 ID number.

In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventative actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, UK 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 15.2).

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).

15.4 Clinical Trial Disclosures and Publication

15.4.1 Clinical Trial Registration and Results Disclosure

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 before study start and disclose the results of those trials in a manner and timeframe compliant with Takeda policy and all applicable laws and regulations. Clinical trial registration and results disclosures will occur on ClinicalTrials.gov, other clinical trial registries/databases as required by law, and on Takeda's corporate website(s).

15.4.2 Publication

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.

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 venue (eg, congress, journal) will appropriately reflect contributions to the production, review, and approval of the document.

15.5 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 has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 DISSEMINATION OF NEW INFORMATION

When new information important to the proper conduct of the clinical study becomes available, such as on diseases, impairment, and deaths suspected to be due to the effect of the study drug, onset of infections suspected to be due to the use of the study drug, and other information related to study drug quality, efficacy, and safety, the sponsors will inform the investigators and heads of study sites in writing in a timely manner.

When the investigator receives information which the investigator judges may affect the intention of subjects to continue participation in the clinical study, the investigator will make available this information immediately to subjects and their legally acceptable representative, to be recorded in writing, and confirm whether the subject will continue to participate in the study.

17.0 REFERENCES

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18.0 APPENDIX

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