Statistical Analysis Plan

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: Version 1.0 / 5-Sep-2025

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.

STATISTICAL ANALYSIS PLAN for Final Analysis

Study Number: *TAK-625-3002*

Study 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*

Phase: *3*

Version: *1.0*

Date: *5-Sep-2025*

Prepared by: [redacted]

Based on:

Protocol Version: *Amendment 2*

Protocol Date: *08-Dec-2022*

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
[Original version]		[Not Applicable]

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ABBREVIATIONS

AE	adverse event
AECI	adverse event of clinical interest
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APRI	AST to platelet ratio index
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
7αC4	7α-hydroxy-4-cholesten-3-one
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
[redacted]	[redacted]
ECG	Electrocardiogram
FGF-19	fibroblast growth factor 19
FIB-4	fibrosis-4
GGT	gamma-glutamyl transferase
HCC	hepatocellular carcinoma
HDL-C	high density lipoprotein-cholesterol
HRQoL	health-related quality of life
ItchRO(Obs)	ItchRO Observer
ItchRO(Pt)	ItchRO Patient
ITT	intention-to-treat set
KM	Kaplan-Meier
LDL-C	low density lipoprotein-cholesterol
LLN	lower limit of normal
LOCF	last observation carried forward
LS means	least square means
LSV	lipid soluble vitamin
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intention-to-treat set
PEBD	partial external biliary diversion
[redacted]	[redacted]
PFIC	progressive familial intrahepatic cholestasis
PK	pharmacokinetic
PPS	per-protocol analysis set
PRO	patient-reported outcomes
PT	preferred term
Q1	25th percentile
Q3	75th percentile
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QOL	quality-of-life
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	system organ class
TEAE	treatment-emergent adverse event
TG	triglycerides
TSB	total serum bilirubin
ULN	upper limit of normal
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective(s)

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

1.1.3 Additional Objective(s)

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

1.2 Endpoints

1.2.1 Primary Endpoint(s)

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

1.2.2 Secondary Endpoint(s)

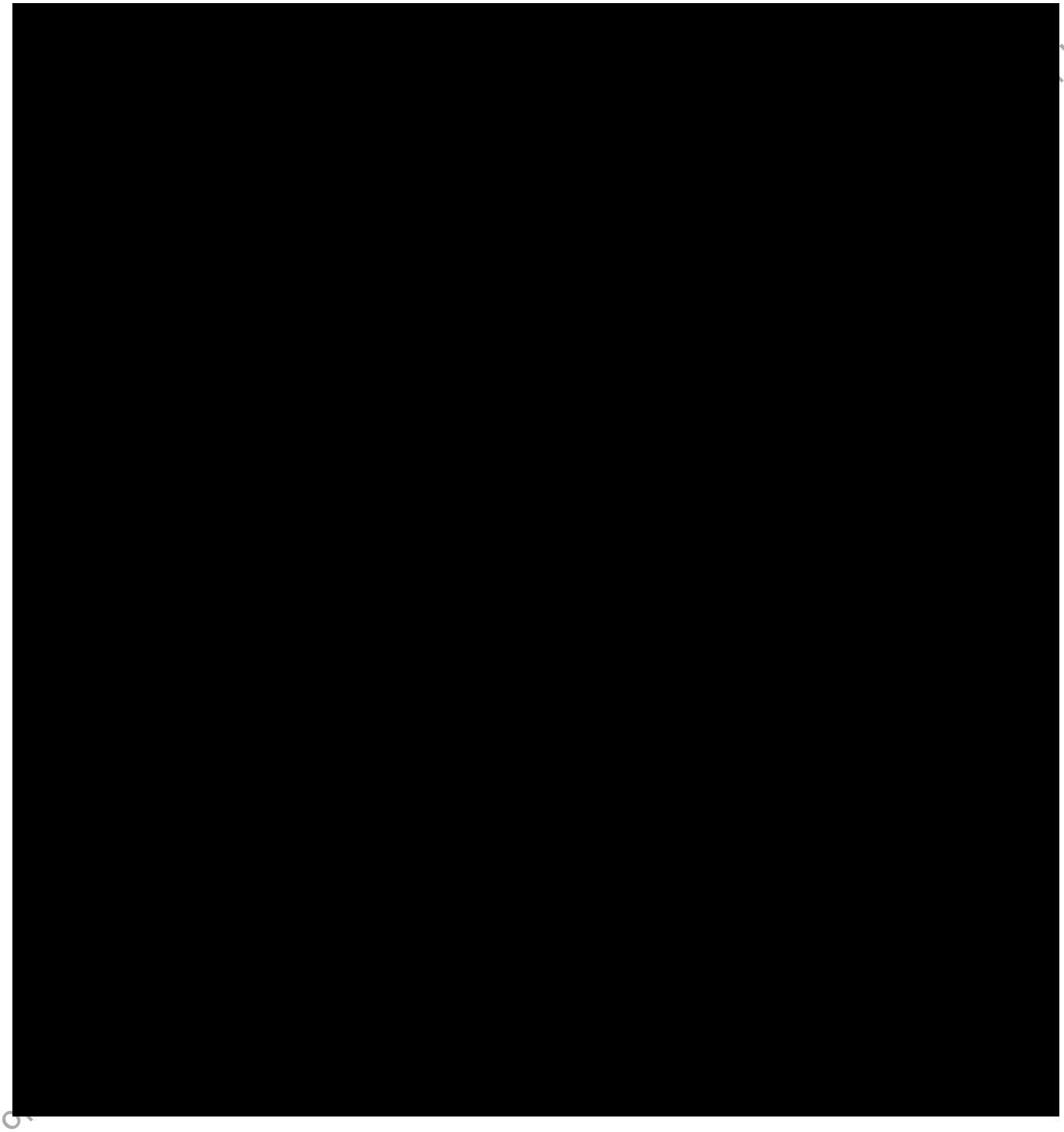
1.2.2.1 Key Secondary Endpoints(s)

- *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*

1.2.2.2 Secondary Endpoint(s)

- *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.*

[redacted]



1.2.4 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*

1.2.5 Other Endpoints

1.2.5.1 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 morning dose at Week 14 (or any visit up to Week 26).*

1.3 Estimand(s)

Not Applicable.

2.0 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 year 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 Protocol 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 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 Protocol 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):

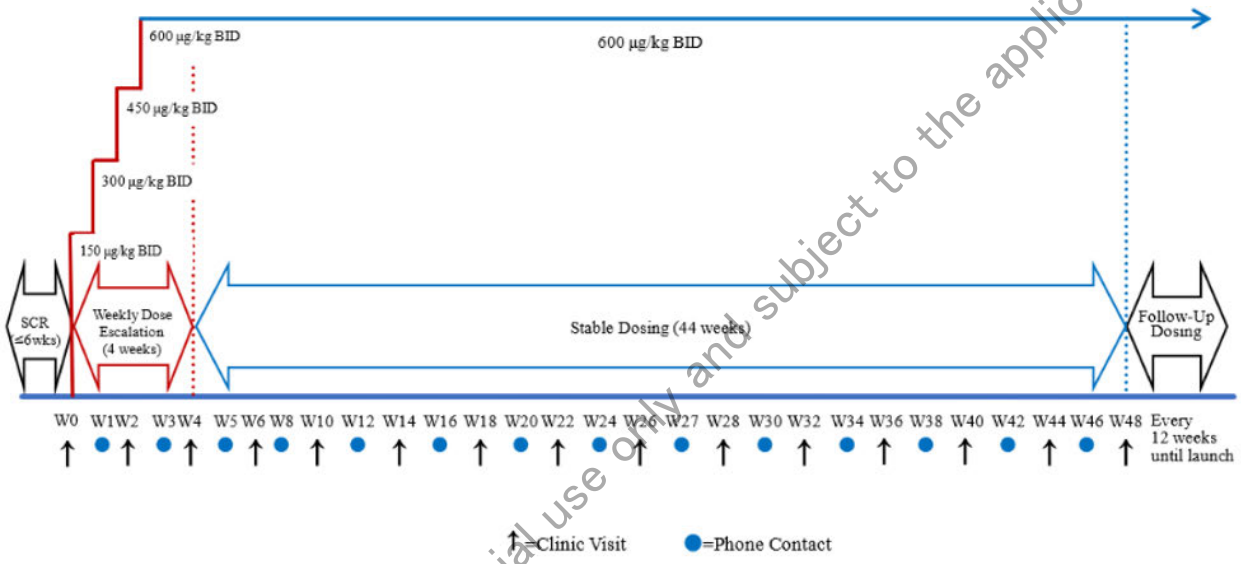
Additionally, in the follow-up dosing period, each subject will continue dosing with study drug. The safety evaluation will be performed in all the subjects every 12 weeks from Week 48 visit until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if 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 2.a. A schedule of assessments is listed in Protocol Appendix A.

Figure 2.a Schematic Study Design



ID=twice daily, SCR=screening, W=week, wks=weeks

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

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.

5.0 ANALYSIS SETS

5.1 All Subjects Who Signed the Informed Consent Form

All subjects who signed the informed consent form.

5.2 All Subjects Who Did Not Enter the Treatment Period

All subjects who did not enter the treatment period.

5.3 Safety Analysis Set

All subjects who received at least one dose of study drug.

5.4 Intention-to-treat set (ITT)

All subjects who received at least one dose of study drug.

5.5 Per-Protocol Analysis Set (PPS)

All ITT subjects who did not have any of the following major protocol deviations and whose primary endpoint was evaluable.

- Subjects who did not meet inclusion criteria #3, 4, 5, 6.
- Subjects who met exclusion criteria #1,2, 3, 4, 5, 6, 7, 9, 15, 16, 17, 19.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

The following definitions and calculation formulas will be used.

- **Treatment-emergent adverse event (TEAE)**: An adverse event whose date of onset occurs on or after the start of study drug.
- **Pretreatment event (PTE)**: Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug.
- **Descriptive statistics for endpoints**: Number of subjects, mean, standard deviation, standard error, maximum, minimum, and quartiles (Q1, median, and Q3).
- **Duration of exposure to study drug (days)**: {Date of last dose of study drug - date of first dose of study drug} + 1.
- **Duration of study after baseline (days)**: {Date of last visit/contact - date of first dose of study drug} + 1.
- **Study drug compliance (%)**: Number of study drugs taken / (duration of exposure to study drug * 2) * 100 (rounded to 1 decimal place).
- **Dose Level (µg/kg)**: Strength of study drug taken (mg) / (last available body weight (kg) prior to or on the day of study drug taken) * 1000.
- **Total Drug Exposure (µg/kg)**: Sum of {number of study drugs taken * dose level received (µg/kg)}.
- **Average Daily Dose (µg/kg/day)**: Total Drug Exposure (µg/kg) / Duration of exposure to study drug (days).
- **ItchRO (Obs/Pt) Daily Maximum of Morning and Evening Scores**: Maximum of morning and evening severity scores for each day. The morning and evening severity scores

of the same day should be used for the calculation. Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) itching.

- **Time to liver-associated events**: PEBD surgery, listing for liver transplantation, liver decompensation [hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis] events, hepatocellular carcinoma (HCC), death, and other.
- **Estimated Total Lipids (mg/dL)**: Cholesterol (mg/dL) + Triglycerides (mg/dL)
- **Ratio of Alpha-tocopherol to Estimated Total Lipids (mg/g)**: 1000 * Alpha-tocopherol (mg/dL) / Estimated Total Lipids (mg/dL). For Alpha-tocopherol concentrations reported as below the minimum quantitation limit, half of the minimum quantitation limit is used in the calculation.
- **Corrected Sodium (mEq/L)**: sodium (mEq/L) + (0.002 * Triglycerides (mg/dL)).
- **FIB-4**: (Age (years) * AST (U/L)) / (platelet count (10^9/L) * sqrt(ALT(U/L)))
  - Age (years) is years at sample collection visit.
- **APRI**: 100 * (AST (U/L) / AST ULN(U/L)) / (platelet count (10^9/L))
  - ULN is upper limit normal
- **Significant Protocol Deviation**: Deviation defined in the PDMP as "Important PD" whose Severity Classifications is "major" or "critical".
- **Time since original diagnosis of PFIC (months)**: (date of first dose – date of original diagnosis of PFIC + 1) / 30.4375

When reporting derived values or parameters, following presenting rules will be applied.

- For sBA, ItchRO: For rules on rounding and decimal presentation of these statistics, along with the rules for presenting certain derived values see below.
  - For measures of median and mean, use 3 decimal places.
  - For measures of standard deviation, standard error of the mean and CI, use 4 decimal places.
  - For measures of minimum and maximum values as well as observed value (for Listing), use 2 decimal places.
  - >=5 is rounded up away from zero, whereas <5 is rounded down toward zero, to account for rounding of negative numbers.
  - For p-values use 3 decimal places.
  - Presentation of p-values display p-values that would round to 0.000 as <0.001.
- Other than sBA, and ItchRO: For rules on rounding and decimal presentation of these statistics, along with the rules for presenting certain derived values see below.

- For measures of median and mean, use 1 decimal place beyond those used for the measurement.
- For measures of standard deviation, standard error of the mean and CI, use 2 decimal places beyond those used for the measurement.
- For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
- >=5 is rounded up away from zero, whereas <5 is rounded down toward zero, to account for rounding of negative numbers.
- For p-values use 3 decimal places.
- Presentation of p-values display p-values that would round to 0.000 as <0.001.
- BMI should be rounded to 1 decimal place for reporting.
- Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.
- Averaged lab results (e.g. Diastolic/Systolic Blood Pressure and Pulse [when taken in triplicate]) should be rounded to 1 decimal place for reporting.

6.2 Analysis Approach

6.2.1 Analysis Cohort

Analyses described in section 6.3 ~ 6.8 will be performed for primary cohort.

6.2.2 Analysis Approach for Continuous Efficacy Endpoints

For efficacy endpoints, all continuous endpoints in this trial will use the analysis method below unless stated otherwise in the section specific to an endpoint.

- Descriptive statistics and two-sided 95% confidence interval of mean will be provided for observed values (baseline and post-baseline visits) and changes from baseline (each post-baseline visit - baseline). For endpoint with multiple visits, these will be provided by visit.

6.2.3 Analysis Approach for Binary Efficacy Endpoints

For efficacy endpoints, all binary endpoints in this trial will use the analysis method below unless stated otherwise in the section specific to an endpoint.

- Frequency distribution will be provided by visit, with proportion and the two-sided 95% confidence interval. For endpoint with multiple visits, these will be provided by visit.

6.2.4 Analysis Approach for Time-to-Event Efficacy Endpoints

For efficacy endpoints, all time-to-event endpoints in this study will use the analysis method below unless stated otherwise in the section specific to an endpoint.

- The event-free survival rate and the two-sided 95% confidence intervals will be provided using the Kaplan-Meier method. The event-free survival rate will also be plotted.
  Time to event will be defined as the date of first dose of study drug to the event which comes fastest. For subjects without an event, time to event will be defined as the date of first dose of study drug to the censoring date, which is the date of the last study visit/contact.

6.3 Disposition of Subjects

6.3.1 Study Information

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

6.3.2 Disposition of Subjects

Analysis Set:	ITT	
Analysis Endpoint(s) :	Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[AE, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Other]
	Completion Status of All Planned Study Visits	[Completed Study, Prematurely Discontinued Study]
	Reason for Discontinuation of Study	[AE, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Other]
Analytical Method(s) :	(1) Disposition of Subjects	
	Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of	

subjects who prematurely discontinued will be used as the denominator.

6.3.3 Protocol Deviations and Analysis Sets

6.3.3.1 Significant Protocol Deviations

Analysis Set:	ITT	
Analysis Endpoint(s) :	Significant Protocol Deviation	[Informed Consent and Process, Inclusion Criteria, Exclusion Criteria, Concomitant Medication, Laboratory Assessment, Study Procedures (not safety and efficacy related), Safety, Visit Schedule, IP conditions, IP preparation, IP administration, Subject IP Compliance, Efficacy, Subject Discontinuation, Administrative, Patient Reported Outcomes, PK/PD, Other Criteria]
Analytical Method(s) :	(1) Protocol Deviations	

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

6.3.3.2 Analysis Sets

Analysis Set:	ITT	
Analysis Endpoint(s) :		
	Handling of Subjects	[Categories are based on the definitions in Section 5.0]
	Analysis Sets	
	ITT	[Included]
	PPS	[Included]
	Safety Analysis Set	[Included]
Analytical Method(s) :	(1) Subjects Excluded from Analysis Sets	
	(2) Analysis Sets	

Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate

category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

6.4 Concomitant Medications

Analysis Set: ITT

Analysis Endpoint(s) : Concomitant Medications

Analytical Method(s) : (1) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Anatomical Therapeutic Chemical Level 2 and Preferred Medication Name

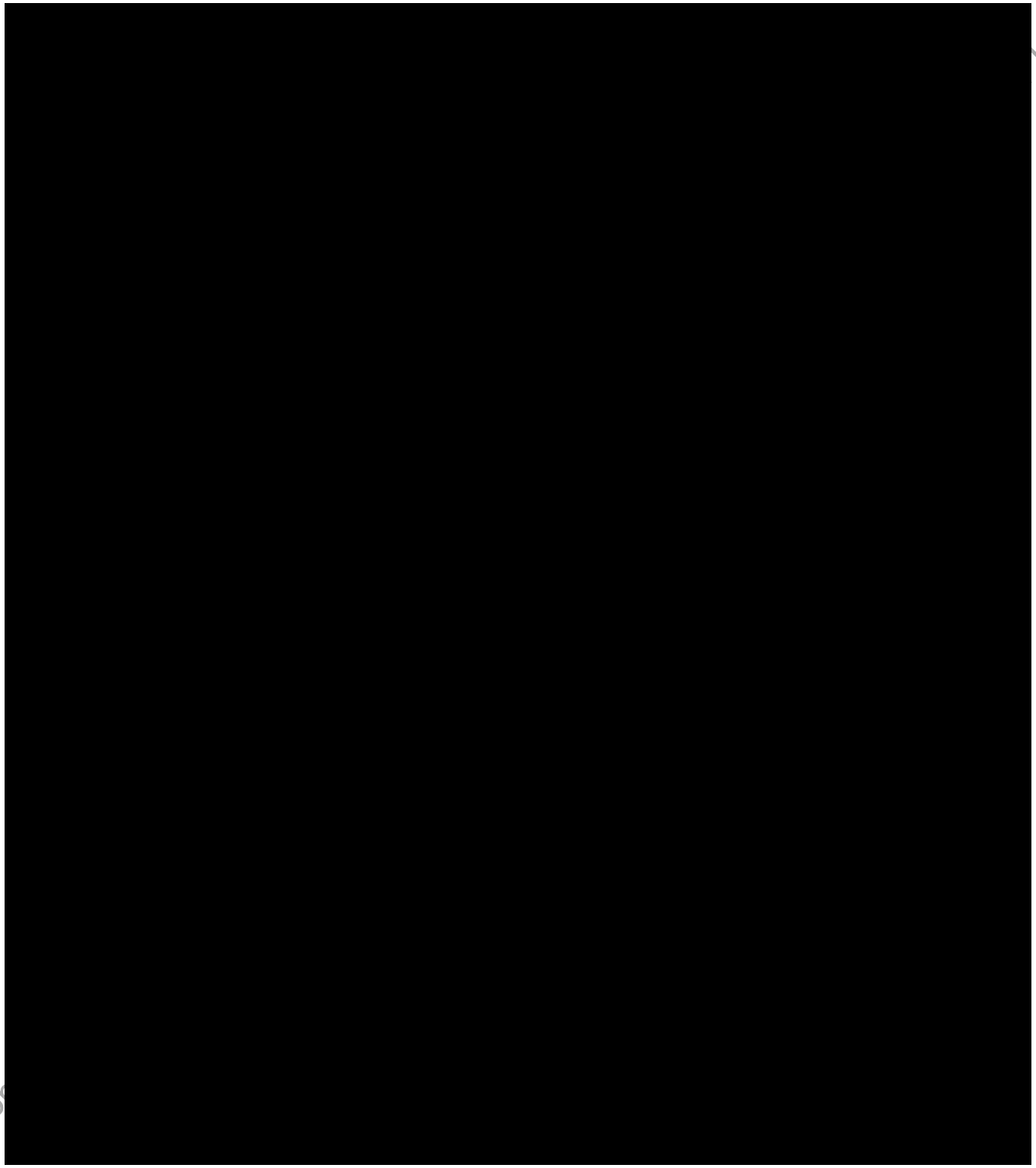
Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using anatomical therapeutic chemical level 2 and preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication names will be counted only once for that preferred medication names. For anatomical therapeutic chemical level 2, same manners in counting frequency.

6.5 Extent of Exposure and Compliance

Analysis Set:	ITT	
Analysis Endpoint(s) :	Duration of Exposure to Study Drug (days)	[0<= - <= 28, 29 <= - <= Max]
	Study Drug Compliance (%)	[Min<= - < 80, 80 <= - <= 100, 100< - <=Max]
	Total Drug Exposure (µg/kg)	
	Average Daily Dose (µg/kg/day)	
Analytical Method(s) :	(1) Study Drug Exposure, Compliance, Total Drug Exposure and Average Daily Dose	
	Frequency distributions for categorical endpoints and descriptive statistics for continuous endpoints will be provided.	

6.6 Efficacy Analysis

[redacted]



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6.7 Safety Analysis

6.7.1 Adverse Events

6.7.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Endpoint(s) :	TEAE	
Categories:	Relationship to Study Drug	[Related, Not Related]
	Intensity	[Mild, Moderate, Severe]

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

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3) , and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

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

6.7.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:	Safety Analysis Set	
Analysis Endpoint(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
	Time of Onset (day)	[1 – 28, 29 - 197, 198 - 336, 337 - Max]
Analytical Method(s) :	The following summaries will be provided using frequency distribution.	

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(10) Treatment-Emergent Adverse Events of Clinical Interest by System Organ Class and Preferred Term

(11) Drug-Related Treatment-Emergent Adverse Events of Clinical Interest by System Organ Class and Preferred Term

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

Number of subjects

- Summary tables other than (5), (6) and (9)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.
- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.
- Summary table for (9)
  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of

subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

6.7.2 Clinical Laboratory Evaluations

6.7.2.1 Laboratory Tests other than Urinalysis

Analysis Set:	Safety Analysis Set
Analysis Endpoint(s) :	See Section 9.3.6.
Visit:	Using the visits (Baseline to post Baseline visits) of the visit window defined in Section 9.2.2.
Analytical Method(s) :	For each endpoint, summaries (1) to (3) will be provided.

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

(2) Case Plots
Plots over time for each subject will be presented.

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

6.7.2.2 Urinalysis

Analysis Set:	Safety Analysis Set
Analysis Endpoint(s) :	See Section 9.3.6.
Visit:	Using the visits (Baseline to post Baseline visits) of the visit window defined in Section 9.2.2.
Analytical Method(s) :	For pH and specific gravity, summaries (1) , (2) and (4) will be provided. For each endpoint other than pH and specific gravity, summaries (3) and (4) will be provided.

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

Descriptive statistics for observed values and changes from baseline (each post-baseline visit - Baseline) will be provided for each visit.

(2) Case Plots
Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

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

6.7.3 Vital Signs, Weight and Height

Analysis Set:	Safety Analysis Set	
Analysis Endpoint(s) :	Systolic Blood Pressure	Diastolic Blood Pressure
	Heart Rate	Body Temperature
	Weight	Height
	BMI	Respiration Rate
Visit:	Using the visits (Baseline to post Baseline visits) of the visit window defined in Section 9.2.2.	
Analytical Method(s) :	For each endpoint, summaries (1) and (2) will be provided.	

(1) Summary of Vital Signs, Weight and Height, and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit - Baseline) will be provided for each visit.

(2) Case Plots
Plots over time for each subject will be presented.

6.7.4 ECGs

Analysis Set:	Safety Analysis Set	
Analysis Endpoint(s) :	Heart Rate	
	RR Interval	
	PR Interval	
	QRS Interval	
	QT Interval	
	QTcF Interval	
	Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Visit:	Using the visits (Baseline to post Baseline visits) of the visit window defined in Section 9.2.2.	
Analytical Method(s) :	For each endpoint other than 12-lead ECG interpretations, summaries (1) and (2) will be provided.	
	For ECG interpretation, summary (3) will be provided.	
	(1) Summary of ECG Parameters and Change from Baseline by Visit Descriptive statistics for observed values and changes from baseline (each post-baseline visit - Baseline) will be provided for each visit.	
	(2) Case Plots Plots over time for each subject will be presented.	
	(3) Summary of Shift of ECG Interpretation Shift table showing the number of subjects in each category at baseline and each post-baseline visit will be provided.	

6.7.5 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis Set:	Safety Analysis Set
Analysis Endpoint(s) :	TEAE
Analytical Method(s) :	TEAEs will be summarized in the same way as in Section 6.7.1.2. All summaries will be presented in Japanese.

6.8 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.8.1 Pharmacokinetic Analysis

Not applicable.

6.9 Other Analyses

6.9.1 Analyses for Overall Supplemental Cohort

Cohort:	Overall Supplemental Cohort
Analytical Method(s) :	The same analyses in section 6.3 ~ 6.8 will be performed for overall supplemental cohort.

6.9.2 Analyses for All Cohorts Combined

Cohort:	All Cohorts Combined
Analytical Method(s) :	The same analyses in section 6.3 ~ 6.8 will be performed for all cohorts combined.

7.0 REFERENCES

[1] World Health Organization (WHO) growth charts "A SAS Program for the WHO Growth Charts (ages 0 to < 2 years)"
https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas-who.htm

[2] Centers for Disease Control (CDC) growth charts "A SAS Program for the 2000 CDC Growth Charts (ages 0 to < 20 years)"
https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

There was no change to the protocol planned analyses.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

9.2.1 Definition of Study Days

The following definitions and calculation formulas will be used.

- Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. If the date of the observation is

on the same date or after the day of the first dose, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.

- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1.

9.2.2 Definition of Study Visit Windows

When calculating Study Day relative to a reference date (i.e., date of first dose of study drug [Day 1]) , if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

When calculating Follow-up Day relative to a reference date (i.e., date of last dose of study drug [Follow-up Day 0]) , it will be calculated as: date of observation - reference date. Hence, reference day is always Follow-up Day 0.

All evaluable data (i.e., non-missing data) will be handled according to the following rules.

9.2.2.1 Endpoints other than ItchRO Scores and PK Samples

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used. For laboratory test data, if there are two observations of both central laboratory sample and local sample on the same date, central laboratory sample data will be used. Values less than or equal to the lower limit of quantification will be treated as one-half of the lower limit value when calculating the descriptive statistics. Values greater than or equal to the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

Table 9.1 Visit Window of sBA, sBA subspecies, C4, Serum Storage Sample

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 2	Study Day: 15	2 - 29	< 15
Week 6	Study Day: 43	30 - 57	< 15
Week 10	Study Day: 71	58 - 85	< 15
Week 14	Study Day: 99	86 - 113	< 15
Week 18	Study Day: 127	114 - 141	< 15

Table 9.1 Visit Window of sBA, sBA subspecies, C4, Serum Storage Sample

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week 22	Study Day: 155	142 - 169	< 15
Week 26	Study Day: 183	170 - 190	< 15
Week 28	Study Day: 197	191 - 211	< 15
Week 32	Study Day: 225	212 - 239	< 15
Week 36	Study Day: 253	240 - 267	< 15
Week 40	Study Day: 281	268 - 295	< 15
Week 44	Study Day: 309	296 - 323	< 15
Week 48	Study Day: 337	324 - 379	< 15
Week (48 + 12 * n) (n=1, 2, …)	Study Day: 337 + 12 * 7 * (n)	(337 + 12 * 7 * (n) - 41) - (337 + 12 * 7 * (n) + 42)	< 15

Table 9.2 Visit Window of Vital Signs, Weight and Height, [redacted] for pruritus

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 2	Study Day: 15	2 - 22	< 15
Week 4	Study Day: 29	23 - 36	< 15
Week 6	Study Day: 43	37 - 57	< 15
Week 10	Study Day: 71	58 - 85	< 15
Week 14	Study Day: 99	86 - 113	< 15
Week 18	Study Day: 127	114 - 141	< 15
Week 22	Study Day: 155	142 - 169	< 15

Table 9.2 Visit Window of Vital Signs, Weight and Height, [redacted] for pruritus

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week 26	Study Day: 183	170 - 190	< 15
Week 28	Study Day: 197	191 - 211	< 15
Week 32	Study Day: 225	212 - 239	< 15
Week 36	Study Day: 253	240 - 267	< 15
Week 40	Study Day: 281	268 - 295	< 15
Week 44	Study Day: 309	296 - 323	< 15
Week 48	Study Day: 337	324 - 379	< 15
Week (48 + 12 * n) (n=1, 2, …)	Study Day: 337 + 12 * 7 * (n)	(337 + 12 * 7 * (n) - 41) - (337 + 12 * 7 * (n) + 42)	< 15

Table 9.3 Urinalysis, Cholestasis Biomarkers (FGF19, Autotaxin)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 6	Study Day: 43	2 - 57	< 15
Week 10	Study Day: 71	58 - 99	< 15
Week 18	Study Day: 127	100 - 155	< 15
Week 26	Study Day: 183	156 – 197	< 15
Week 32	Study Day: 225	198 - 253	< 15
Week 40	Study Day: 281	254 - 309	< 15
Week 48	Study Day: 337	310 - 379	< 15

Table 9.3 Urinalysis, Cholestasis Biomarkers (FGF19, Autotaxin)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week (48 + 12 * n) (n=1, 2, …)	Study Day: 337 + 12 * 7 * (n)	(337 + 12 * 7 * (n) - 41) - (337 + 12 * 7 * (n) + 42)	< 15

Table 9.4 Lipid Panel, Lipid Soluble Vitamins

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 – 1	
Week 6	Study Day: 43	2 – 57	< 15
Week 10	Study Day: 71	58 – 85	< 15
Week 14	Study Day: 99	86 – 113	< 15
Week 18	Study Day: 127	114 – 141	< 15
Week 22	Study Day: 155	142 – 169	< 15
Week 26	Study Day: 183	170 – 197	< 15
Week 32	Study Day: 225	198 - 253	< 15
Week 40	Study Day: 281	254 - 309	< 15
Week 48	Study Day: 337	310 - 379	< 15
Week (48 + 12 * n) (n=1, 2, …)	Study Day: 337 + 12 * 7 * (n)	(337 + 12 * 7 * (n) - 41) - (337 + 12 * 7 * (n) + 42)	< 15

Table 9.5 CBC, Coagulation, Chemistry Panel

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 2	Study Day: 15	2 - 29	< 15
Week 6	Study Day: 43	30 - 57	< 15
Week 10	Study Day: 71	58 - 85	< 15
Week 14	Study Day: 99	86 - 113	< 15
Week 18	Study Day: 127	114 - 141	< 15
Week 22	Study Day: 155	142 - 169	< 15
Week 26	Study Day: 183	170 - 197	< 15
Week 32	Study Day: 225	198 - 253	< 15
Week 40	Study Day: 281	254 - 309	< 15
Week 48	Study Day: 337	310 - 379	< 15
Week (48 + 12 * n) (n=1, 2, …)	Study Day: 337 + 12 * 7 * (n)	(337 + 12 * 7 * (n) - 41) - (337 + 12 * 7 * (n) + 42)	< 15

Table 9.6 Visit Window of ECGs, AFP

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 10	Study Day: 71	2 - 127	< 15
Week 26	Study Day: 183	128 - 197	< 15
Week 48	Study Day: 337	198 - 379	< 15

Table 9.6 Visit Window of ECGs, AFP

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week (48 + 12 * n) (n=1, 2, …)	Study Day: 337 + 12 * 7 * (n)	(337 + 12 * 7 * (n) - 41) - (337 + 12 * 7 * (n) + 42)	< 15

[redacted]

9.2.2.2 PK Samples

Not applicable.

9.2.2.3 Average ItchRO Scores

For each visit other than Week 6, average ItchRO score is defined as the average of the scores (morning, evening, or daily maximum of morning and evening) over the visit consisting of the 28 days on or before the scheduled Study Day (i.e., the sum of the scores divided by the number of non-missing scores). The answer "I don't know" will be treated as missing.

For Week 6, average ItchRO score is defined as the average of the scores (morning, evening, or daily maximum of morning and evening) over the visit consisting of the 41 days on or before the scheduled Study Day (i.e., the sum of the scores divided by the number of non-missing scores). The answer "I don't know" will be treated as missing.

In the event that a subject/caregiver failed to complete the morning/evening report, the morning/evening score for that day will be treated as missing data. If 25% or more ItchRO scores for the post-baseline visit are missing, the average ItchRO score at that visit will be treated as missing. The restriction is not set for baseline average ItchRO scores.

Table 9.8 Visit Window of Average ItchRO Score

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: -1	-28 - -1	
Week 6	Study Day: 42	2 - 42	< 15
Week 10	Study Day: 70	43 - 70	< 15
Week 14	Study Day: 98	71 - 98	< 15
Week 18	Study Day: 126	99 - 126	< 15
Week 22	Study Day: 154	127 - 154	< 15
Week 26	Study Day: 182	155 - 182	< 15
Week 28	Study Day: 197	170 - 197	< 15
Week 32	Study Day: 225	198 - 225	< 15
Week 36	Study Day: 253	226 - 253	< 15
Week 40	Study Day: 281	254 - 281	< 15
Week 44	Study Day: 309	282 - 309	< 15
Week 48	Study Day: 337	310 - 337	< 15
Week (48 + 12 * n) (n=1, 2, …)	Study Day: 337 + 12 * 7 * (n)	(337 + 12 * 7 * (n) - 27) - (337 + 12 * 7 * (n))	< 15

9.2.3 Partial Date Conventions

For Medication History and Concomitant Medication, if their stop date is partially/completely missing, following handling rules will be applied.

if (CMCAT="MEDICATION HISTORY") then "(1) Medical History " ;

else if (CMENRTPT="ONGOING") then "(3) Concomitant Medication" ;

else if

(. < medication end year < TAK-625 start year) or

(medication end year = TAK-625 start year and

. < medication end month < TAK-625 start month) or

(medication end year = TAK-625 start year and

medication end month = TAK-625 start month and

. < medication end date < TAK-625 start date) then "(2) Concomitant Medication" ;

else "(3) Concomitant Medication" ;

9.3 Derivation of Endpoints

9.3.1 Primary Efficacy Endpoints

Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) itching. The derivation method for the primary efficacy endpoint will be described below.

After the derivation described in section 9.2.2.3, each subject will have a baseline (Week 0) 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 (i.e., the sum of the average morning ItchRO (Obs) severity scores divided by the number of non-missing morning severity scores).

9.3.2 Average ItchRO Scores [redacted]

For ItchRO scores, both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) or more frequent (Item 3) itching. After the derivation described in section 9.2.2.3, the following endpoints will be derived the same procedures as section 9.3.1.

[redacted]

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

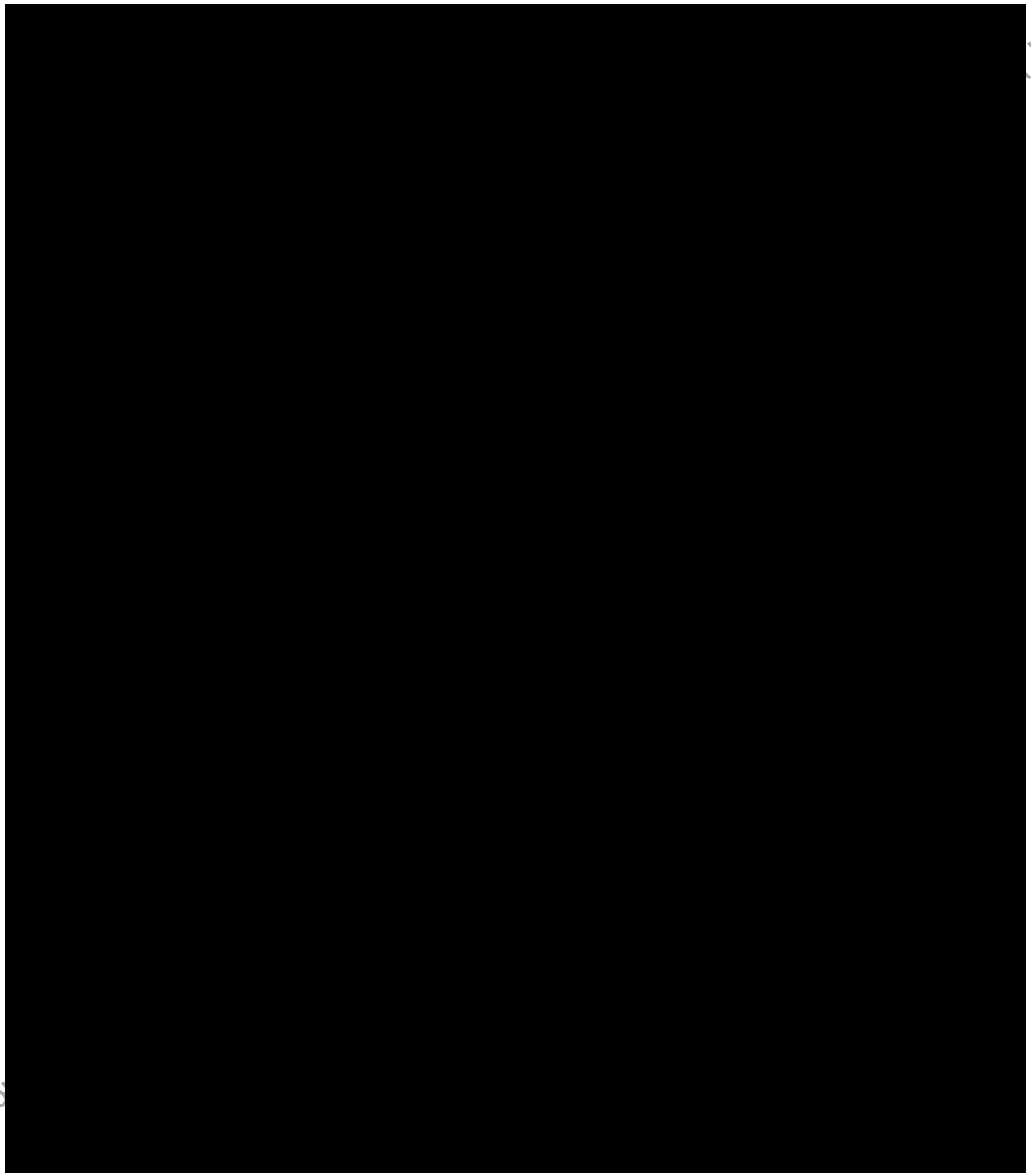
- **Change in the average ItchRO (Obs/Pt) severity and frequency (based on daily maximum of morning and evening severity scores) between baseline and average of Week 15 through Week 26.**
- **Change in the average morning ItchRO (Obs/Pt) frequency score between baseline and average of Week 15 through Week 26.**
- **Change in the average evening ItchRO (Obs/Pt) frequency score between baseline and average of Week 15 through Week 26.**

[redacted]

9.3.3 Responder Endpoints

- **Subjects who experience an sBA control**: subjects with a reduction to <102 µMol/L, or a reduction of >75%, or normalization) from baseline through Week 26

[redacted]



[redacted]

9.3.5 Z-scores

Z-scores of weight, height and BMI are based on a subject's gender and age at each scheduled visit. For subjects less than 24 months of age, the World Health Organization (WHO) growth charts are recommended by the Centers for Disease Control (CDC) and will be used to derive z-scores. For subjects at least 24 months of age, the CDC growth charts will be used to derive z-scores.

Age at which height and weight were measured should be used for calculating z-scores, not using age at baseline.

9.3.6 Lists of Laboratory Tests

Hematology (CBC with Differential)
Hematocrit
Hemoglobin
MCV, MCH, MCHC
Red blood cells
Platelets
White blood cells
WBC Differential (% and absolute)
Neutrophils
Eosinophils
Basophils
Lymphocytes
Monocytes

Coagulation
aPTT (sec)
INR
PT (sec)

Chemistry
Albumin
ALP
Amylase
ALT (SGPT)
AST (SGOT)
Bicarbonate
Bilirubin, direct (conjugated)
TSB
BUN
Calcium
Chloride
Creatinine
GGT
Glucose
Lipase
Phosphate
Potassium
Sodium
Corrected Sodium
Total protein
Total sBA (enzymatic assay)
Uric Acid
Measured serum Osmolality

Lipid Panel
Total cholesterol
LDL-C (direct)
HDL-C
TG

Cholestasis Biomarkers
sBA (LC-MS)
sBA subspecies
7alpha-hydroxy-4-cholesten-3-one (C4)
FGF-19
Autotaxin

Lipid Soluble Vitamins
25-hydroxy vitamin D
Retinol
RBP
Alpha-tocopherol
Estimated Total Lipids
Ratio of Alpha-tocopherol to Estimated Total Lipids

Urinalysis
pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Occult blood and cells
Nitrite
Urobilinogen
Leukocyte esterase
Microscopic examination
Oxalate
Urinary creatinine

Marker of HCC
AFP*

*only listing will be provided.

9.3.7 Table for AECI

The categories of AECI will follow ones in CRF.

9.3.8 Significance Level and Confidence Coefficient

- Significance level: 5% (two-sided)
- Confidence coefficient: 95% (two-sided)

9.4 Analysis Software

SAS (version 9.4)

Signature Page for TAK-625-3002 16-1-9-1 Statistical Analysis Plan for Final Ana
Title: TAK-625-3002 16.1.9.1 Statistical Analysis Plan for Final Analysis 2025-0

Approval Task	[redacted]

Document Number: TDN-000602664 v1.0

STATISTICAL ANALYSIS PLAN for Week 26

Study Number: *TAK-625-3002*

Study 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*

Phase: *3*

Version: *2.0*

Date: *10-Nov-2023*

Prepared by: [redacted]

Based on:

Protocol Version: *Amendment 2*

Protocol Date: *08-Dec-2022*

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0	01-Jul-2022	Not Applicable
2.0		See Section 9.1

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
AECI	adverse event of clinical interest
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APRI	AST to platelet ratio index
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
7αC4	7α-hydroxy-4-cholesten-3-one
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
[redacted]	[redacted]
ECG	Electrocardiogram
FGF-19	fibroblast growth factor 19
FIB-4	fibrosis-4
GGT	gamma-glutamyl transferase
HCC	hepatocellular carcinoma
HDL-C	high density lipoprotein-cholesterol
HRQoL	health-related quality of life
ItchRO(Obs)	ItchRO Observer
ItchRO(Pt)	ItchRO Patient
ITT	intention-to-treat set
KM	Kaplan-Meier
LDL-C	low density lipoprotein-cholesterol
LLN	lower limit of normal
LOCF	last observation carried forward
LS means	least square means
LSV	lipid soluble vitamin
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intention-to-treat set
PEBD	partial external biliary diversion
[redacted]	[redacted]
PFIC	progressive familial intrahepatic cholestasis
PK	pharmacokinetic
PPS	per-protocol analysis set
PRO	patient-reported outcomes
PT	preferred term
Q1	25th percentile
Q3	75th percentile
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QOL	quality-of-life
RBP	retinol binding protein
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	system organ class
TEAE	treatment-emergent adverse event
TG	triglycerides
TSB	total serum bilirubin
ULN	upper limit of normal
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

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

1.1.2 Secondary Objective(s)

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

1.1.3 Additional Objective(s)

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

1.2 Endpoints

1.2.1 Primary Endpoint(s)

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

1.2.2 Secondary Endpoint(s)

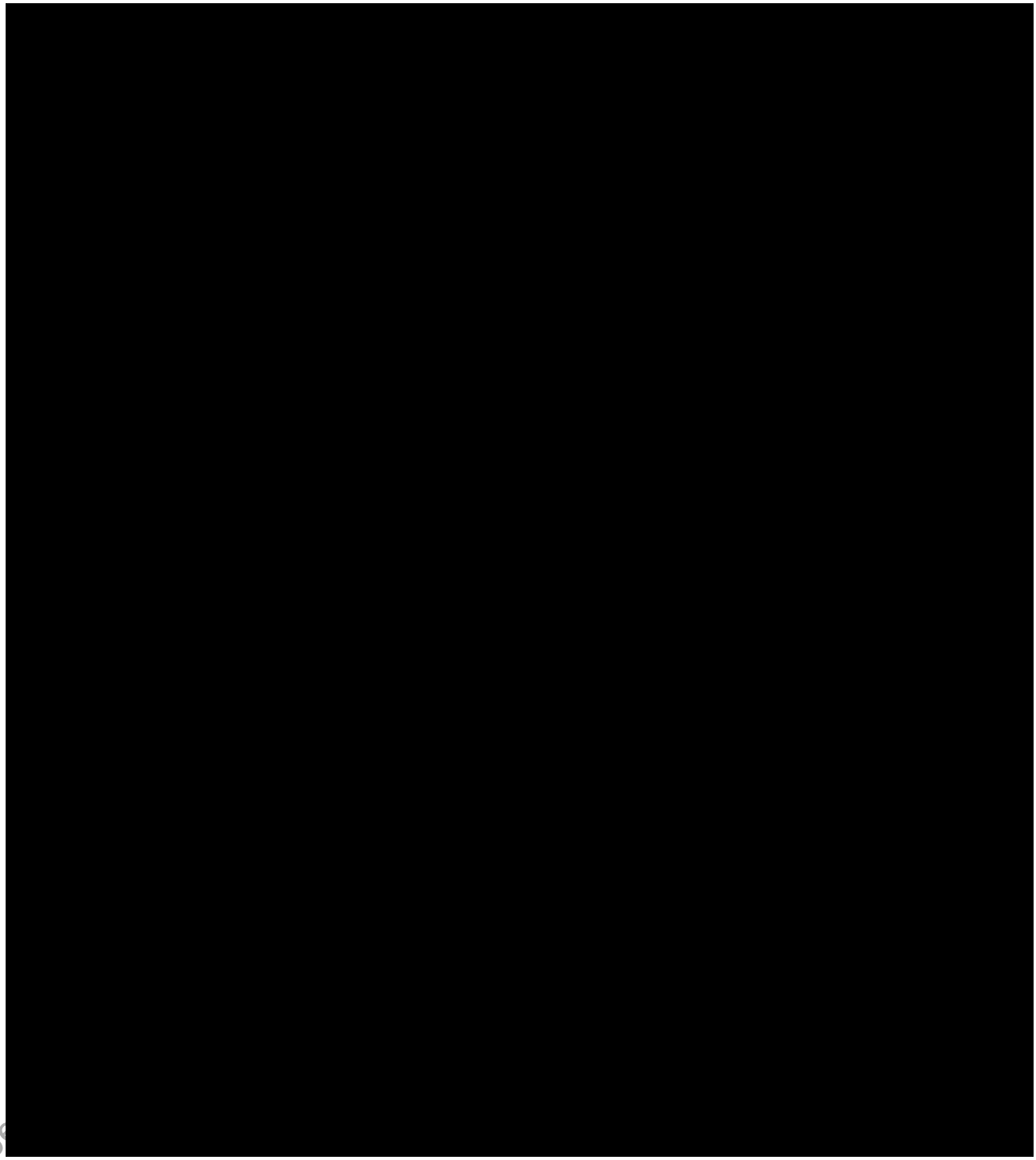
1.2.2.1 Key Secondary Endpoints(s)

- *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*

1.2.2.2 Secondary Endpoint(s)

- *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.*

[redacted]



1.2.4 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*

1.2.5 Other Endpoints

1.2.5.1 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 morning dose at Week 14 (or any visit up to Week 26).*

1.3 Estimand(s)

Not Applicable.

2.0 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 year 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 Protocol 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 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 Protocol 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):

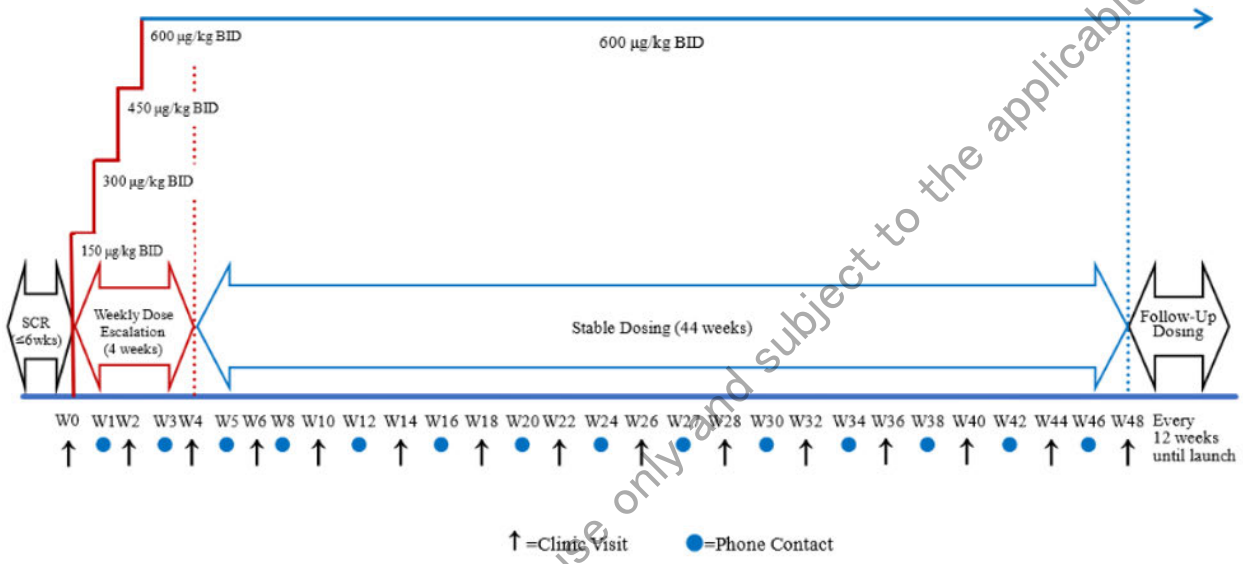
Additionally, in the follow-up dosing period, each subject will continue dosing with study drug. The safety evaluation will be performed in all the subjects every 12 weeks from Week 48 visit until TAK-625 is approved or available in Japan commercially, or if the subject withdraws from the study, or if 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 2.a. A schedule of assessments is listed in Protocol Appendix A.

Figure 2.a Schematic Study Design



ID=twice daily, SCR=screening, W=week, wks=weeks

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

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.

5.0 ANALYSIS SETS

5.1 All Subjects Who Signed the Informed Consent Form

All subjects who signed the informed consent form.

5.2 All Subjects Who Did Not Enter the Treatment Period

All subjects who did not enter the treatment period.

5.3 Safety Analysis Set

All subjects who received at least one dose of study drug.

5.4 Intention-to-treat set (ITT)

All subjects who received at least one dose of study drug.

5.5 Per-Protocol Analysis Set (PPS)

All ITT subjects who did not have any of the following major protocol deviations and whose primary endpoint was evaluable.

- Subjects who did not meet inclusion criteria #3, 4, 5, 6.
- Subjects who met exclusion criteria #1,2, 3, 4, 5, 6, 7, 9, 15, 16, 17, 19.

6.0 STATISTICAL ANALYSIS

Statistical analyses will be performed using all subjects' data up to Week 26 (i.e., up to Day 197) after the data are locked. PK analysis will be performed using all subjects' data up to Week 10 after the data are locked.

6.1 General Considerations

The following definitions and calculation formulas will be used.

- **Treatment-emergent adverse event (TEAE)**: An adverse event whose date of onset occurs on or after the start of study drug. TEAEs whose date of onset occurred on or before Week 26 visit (i.e. the latest visit by Day 197), will be summarized.
- **Pretreatment event (PTE)**: Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of study drug.
- **Concomitant medication**: Concomitant medications whose start date occurred on or before Week 26 visit (i.e. the latest visit by Day 197), will be summarized.
- **Descriptive statistics for endpoints other than PK**: Number of subjects, mean, standard deviation, standard error, maximum, minimum, and quartiles (Q1, median, and Q3).
- **Descriptive statistics for PK**: Number of subjects, mean, standard deviation, maximum, median, minimum, coefficient of variation, and geometric mean.
- **Duration of exposure to study drug (days)**: {Date of last dose of study drug or Week 26 visit (i.e. the latest visit by Day 197) which comes faster - date of first dose of study drug} + 1.
- **Duration of study after baseline (days)**: {Date of last visit/contact or Week 26 visit (i.e. the latest visit by Day 197) which comes faster - date of first dose of study drug} + 1.

- **Study drug compliance (%)**: Number of study drugs taken / (duration of exposure to study drug * 2) * 100 (rounded to 1 decimal place).
- **Dose Level (µg/kg)**: Strength of study drug taken (mg) / (last available body weight (kg) prior to or on the day of study drug taken) * 1000.
- **Dose Level Categories for PK (µg/kg)**: Categorize by following below calculation rule:

  If Min <= dose level < 225 µg/kg, then dose level category = 150 µg/kg; if 225 µg/kg <= dose level < 375 µg/kg, then dose level ＞category = 300 µg/kg; if 375 µg/kg <= dose level < 525 µg/kg, then dose level category = 450 µg/kg; if 525 µg/kg <= dose level <= Max, then dose level category = 600 µg/kg.
- **Total Drug Exposure (µg/kg)**: Sum of {number of study drugs taken * dose level received (µg/kg)}.
- **Average Daily Dose (µg/kg/day)**: Total Drug Exposure (µg/kg) / Duration of exposure to study drug (days).
- **ItchRO (Obs/Pt) Daily Maximum of Morning and Evening Scores**: Maximum of morning and evening severity scores for each day. The morning and evening severity scores of the same day should be used for the calculation. Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) itching.
- **Time to liver-associated events**: PEBD surgery, listing for liver transplantation, liver decompensation [hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis] events, hepatocellular carcinoma (HCC), death, and other.
- **Estimated Total Lipids (mg/dL)**: Cholesterol (mg/dL) + Triglycerides (mg/dL)
- **Ratio of Alpha-tocopherol to Estimated Total Lipids (mg/g)**: 1000 * Alpha-tocopherol (mg/dL) / Estimated Total Lipids (mg/dL). For Alpha-tocopherol concentrations reported as below the minimum quantitation limit, half of the minimum quantitation limit is used in the calculation.
- **Corrected Sodium (mEq/L)**: sodium (mEq/L) + (0.002 * Triglycerides (mg/dL)).
- **FIB-4**: (Age (years) * AST (U/L)) / (platelet count (10^9/L) * sqrt(ALT(U/L)))
  - Age (years) is years at sample collection visit.
- **APRI**: 100 * (AST (U/L) / AST ULN(U/L)) / (platelet count (10^9/L))
  - ULN is upper limit normal
- **Significant Protocol Deviation**: Deviation defined in the PDMP as “Important PD” whose Severity Classifications is “major” or “critical”.
- **Time since original diagnosis of PFIC (months)**: (date of first dose – date of original diagnosis of PFIC + 1) / 30.4375.

When reporting derived values or parameters, following presenting rules will be applied.

- For sBA, ItchRO: For rules on rounding and decimal presentation of these statistics, along with the rules for presenting certain derived values see below.
  - For measures of median and mean, use 3 decimal places.
  - For measures of standard deviation, standard error of the mean and CI, use 4 decimal places.
  - For measures of minimum and maximum values as well as observed value (for Listing), use 2 decimal places.
  - >=5 is rounded up away from zero, whereas <5 is rounded down toward zero, to account for rounding of negative numbers.
  - For p-values use 3 decimal places.
  - Presentation of p-values display p-values that would round to 0.000 as <0.001.
- Other than sBA, and ItchRO: For rules on rounding and decimal presentation of these statistics, along with the rules for presenting certain derived values see below.
  - For measures of median and mean, use 1 decimal place beyond those used for the measurement.
  - For measures of standard deviation, standard error of the mean and CI, use 2 decimal places beyond those used for the measurement.
  - For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
  - >=5 is rounded up away from zero, whereas <5 is rounded down toward zero, to account for rounding of negative numbers.
  - For p-values use 3 decimal places.
  - Presentation of p-values display p-values that would round to 0.000 as <0.001.
  - BMI should be rounded to 1 decimal place for reporting.
  - Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.
  - Averaged lab results (e.g. Diastolic/Systolic Blood Pressure and Pulse [when taken in triplicate]) should be rounded to 1 decimal place for reporting.

6.2 Analysis Approach

6.2.1 Analysis Cohort

Analyses described in section 6.3 ~ 6.9 will be performed for primary cohort.

6.2.2 Analysis Approach for Continuous Efficacy Endpoints

For efficacy endpoints, all continuous endpoints in this trial will use the analysis method below unless stated otherwise in the section specific to an endpoint.

- Descriptive statistics and two-sided 95% confidence interval of mean will be provided for observed values (baseline and post-baseline visits) and changes from baseline (each post-baseline visit - baseline). For endpoint with multiple visits, these will be provided by visit.

6.2.3 Analysis Approach for Binary Efficacy Endpoints

For efficacy endpoints, all binary endpoints in this trial will use the analysis method below unless stated otherwise in the section specific to an endpoint.

- Frequency distribution will be provided by visit, with proportion and the two-sided 95% confidence interval. For endpoint with multiple visits, these will be provided by visit.

6.2.4 Analysis Approach for Time-to-Event Efficacy Endpoints

For efficacy endpoints, all time-to-event endpoints in this study will use the analysis method below unless stated otherwise in the section specific to an endpoint.

- The event-free survival rate and the two-sided 95% confidence intervals will be provided using the Kaplan-Meier method. The event-free survival rate will also be plotted.
  Time to event will be defined as the date of first dose of study drug to the event which comes fastest. For subjects without an event, time to event will be defined as the date of first dose of study drug to the censoring date, which is the date of the last study visit/contact.

6.3 Disposition of Subjects

6.3.1 Study Information

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

6.3.2 Screen Failures

Analysis Set:	All Subjects Who Did Not Enter the Treatment Period	
Analysis Endpoint(s) :	Age (years)	
	Gender	[Male, Female]
Analytical Method(s) :	(1) Screen Failures	
	Frequency distributions for categorical endpoints and descriptive statistics for continuous endpoints will be provided.	

6.3.3 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Endpoint(s) :	Eligibility Status	[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]
	Primary Reason for Subject Not Being Eligible	[AE, Screen Failure (Did not meet inclusion criteria or did meet exclusion criteria), Protocol Deviation, Lost to Follow-up, Pregnancy, Withdrawal by Subject, Study Terminated by Sponsor, Other]
Analytical Method(s) :	(1) Eligibility for Entrance into the Treatment Period	
	Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.	

6.3.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:	ITT	
Analysis Endpoint(s) :	Status of Entrance into the Treatment Period	[Entered]
Stratum:	Site	[Site numbers will be used as categories]
Analytical Method(s) :	(1) Number of Subjects Enrolled by Site	
	Frequency distribution will be provided for each stratum.	

6.3.5 Disposition of Subjects

Analysis Set:	ITT	
Analysis Endpoint(s) :	Study Drug Completion Status	[Ongoing, Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[AE, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Other]
	Completion Status of All Planned Study Visits	[Ongoing, Completed Study, Prematurely Discontinued Study]
	Reason for Discontinuation of Study	[AE, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Other]
Analytical Method(s) :	(1) Disposition of Subjects Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.	

6.3.6 Protocol Deviations and Analysis Sets

6.3.6.1 Significant Protocol Deviations

Analysis Set:	ITT	
Analysis Endpoint(s) :	Significant Protocol Deviation	[Informed Consent and Process, Inclusion Criteria, Exclusion Criteria, Concomitant Medication, Laboratory Assessment, Study Procedures (not safety and efficacy related), Safety, Visit Schedule, IP conditions, IP preparation, IP administration, Subject IP Compliance, Efficacy, Subject Discontinuation, Administrative, Patient Reported Outcomes, PK/PD, Other Criteria]
Analytical Method(s) :	(1) Protocol Deviations	

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

6.3.6.2 Analysis Sets

Analysis Set: ITT

Analysis Endpoint(s) :

Handling of Subjects	[Categories are based on the definitions in Section 5.0]
Analysis Sets	
ITT	[Included]
PPS	[Included]
Safety Analysis Set	[Included]

Analytical Method(s) : (1) Subjects Excluded from Analysis Sets
(2) Analysis Sets

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

6.4 Demographic and Other Baseline Characteristics

6.4.1 Demographic and Baseline Characteristics

Analysis Set: ITT

Analysis Endpoint(s) :

Age (years)	[Min<= - < 9, 9<= - <=18, 18< - <=Max]
	[Min<= - <7, 7<= - <=Max]
Gender	[Male, Female]
Height (cm)	
Weight (kg)	
BMI (kg/m2)	
Height z-score	
Weight z-score	

BMI z-score	
Time Since Original Diagnosis of PFIC, in Months	
Used Anything to Treat Itch in the Past	[Yes, No]
Type of Therapy Used to Treat Itch in the Past (multiple count)	
Topical	
Oral	
Other	
Specific Therapy Used to Treat Itch in the Past	
Topical Corticosteroids	
Topical Calcineurin Inhibitors	
Topical Antihistamines	
Menthol	
Capsaicin	
Salicylic acid	
Local Anesthetics	
Androgens	
Anticholestatic Agents	
Anticonvulsants	
Antidepressants	
Antihistamines	
Anti-Oxidants	
Binding Resins	
Colchicine	

Cannabinoid Agonist

Enzyme Inducers

Immunosuppressants

Opiate Antagonists

Serotonin Antagonists

Ursodeoxycholic Acid

IBAT Inhibitors

Surgical Interruption of the Enterohepatic Circulation

Phototherapy

Hemofiltration

Plasmapheresis

Nasal Biliary Drainage

Other

ItchRO(Obs) 4-week Morning Average Severity (Item 1) Score

ItchRO(Obs) 4-week Morning Average Frequency (Item 3) Score

[redacted]

sBA (LC MS)

PFIC Subtype [PFIC1, PFIC2, PFIC3, PFIC4, PFIC5, PFIC6]

Analytical Method(s) : (1) Demographics and Baseline Characteristics

Frequency distributions for categorical endpoints and descriptive statistics for continuous endpoints will be provided. PFIC subtype will be provided in Section 6.10.1 and 6.10.2 only.

6.4.2 Medical History and Concurrent Medical Conditions

Analysis Set: ITT

Analysis Endpoint(s) : Medical History

Concurrent Medical Conditions

Analytical Method(s) :
(1) Medical History by System Organ Class and Preferred Term
(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

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

6.5 Medication History and Concomitant Medications

Analysis Set: ITT

Analysis Endpoint(s) : Medication History

Concomitant Medications

Analytical Method(s) :
(1) Medication History by Anatomical Therapeutic Chemical Level 2 and Preferred Medication Name
(2) Concomitant Medications That Started and Stopped Prior to Baseline by Anatomical Therapeutic Chemical Level 2 and Preferred Medication Name
(3) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Anatomical Therapeutic Chemical Level 2 and Preferred Medication Name

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using anatomical therapeutic chemical level 2 and preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication names will be counted only once for that preferred medication names. For anatomical therapeutic chemical level 2, same manners in counting frequency.

6.6 Extent of Exposure and Compliance

Analysis Set:	ITT	
Analysis Endpoint(s) :	Duration of Exposure to Study Drug (days)	[0<= - <= 28, 29 <= - <= Max]
	Study Drug Compliance (%)	[Min<= - < 80, 80 <= - <= 100, 100< - <=Max]
	Total Drug Exposure (µg/kg)	
	Average Daily Dose (µg/kg/day)	
Analytical Method(s) :	(1) Study Drug Exposure, Compliance, Total Drug Exposure and Average Daily Dose	

Frequency distributions for categorical endpoints and descriptive statistics for continuous endpoints will be provided.

6.7 Efficacy Analysis

6.7.1 Primary Endpoint Analysis

6.7.1.1 Primary Analysis

Analysis Set:	ITT
Analysis Endpoint(s):	Change in the average morning ItchRO (Obs) severity score between baseline and average of Week 15 through Week 26
Analytical Method(s):	See Section 6.2.2.

6.7.1.2 Sensitivity Analysis

Analysis Set:	PPS
Analysis Endpoint(s):	Change in the average morning ItchRO (Obs) severity score between baseline and average of Week 15 through Week 26
Analytical Method(s):	See Section 6.2.2. For supportive analysis the same analysis as the primary analysis will be performed using the PPS to confirm robustness of the results.

6.7.1.3 Supplementary Analyses

Analysis Set:	ITT
Analysis Endpoint(s):	Change in the average morning ItchRO (Obs) severity score between baseline and average of Week 15 through Week 26
Analytical Method(s):	If possible, the endpoint will be analyzed using a MMRM model. The repeated measures include post-baseline visits (i.e., Week 6, 10, 14, 18, 22, and 26), with change from baseline in the 6- or 4-week average morning ItchRO(Obs) severity score as the response. The MMRM will also include visit, baseline and baseline-by-visit interaction as fixed effects. LS means and the two-sided 95% confidence intervals will be provided using the contrast across the last 12 weeks of the study (i.e., Weeks 18, 22, and 26 combined). In other words, the analytical solution from the MMRM is an equally weighted average of the 3 individual visit-specific estimates over the time period of interest (i.e., Weeks 18, 22, and 26). The unstructured variance/covariance matrix will be used to model the variances and covariances. However, if the numerical algorithm for estimation of the mixed model fails to converge, the alternative variance/covariance matrix structures will be used (e.g., heterogeneous autoregressive of order 1). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

6.7.2 Secondary Endpoints Analysis

6.7.2.1 Key Secondary Endpoints

Analysis Set:	ITT
Analysis Endpoint(s):	• 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
Analytical Method(s):	See Section 6.2.2.

6.7.2.2 Sensitivity Analysis

Analysis Set: PPS

Analysis Endpoint(s):
- 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

Analytical Method(s): See Section 6.2.2. For supportive analysis the same analysis as the primary analysis will be performed using the PPS to confirm robustness of the results.

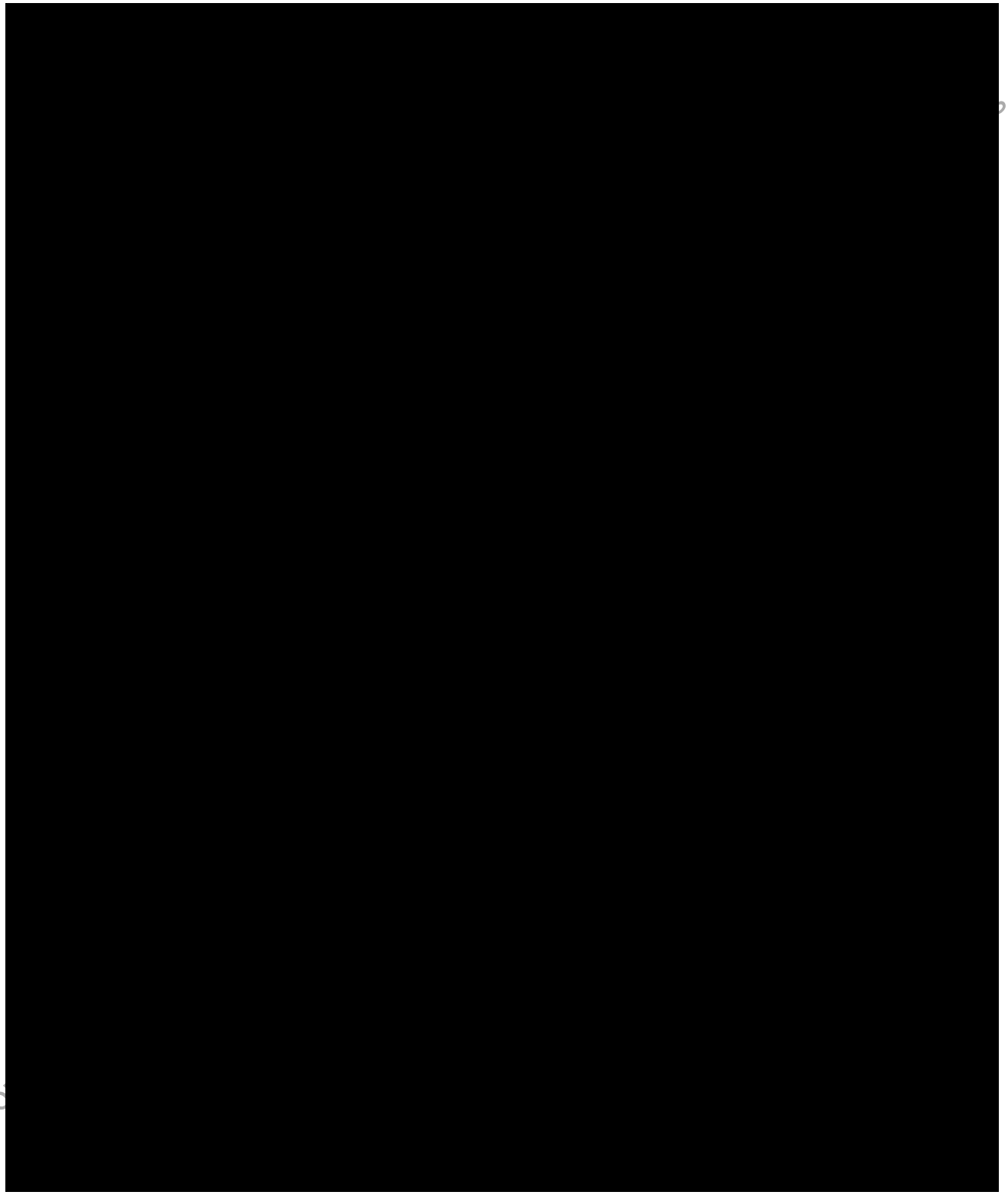
6.7.2.3 Secondary Endpoints

Analysis Set: ITT

Analysis Endpoint(s):
- Proportion of subjects who experience an sBA control
- 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

Analytical Method(s): See Section 6.2.2 ~ 6.2.3.

[redacted]



[redacted]

6.7.4 Subgroup Analysis

Analysis Set: ITT

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

Subgroup(s): Age [Min<= - <7, 7<= - <=Max]

	Gender	[Male, Female]
Analytical Method(s):	Descriptive statistics will be provided for above each subgroup.	

6.8 Safety Analysis

6.8.1 Adverse Events

6.8.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Endpoint(s) :	TEAE	
Categories:	Relationship to Study Drug	[Related, Not Related]
	Intensity	[Mild, Moderate, Severe]

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

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3) , and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

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

6.8.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:	Safety Analysis Set	
Analysis Endpoint(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
	Time of Onset (day)	[1 – 28, 29 - Max]
Analytical Method(s) :	The following summaries will be provided using frequency distribution.	

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(10) Treatment-Emergent Adverse Events of Clinical Interest by System Organ Class and Preferred Term

(11) Drug-Related Treatment-Emergent Adverse Events of Clinical Interest by System Organ Class and Preferred Term

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

Number of subjects

- Summary tables other than (5), (6) and (9)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.
- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.
- Summary table for (9)
  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages for each time interval, the number of subjects at risk (i.e., subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of

subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

6.8.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Endpoint(s) : PTE

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

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

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

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

Number of subjects

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

6.8.2 Clinical Laboratory Evaluations

6.8.2.1 Laboratory Tests other than Urinalysis

Analysis Set: Safety Analysis Set

Analysis Endpoint(s) : See Section 9.3.6.

Visit: Using the visits (Baseline to Week 26) of the visit window defined in Section 9.2.2.

Analytical Method(s) : For each endpoint, summaries (1) to (3) will be provided.

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

(2) Case Plots
Plots over time for each subject will be presented.

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

6.8.2.2 Urinalysis

Analysis Set:	Safety Analysis Set
Analysis Endpoint(s) :	See Section 9.3.6.
Visit:	Using the visits (Baseline to Week 26) of the visit window defined in Section 9.2.2.
Analytical Method(s) :	For pH and specific gravity, summaries (1) , (2) and (4) will be provided. For each endpoint other than pH and specific gravity, summaries (3) and (4) will be provided.

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

(2) Case Plots
Plots over time for each subject will be presented.

(3) Number of Subjects in Categories of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

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

6.8.3 Vital Signs, Weight and Height

Analysis Set:	Safety Analysis Set

Analysis Endpoint(s) :	Systolic Blood Pressure	Diastolic Blood Pressure
	Heart Rate	Body Temperature
	Weight	Height
	BMI	Respiration Rate

Visit: Using the visits (Baseline to Week 26) of the visit window defined in Section 9.2.2.

Analytical Method(s) : For each endpoint, summaries (1) and (2) will be provided.

(1) Summary of Vital Signs, Weight and Height, and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit - Baseline) will be provided for each visit.

(2) Case Plots
Plots over time for each subject will be presented.

6.8.4 ECGs

Analysis Set: Safety Analysis Set

Analysis Endpoint(s) :	Heart Rate	
	RR Interval	
	PR Interval	
	QRS Interval	
	QT Interval	
	QTcF Interval	
	Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit: Using the visits (Baseline to Week 26) of the visit window defined in Section 9.2.2.

Analytical Method(s) : For each endpoint other than 12-lead ECG interpretations, summaries (1) and (2) will be provided.

For ECG interpretation, summary (3) will be provided.

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from

baseline (each post-baseline visit - Baseline) will be provided for each visit.

(2) Case Plots
Plots over time for each subject will be presented.

(3) Summary of Shift of ECG Interpretation
Shift table showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

6.8.5 Displays of Treatment-Emergent Adverse Events (Japanese)

Analysis Set: Safety Analysis Set

Analysis Endpoint(s) : TEAE

Analytical Method(s) : TEAEs will be summarized in the same way as in Section 6.8.1.2. All summaries will be presented in Japanese.

6.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.9.1 Pharmacokinetic Analysis

6.9.1.1 Plasma Concentrations

Analysis Set: Safety Analysis Set

Analysis Endpoint(s) : Plasma concentrations of TAK-625

Visit: Using the visits of the visit window defined in Section 9.2.2.2

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

(1) Summary of Plasma Concentrations by Visit
Descriptive statistics will be provided by visit by dose level categories administered just before sample collection.

6.10 Other Analyses

6.10.1 Analyses for Overall Supplemental Cohort

Cohort: Overall Supplemental Cohort

Analytical Method(s) : The same analyses in section 6.3 ~ 6.9 will be performed for overall supplemental cohort.

6.10.2 Analyses for All Cohorts Combined

Cohort: All Cohorts Combined

Analytical Method(s) : The same analyses in section 6.3 ~ 6.9 will be performed for all cohorts combined.

7.0 REFERENCES

[1] World Health Organization (WHO) growth charts "A SAS Program for the WHO Growth Charts (ages 0 to < 2 years)"
https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas-who.htm

[2] Centers for Disease Control (CDC) growth charts "A SAS Program for the 2000 CDC Growth Charts (ages 0 to < 20 years)"
https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

There was no change to the protocol planned analyses.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

From the SAP version 1.0, the major updates except minor updates like error correction were following parts.

Section [redacted]

Before the change

Not applicable.

After the change

[redacted]

[redacted]

Reason for the change

Some exploratory endpoints were added when protocol had been amended.

Section 6.0 STATISTICAL ANALYSIS

Before the change

Not applicable.

After the change

Statistical analyses will be performed using all subjects' data up to Week 26 (i.e., up to Day 197) after the data are locked. PK analysis will be performed using all subjects' data up to Week 10 after the data are locked.

Reason for the change

To make the target range of the Interim analysis clear.

Section 6.1 General Considerations

Before the change

- **Descriptive statistics**: Number of subjects, mean, standard deviation, standard error, maximum, minimum, and quartiles (Q1, median, and Q3).
- **Duration of exposure to study drug (days)**: Date of last dose of study drug - date of first dose of study drug + 1.
- **Duration of study after baseline (days)**: Date of last visit/contact - date of first dose of study drug + 1.

…

- **Time to liver-associated events**: PEBD surgery, listing for liver transplantation, liver decompensation [hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis] events, hepatocellular carcinoma (HCC), death.

After the change

- **Descriptive statistics for endpoints other than PK**: Number of subjects, mean, standard deviation, standard error, maximum, minimum, and quartiles (Q1, median, and Q3).
- **Descriptive statistics for PK**: Number of subjects, mean, standard deviation, maximum, median, minimum, coefficient of variation, and geometric mean.

- **Duration of exposure to study drug (days)**: {Date of last dose of study drug or Week 26 visit (i.e. the latest visit by Day 197) which comes faster - date of first dose of study drug} + 1.
- **Duration of study after baseline (days)**: {Date of last visit/contact or Week 26 visit (i.e. the latest visit by Day 197) which comes faster - date of first dose of study drug} + 1.

…

- **Dose Level (µg/kg)**: Strength of study drug taken (mg) / (last available body weight (kg) prior to or on the day of study drug taken) * 1000.
- **Dose Level Categories for PK (µg/kg)**: Categorize by following below calculation rule.

  If Min <= dose level < 225 µg/kg, then dose level category = 150 µg/kg; if 225 µg/kg <= dose level < 375 µg/kg, then dose level ＞category = 300 µg/kg; if 375 µg/kg <= dose level < 525 µg/kg, then dose level category = 450 µg/kg; if 525 µg/kg <= dose level <= Max, then dose level category = 600 µg/kg.
- **Total Drug Exposure (µg/kg)**: Sum of {number of study drugs taken * dose level received (µg/kg)}.
- **Average Daily Dose (µg/kg/day)**: Total Drug Exposure (µg/kg) / Duration of exposure to study drug (days).

…

- **Time to liver-associated events**: PEBD surgery, listing for liver transplantation, liver decompensation [hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis] events, hepatocellular carcinoma (HCC), death, and other.

…

- **Corrected Sodium (mEq/L)**: sodium (mEq/L) + (0.002 * Triglycerides (mg/dL)).
- **FIB-4**: (Age (years) * AST (U/L)) / (platelet count (10^9/L) * sqrt(ALT(U/L)))
  - Age (years) is years at sample collection visit.
- **APRI**: 100 * (AST (U/L) / AST ULN(U/L)) / (platelet count (10^9/L))
  - ULN is upper limit normal
- **Significant Protocol Deviation**: Deviation defined in the PDMP as “Important PD” whose Severity Classifications is “major” or “critical”.
- **Time since original diagnosis of PFIC (months)**: (date of first dose – date of original diagnosis of PFIC + 1) / 30.4375.

Reason for the change

Some calculation rules and definitions were added and updated.

Section 6.1 General Considerations

Before the change

Not applicable.

After the change

When reporting derived values or parameters, following presenting rules will be applied.

- For sBA, ItchRO: For rules on rounding and decimal presentation of these statistics, along with the rules for presenting certain derived values see below.
  - For measures of median and mean, use 3 decimal places.
  - For measures of standard deviation, standard error of the mean and CI, use 4 decimal places.
  - For measures of minimum and maximum values as well as observed value (for Listing), use 2 decimal places.
  - >=5 is rounded up away from zero, whereas <5 is rounded down toward zero, to account for rounding of negative numbers.
  - For p-values use 3 decimal places.
  - Presentation of p-values display p-values that would round to 0.000 as <0.001.
- Other than sBA, and ItchRO: For rules on rounding and decimal presentation of these statistics, along with the rules for presenting certain derived values see below.
  - For measures of median and mean, use 1 decimal place beyond those used for the measurement.
  - For measures of standard deviation, standard error of the mean and CI, use 2 decimal places beyond those used for the measurement.
  - For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
  - >=5 is rounded up away from zero, whereas <5 is rounded down toward zero, to account for rounding of negative numbers.
  - For p-values use 3 decimal places.
  - Presentation of p-values display p-values that would round to 0.000 as <0.001.
  - BMI should be rounded to 1 decimal place for reporting.
  - Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.
  - Averaged lab results (e.g. Diastolic/Systolic Blood Pressure and Pulse [when taken in triplicate]) should be rounded to 1 decimal place for reporting.

Reason for the change

Presenting rules in TLF were added.

Section 6.3.2 Screen Failures

Before the change

Analysis Endpoint(s): Age (months)

After the change

Not applicable.

Reason for the change

No infant subjects who failed screening.

Section 6.3.5 Disposition of Subjects

Before the change

Analysis Endpoint(s) : Study Drug Administration Status, [Eligible but Not Treated]

Reason for Not Being Treated, [AE, Screen Failure (Did not meet inclusion criteria or did meet exclusion criteria), Protocol Deviation, Lost to Follow-up, Pregnancy, Withdrawal by Subject, Study Terminated by Sponsor, Other]

Study Drug Completion Status, [Completed Study Drug, Prematurely Discontinued Study Drug]

Completion Status of All Planned Study Visits, [Completed Study, Prematurely Discontinued Study]

Analytical Method(s): Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

After the change

Analysis Endpoint(s) :

Study Drug Completion Status, [Ongoing, Completed Study Drug, Prematurely Discontinued Study Drug]

Completion Status of All Planned Study Visits, [Ongoing, Completed Study, Prematurely Discontinued Study]

Analytical Method(s): Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

Reason for the change

These analysis endpoints were not appropriate for ITT population. The category of "Ongoing" was added because this SAP is for Interim analysis.

Section 6.3.6.1 Significant Protocol Deviations

Before the change

Analysis Endpoint(s): Significant Protocol Deviations, [AE, Screen Failure (Did not meet inclusion criteria or did meet exclusion criteria), Protocol Deviation, Lost to Follow-up, Pregnancy, Withdrawal by Subject, Study Terminated by Sponsor, Other]

After the change

Analysis Endpoint(s): Significant Protocol Deviations, [Informed Consent and Process, Inclusion Criteria, Exclusion Criteria, Concomitant Medication, Laboratory Assessment, Study Procedures (not safety and efficacy related), Safety, Visit Schedule, IP conditions, IP preparation, IP administration, Subject IP Compliance, Efficacy, Subject Discontinuation, Administrative, Patient Reported Outcomes, PK/PD, Other Criteria]

Reason for the change

Change it from CRF category to CTMS category.

Section 6.4.1 Demographic and Baseline Characteristics

Before the change

Analysis Endpoint(s): Age (years), [Min<= - < 9, 9<= - <=18, 18< - <=Max]

After the change

Analysis Endpoint(s): Age (years), [Min<= - < 9, 9<= - <=18, 18< - <=Max]

[Min<= - <7, 7<= - <=Max]

Reason for the change

Added CTD analysis category.

Section 6.6 Extent of Exposure and Compliance

Before the change

Analysis Endpoint(s) : Not applicable.

Analytical Method(s) : (1) Study Drug Exposure and Compliance

After the change

Analysis Endpoint(s) : Total Drug Exposure (µg/kg), Average Daily Dose (µg/kg/day)

Analytical Method(s) : (1) Study Drug Exposure, Compliance, Total Drug Exposure and Average Daily Dose

Reason for the change

Added additional endpoints.

Section [redacted]

Before the change

Analysis Endpoint(s):

…

[redacted]

…

After the change

Analysis Endpoint(s):

…

[redacted]

Reason for the change

Added new exploratory endpoints when protocol had been amended.

Section 6.7.3.3 Responder Analysis

Before the change

Not applicable.

After the change

Analysis Set:, ITT

[redacted]

Reason for the change

Added new exploratory endpoints when protocol had been amended.

Section 6.7.4 Subgroup Analysis

Before the change

Subgroup(s): Age, [Min<= - < 9, 9<= - <=18, 18< - <=Max]

After the change

Subgroup(s): Age, [Min<= - <7, 7<= - <=Max]

Reason for the change

To be consistent with CTD analysis.

Section 6.9.1.1 Plasma Concentrations

Before the change

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

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

After the change

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

(1) Summary of Plasma Concentrations by Visit Descriptive statistics will be provided by visit by dose level categories administered just before sample collection.

Reason for the change

To incorporate new Clinical pharmacology insight.

Section 9.2.1 Definition of Study Days

Before the change

The following definitions and calculation formulas will be used.

- Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. If the date of the observation is on the same date or after the day of the first dose, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.
- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1. Follow-up Day will be calculated relative to Day 1.

After the change

The following definitions and calculation formulas will be used.

- Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. If the date of the observation is on the same date or after the day of the first dose, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.
- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1.

Reason for the change

Error correction.

Section 9.2.2.1 Endpoints other than ItchRO Scores and PK Samples

Before the change

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used.

After the change

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used. For laboratory test data, if there are two observations of both central laboratory sample and local sample on the same date, central

laboratory sample data will be used. Values less than or equal to the lower limit of quantification will be treated as one-half of the lower limit value when calculating the descriptive statistics. Values greater than or equal to the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

Reason for the change

Added handling rule for the lower limit of quantification value.

Section 9.2.2.2 PK Samples

Before the change

Study Time (hour) is defined as the difference from the PK sampling time at the visit date to the time of study drug taken at the visit date (rounded to 1 decimal place(s)).

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Time to the scheduled Study Time will be used. If there are two observations equidistant to the scheduled Study Time, the earlier observation will be used.

Table 9.8 Visit Window of PK

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day	Scheduled Study Time	Study Time (hours)
Pre-dose at Week 10	Study Day:	71	71	Study Time (hour): 0	-5.0 ~ 0.0
2.5 Hours after Morning Dose at Week 10	Study Day:	71	71	Study Time (hour): 2.5	1.5 ~ 3.5
Pre-dose at Week 14 ~ 26	Study Day:	99	99 – 183	Study Time (hour): 0	-5.0 ~ 0.0
0.5 Hours after Morning Dose at Week 14 ~ 26	Study Day:	99	99 – 183	Study Time (hour): 0.5	0.0 ~ 1.0

After the change

Study Time (hour) is defined as the difference from the PK sampling time at the visit date to the time of study drug taken at the visit date (rounded to 1 decimal place(s)).

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Time to the scheduled Study Time will be used. If there are two observations equidistant to the scheduled Study Time, the earlier observation will be used. Values less than the lower limit of quantification will be treated as zero when calculating the descriptive statistics.

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day	Scheduled Study Time	Study Time (hours)
Pre-dose at Week 10	Study Day:	71	57 – 85	Study Time (hour): 0	-5.0 ~ 0.0
2.5 Hours after Morning Dose at Week 10	Study Day:	71	57 - 85	Study Time (hour): 2.5	1.5 ~ 3.5

Reason for the change

Added handling rule for the lower limit of quantification value. For Visit window, some Visits were removed because it's possible that samples at these visits not to be collected at Interim analysis. For Time interval, previous one was too narrow and inappropriate.

Section 9.2.3 Partial Date Conventions

Before the change

Not applicable.

After the change

9.2.3 Partial Date Conventions

For Medication History and Concomitant Medication, if their stop date is partially/completely missing, following handling rules will be applied.

if (CMCAT="MEDICATION HISTORY") then "(1) Prior Medication" ;

else if (CMENRTPT="ONGOING") then "(3) Concomitant Medication" ;

else if

(. < medication end year < TAK-625 start year) or

(medication end year = TAK-625 start year and

. < medication end month < TAK-625 start month) or

(medication end year = TAK-625 start year and

medication end month = TAK-625 start month and

. < medication end date < TAK-625 start date) then "(2) Concomitant Medication" ;

else "(3) Concomitant Medication" ;

Reason for the change

To make it clear how to handle partial date.

Section 9.3.2 Average ItchRO Scores

Before the change

Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) or more frequent (Item 3) itching. After the derivation described in section 9.2.2.3, the following endpoints will be derived the same procedures as section 9.3.1.

[redacted]

- **Change in the average evening ItchRO (Obs/Pt) severity score between baseline and average of Week 15 through Week 26.**
- **Change in the average ItchRO (Obs/Pt) severity (based on daily maximum of morning and evening severity scores)**
- **Change in the average morning ItchRO (Obs/Pt) frequency score between baseline and average of Week 15 through Week 26.**
- **Change in the average evening ItchRO (Obs/Pt) frequency score between baseline and average of Week 15 through Week 26.**

After the change

For ItchRO scores, both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) or more frequent (Item 3) itching. After the derivation described in section 9.2.2.3, the following endpoints will be derived the same procedures as section 9.3.1.

[redacted]

[redacted]

- **Change in the average evening ItchRO (Obs/Pt) severity score between baseline and average of Week 15 through Week 26.**
- **Change in the average ItchRO (Obs/Pt) severity and frequency (based on daily maximum of morning and evening severity scores) between baseline and average of Week 15 through Week 26.**
- **Change in the average morning ItchRO (Obs/Pt) frequency score between baseline and average of Week 15 through Week 26.**
- **Change in the average evening ItchRO (Obs/Pt) frequency score between baseline and average of Week 15 through Week 26.**

[redacted]

Reason for the change

Added new exploratory endpoints when protocol had been amended.

Section 9.3.3 Responder Endpoints

Before the change

- **Subjects who experience an sBA control**: subjects with a reduction to <102 µMol/L, or a reduction of >75%, or normalization) from baseline through Week 26

After the change

- **Subjects who experience an sBA control**: subjects with a reduction to <102 µMol/L, or a reduction of >75%, or normalization) from baseline through Week 26

[redacted]

Reason for the change

Added new exploratory endpoints when protocol had been amended.

Section 9.3.6 Lists of Laboratory Tests

Before the change

Not applicable.

After the change

Total sBA (enzymatic assay)

Reason for the change

Error correction.

9.2 Data Handling Conventions

9.2.1 Definition of Study Days

The following definitions and calculation formulas will be used.

- Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. If the date of the observation is on the same date or after the day of the first dose, Study Day will be calculated relative to Study Day 1. Otherwise, Study Day will be calculated relative to Study Day -1.
- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1.

9.2.2 Definition of Study Visit Windows

When calculating Study Day relative to a reference date (i.e., date of first dose of study drug [Day 1]) , if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

When calculating Follow-up Day relative to a reference date (i.e., date of last dose of study drug [Follow-up Day 0]) , it will be calculated as: date of observation - reference date. Hence, reference day is always Follow-up Day 0.

All evaluable data (i.e., non-missing data) will be handled according to the following rules.

9.2.2.1 Endpoints other than ItchRO Scores and PK Samples

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used. For laboratory test data, if there are two observations of both central laboratory sample and local sample on the same date, central laboratory sample data will be used. Values less than or equal to the lower limit of quantification will be treated as one-half of the lower limit value when calculating the descriptive statistics. Values greater than or equal to the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

Table 9.1 Visit Window of sBA, sBA subspecies, C4, Serum Storage Sample

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 2	Study Day: 15	2 - 29	< 15
Week 6	Study Day: 43	30 - 57	< 15
Week 10	Study Day: 71	58 - 85	< 15
Week 14	Study Day: 99	86 - 113	< 15
Week 18	Study Day: 127	114 - 141	< 15
Week 22	Study Day: 155	142 - 169	< 15
Week 26	Study Day: 183	170 - 197	< 15

Table 9.2 Visit Window of Vital Signs, Weight and Height, [redacted]

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 2	Study Day: 15	2 - 22	< 15
Week 4	Study Day: 29	23 - 36	< 15
Week 6	Study Day: 43	37 - 57	< 15
Week 10	Study Day: 71	58 - 85	< 15
Week 14	Study Day: 99	86 - 113	< 15
Week 18	Study Day: 127	114 - 141	< 15
Week 22	Study Day: 155	142 - 169	< 15
Week 26	Study Day: 183	170 - 197	< 15

Table 9.3 Urinalysis, Cholestasis Biomarkers (FGF19)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 6	Study Day: 43	2 - 57	< 15
Week 10	Study Day: 71	58 - 99	< 15
Week 18	Study Day: 127	100 - 155	< 15
Week 26	Study Day: 183	156 – 197	< 15

Table 9.4 Lipid Panel, Lipid Soluble Vitamins

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 – 1	

Table 9.4 Lipid Panel, Lipid Soluble Vitamins

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week 6	Study Day: 43	2 – 57	< 15
Week 10	Study Day: 71	58 – 85	< 15
Week 14	Study Day: 99	86 – 113	< 15
Week 18	Study Day: 127	114 – 141	< 15
Week 22	Study Day: 155	142 – 169	< 15
Week 26	Study Day: 183	170 – 197	< 15

Table 9.5 CBC, Coagulation, Chemistry Panel

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	
Week 2	Study Day: 15	2 - 29	< 15
Week 6	Study Day: 43	30 - 57	< 15
Week 10	Study Day: 71	58 - 85	< 15
Week 14	Study Day: 99	86 - 113	< 15
Week 18	Study Day: 127	114 - 141	< 15
Week 22	Study Day: 155	142 - 169	< 15
Week 26	Study Day: 183	170 - 197	< 15

Table 9.6 Visit Window of ECGs, AFP

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	

Table 9.6 Visit Window of ECGs, AFP

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week 10	Study Day: 71	2 - 127	< 15
Week 26	Study Day: 183	128 - 197	< 15

[redacted]

9.2.2.2 PK Samples

Study Time (hour) is defined as the difference from the PK sampling time at the visit date to the time of study drug taken at the visit date (rounded to 1 decimal place(s)).

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Time to the scheduled Study Time will be used. If there are two observations equidistant to the scheduled Study Time, the earlier observation will be used. Values less than the lower limit of quantification will be treated as zero when calculating the descriptive statistics.

Table 9.8 Visit Window of PK

Visit	Scheduled Study Day (days)		Time Interval (days) Study Day	Scheduled Study Time	Study Time (hours)
Pre-dose at Week 10	Study Day:	71	57 - 85	Study Time 0 (hour):	-5.0 ~ 0.0
2.5 Hours after Morning Dose at Week 10	Study Day:	71	57 - 85	Study Time 2.5 (hour):	1.5 ~ 3.5

9.2.2.3 Average ItchRO Scores

For each visit other than Week 6, average ItchRO score is defined as the average of the scores (morning, evening, or daily maximum of morning and evening) over the visit consisting of the 28 days on or before the scheduled Study Day (i.e., the sum of the scores divided by the number of non-missing scores). The answer "I don't know" will be treated as missing.

For Week 6, average ItchRO score is defined as the average of the scores (morning, evening, or daily maximum of morning and evening) over the visit consisting of the 41 days on or before the scheduled Study Day (i.e., the sum of the scores divided by the number of non-missing scores). The answer "I don't know" will be treated as missing.

In the event that a subject/caregiver failed to complete the morning/evening report, the morning/evening score for that day will be treated as missing data. If 25% or more ItchRO scores for the post-baseline visit are missing, the average ItchRO score at that visit will be treated as missing. The restriction is not set for baseline average ItchRO scores.

Table 9.9 Visit Window of Average ItchRO Score

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline (Week 0)	Study Day: -1	-28 - -1	
Week 6	Study Day: 42	2 - 42	< 15
Week 10	Study Day: 70	43 - 70	< 15
Week 14	Study Day: 98	71 - 98	< 15
Week 18	Study Day: 126	99 - 126	< 15
Week 22	Study Day: 154	127 - 154	< 15
Week 26	Study Day: 182	155 - 182	< 15

9.2.3 Partial Date Conventions

For Medication History and Concomitant Medication, if their stop date is partially/completely missing, following handling rules will be applied.

if (CMCAT="MEDICATION HISTORY") then "(1) Prior Medication" ;

else if (CMENRTPT="ONGOING") then "(3) Concomitant Medication" ;

else if

(. < medication end year < TAK-625 start year) or

(medication end year = TAK-625 start year and

. < medication end month < TAK-625 start month) or

(medication end year = TAK-625 start year and

medication end month = TAK-625 start month and

. < medication end date < TAK-625 start date) then "(2) Concomitant Medication" ;

else "(3) Concomitant Medication" ;

9.3 Derivation of Endpoints

9.3.1 Primary Efficacy Endpoints

Both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) itching. The derivation method for the primary efficacy endpoint will be described below.

After the derivation described in section 9.2.2.3, each subject will have a baseline (Week 0) 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 (i.e., the sum of the average morning ItchRO (Obs) severity scores divided by the number of non-missing morning severity scores).

9.3.2 Average ItchRO Scores [redacted]

For ItchRO scores, both the morning and evening ItchRO reports have a minimum score of 0 and a maximum score of 4, with 4 representing more severe (Item 1) or more frequent (Item 3) itching. After the derivation described in section 9.2.2.3, the following endpoints will be derived the same procedures as section 9.3.1.

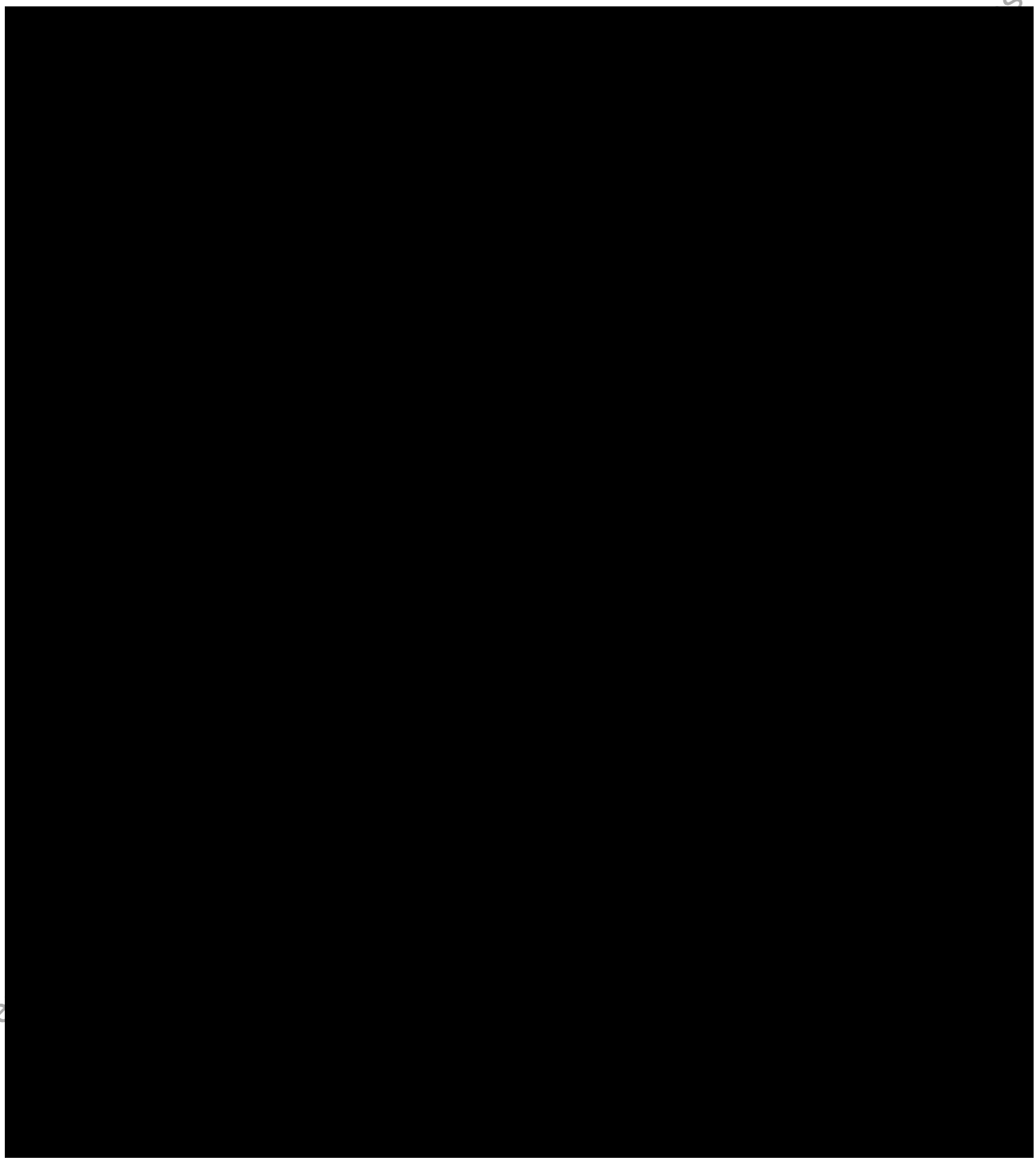
[redacted]

- **Change in the average evening ItchRO (Obs/Pt) severity score between baseline and average of Week 15 through Week 26.**
- **Change in the average ItchRO (Obs/Pt) severity and frequency (based on daily maximum of morning and evening severity scores) between baseline and average of Week 15 through Week 26.**
- **Change in the average morning ItchRO (Obs/Pt) frequency score between baseline and average of Week 15 through Week 26.**
- **Change in the average evening ItchRO (Obs/Pt) frequency score between baseline and average of Week 15 through Week 26.**

[redacted]

9.3.3 Responder Endpoints

- **Subjects who experience an sBA control**: subjects with a reduction to <102 µMol/L, or a reduction of >75%, or normalization) from baseline through Week 26



9.3.5 Z-scores

Z-scores of weight, height and BMI are based on a subject's gender and age at each scheduled visit. For subjects less than 24 months of age, the World Health Organization (WHO) growth charts are recommended by the Centers for Disease Control (CDC) and will be used to derive z-scores. For subjects at least 24 months of age, the CDC growth charts will be used to derive z-scores.

Age at which height and weight were measured should be used for calculating z-scores, not using age at baseline.

9.3.6 Lists of Laboratory Tests

Hematology (CBC with Differential)	**Chemistry**	**Lipid Panel**	**Urinalysis**
Hematocrit	Albumin	Total cholesterol	pH
Hemoglobin	ALP	LDL-C (direct)	Specific gravity
MCV, MCH, MCHC	Amylase	HDL-C	Protein
Red blood cells	ALT (SGPT)	TG	Glucose
Platelets	AST (SGOT)		Ketones
White blood cells	Bicarbonate	**Cholestasis Biomarkers**	Bilirubin
WBC Differential (% and absolute)	Bilirubin, direct (conjugated)	sBA (LC-MS)	Occult blood and cells
Neutrophils	TSB	sBA subspecies	Nitrite
Eosinophils	BUN	7alpha-hydroxy-4-cholesten-3-one (C4)	Urobilinogen
Basophils	Calcium	FGF-19	Leukocyte esterase
Lymphocytes	Chloride	Autotaxin	Microscopic examination
Monocytes	Creatinine		Oxalate
	GGT	**Lipid Soluble Vitamins**	Urinary creatinine
Coagulation	Glucose	25-hydroxy vitamin D	
aPTT (sec)	Lipase	Retinol	
INR	Phosphate	RBP	
PT (sec)	Potassium	Alpha-tocopherol	
	Sodium	Estimated Total Lipids	
	Corrected Sodium	Ratio of Alpha-tocopherol to Estimated Total Lipids	
	Total protein		
	Total sBA (enzymatic assay)		
	Uric Acid		
	Measured serum Osmolality		

9.3.7 Table for AECI

The categories of AECI will follow ones in CRF.

9.3.8 Significance Level and Confidence Coefficient

- Significance level: 5% (two-sided)
- Confidence coefficient: 95% (two-sided)

9.4 Analysis Software

SAS (version 9.4)