

## 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: 2.0 / 10-Nov-2023

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 Week 26

Study Number: TAK-625-3002

applicable terms of Use 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
	use only and
Prepared by:	A CONTRACTOR OF
Based on:	
Protocol Version: Amendment 2	
Protocol Date: 08-Dec-2022	
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## **REVISION HISTORY**

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## **ABBREVIATIONS**

	Statistical Analysis	s Plan 2.0	<u>10Nov2023</u>
	ABBREVIATIO	ONS	, VSt
	AE	adverse event	0
	AECI	adverse event of clinical interest	and s
	AFP	alpha-fetoprotein	LON.
	ALP	alkaline phosphatase	0
	ALT	alanine aminotransferase	201
	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	
		and a second sec	
	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 🎸	Ointention-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	
el.	LSV	lipid soluble vitamin	
.09~	MCH	mean corpuscular hemoglobin	
	MCHC	mean corpuscular hemoglobin concentration	
	MCV	mean corpuscular volume	

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MedDRA	Medical Dictionary for Regulatory Activities	
MITT	modified intention-to-treat set	
PEBD	partial external biliary diversion	~
		XON
PFIC	progressive familial intrahepatic cholestasis	Q
PK	pharmacokinetic	2010
PPS	per-protocol analysis set	il <sup>co.</sup>
PRO	patient-reported outcomes	00.
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	
Hottakeou		

#### 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)

ect to the applicable terms of Use To evaluate primary, secondary, and exploratory endpoints in the supplemental cohort •

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#### 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.

'N SUG

#### 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 ٠

## 1.2.2.2 Secondary Endpoint(s)

- *Proportion of subjects who experience an sBA control (defined as a reduction to <102)*  $\mu$ mol/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.



## 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.  $\diamond$
- $\diamond$ *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 ine applicat [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 only and su dose at Week 14 (or any visit up to Week 26).

#### 1.3 **Estimand(s)**

Not Applicable.

### 2.0 STUDY DESIGN

ce. *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):

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		SO
In the screening period, for subjects who do not have documentation of mutation rel	ated with	
PFIC, a blood sample will be obtained for genotyping. Subjects diagnosed with PFI	C2 (nt-	Ó
PFIC2) will be enrolled in the primary cohort and those with other types of PFIC w	ill be 🧹	5
enrolled in the supplemental cohort. The electronic Diary (eDiary) for assessing pri	ıritus with 🔨	

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 followup will be conducted.

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

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Not Applicable.

## SAMPLE-SIZE DETERMINATION 4.0

*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.

## ANALYSIS SETS 5.0

## All Subjects Who Signed the Informed Consent Form 5.1

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.

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.

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- 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.

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

- 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  $\leq$  dose level  $\leq 225 \ \mu g/kg$ , then dose level category = 150  $\mu g/kg$ ; if 225  $\mu g/kg \leq$ dose level  $< 375 \,\mu\text{g/kg}$ , then dose level  $> \text{category} = 300 \,\mu\text{g/kg}$ ; if 375  $\mu\text{g/kg} \ll \text{dose level}$  $< 525 \ \mu g/kg$ , then dose level category = 450  $\mu g/kg$ ; if 525  $\mu g/kg \leq dose level \leq Max$ , then dose level category =  $600 \mu g/kg$ .

- Total Drug Exposure (µg/kg): Sum of {number of study drugs taken \* dose level received ٠  $(\mu g/kg)$ .
- 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.

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- - > >=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.  $\succ$
- 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.

## **Analysis Approach**

## 6.2.1 **Analysis Cohort**

Analyses described in section  $6.3 \sim 6.9$  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 postbaseline 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

All Subjects Who Signed the I	nformed Consent Form
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]
(1) Eligibility for Entrance int	to the Treatment Period
Frequency distributions will be percentages for the primary rea- total number of ineligible subj	e provided. When calculating asons for subject not being eligible, the ects will be used as the denominator.
bjects Who Entered the Trea	tment Period by Site
ITT	
Status of Entrance into the Treatment Period	[Entered]
Site	[Site numbers will be used as categories]
(1) Number of Subjects Enrol	led by Site
Frequency distribution will be	provided for each stratum.
	All Subjects Who Signed the I Eligibility Status Primary Reason for Subject Not Being Eligible (1) Eligibility for Entrance in Frequency distributions will be percentages for the primary re- total number of ineligible subj <b>bjects Who Entered the Trea</b> ITT Status of Entrance into the Treatment Period Site (1) Number of Subjects Enrol Frequency distribution will be

### 6.3.5 **Disposition of Subjects**

	6.3.5	Disposition of	Subjects		, USK
	Analysis	Set:	ITT		0
	Analysis	Endpoint(s) :	Study Drug Completion Status	[Ongoing, Completed Study Drug, Prematurely Discontinued Study Drug]	2
			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]	
	Analytica	al Method(s) :	(1) Disposition of Subjects		
	6.3.6	Protocol Devi	Frequency distributions will be percentages for the reasons for subjects who prematurely disco denominator. ations and Analysis Sets	provided. When calculating discontinuation, the total number of ontinued will be used as the	
	6.3.6.1	Significant P	rotocol Deviations		
	Analysis	Set:	НТ		
operty	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]	
Pro	Analytica	al Method(s) :	(1) Protocol Deviations		

ITT Handling of Subjects [Categories are based on the definition of Subjects Section of Sec

6.3.6.2 Analysis Sets

Analysis Set:

Analysis Endpoint(s) :

	Handling of Subjects	[Categories are based on the definitions in Section 5.0]
	Analysis Sets	<u></u>
	ITT	[Included].
	PPS	[Included]
	Safety Analysis Set	[Included]
Analytical Method(s) :	(1) Subjects Excluded fr	om 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**

## **Demographic and Baseline Characteristics** 6.4.1

ITT Analysis Set: eroperty of takeda. Analysis Endpoint(s) : Age (years)

[Min<= - < 9, 9<= - <=18, 18< - $\leq Max$ 

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

[Male, Female]

Gender Height (cm) Weight (kg) BMI (kg/m2) Height z-score Weight z-score





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

#### **Medical History and Concurrent Medical Conditions** 6.4.2

Statistical Analysis Plan 2	2.0 10Nov2023
6.4.2 Medical Hi	story and Concurrent Medical Conditions
Analysis Set:	ITT
Analysis Endpoint(s)	: Medical History
	Concurrent Medical Conditions
Analytical Method(s)	<ul> <li>(1) Medical History by System Organ Class and Preferred Term</li> <li>(2) Concurrent Medical Conditions by System Organ Class and Preferred Term</li> </ul>
	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 l	History and Concomitant Medications
Analysis Set:	ITT
Analysis Endpoint(s)	: Medication History
	Concomitant Medications
Analytical Method(s)	<ul> <li>(1) Medication History by Anatomical Therapeutic Chemical Level 2 and Preferred Medication Name</li> <li>(2) Concomitant Medications That Started and Stopped Prior to Baseline by Anatomical Therapeutic Chemical Level 2 and Preferred Medication Name</li> <li>(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</li> </ul>
otar	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

preferred medication names will be counted only once for that preferred medication names. For anatomical therapeutic chemical level 2, same manners in counting frequency.

## inns of Use 6.6 **Extent of Exposure and Compliance** Analysis Set: ITT $[0 \le - \le 28, 29 \le - \le Max]$ Analysis Endpoint(s) : Duration of Exposure to Study Drug (days) [Min<= - < 80, 80 <= - <= 100, 200< -Study Drug Compliance (%) <=Max] Total Drug Exposure ( $\mu$ g/kg) Average Daily Dose $(\mu g/kg/day)$ 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. USE ONLY and 6.7 **Efficacy Analysis** 6.7.1 **Primary Endpoint Analysis** 6.7.1.1 Primary Analysis Analysis Set: ITT Change in the average morning ItchRO (Obs) severity score between Analysis Endpoint(s): baseline and average of Week 15 through Week 26 See Section 6.2.2. Analytical Method(s): 6.7.1.2 Sensitivity Analysis PPS Analysis Set: 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 Property of primary analysis will be performed using the PPS to confirm robustness of the results.

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	· ·	
6.7.1.3	Supplement	tary Analyses
Analysi	s Set:	ITT
Analysi	s Endpoint(s):	Change in the average morning ItchRO (Obs) severity score between baseline and average of Week 15 through Week 26
Analytic	cal Method(s): Secondary F	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.
6.7.2.1	Kev Second	lary Endpoints
Analysi	s Set:	T
Analysi	s Endpoint(s):	<ul> <li>Change in the average morning ItchRO (Obs) frequency score between baseline and average of Week 15 through Week 26</li> </ul>
	. KO	• Change in total sBA between baseline and Week 26
Analytic	cal Method(s):	See Section 6.2.2.
HOTAK		

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Statistical Analysis Plan 2.0	101/10/2025
6.7.2.2 Sensitivity A	nalysis
Analysis Set:	PPS
Analysis Endpoint(s):	<ul> <li>Change in the average morning ItchRO (Obs) frequency score between baseline and average of Week 15 through Week 26</li> </ul>
	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 E	ndpoints (1997)
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.

Property

ns of Use Page 27 of 59 10Nov2023 TAK-625-3002 **Statistical Analysis Plan 2.0** Prope

Statistical	Analysis I lan 2.0			1011012023
				e USE
6.7.4	Subgroup Analy	sis		
Analysis	Set: IT	Т		
Analysis	s Endpoint(s): •	Change in the average mo between baseline and aver	orning ItchRO (Obs) severity s rage of Week 15 through Wee	score k 26
oetd	•	Change in the average mo between baseline and aver	orning ItchRO (Obs) frequency rage of Week 15 through Wee	y score k 26
RKOZ	•	Change in total sBA betw	een baseline and Week 26	
Subgrou	up(s): A	ge	[Min<= - <7, 7<= - <=Max	]

	Candan	[Mala Escala]
Analytical Mathad(a).	Gender	[Male, Female]
Analytical Method(s):	Descriptive statistics will	i be provided for above each subgroup.
6.8 Safety Analysis	8	10 <sup>5</sup>
6.8.1 Adverse Even	ts	DIE
6.8.1.1 Overview of	Treatment-Emergent Adve	erse Events
Analysis Set:	Safety Analysis Set	R
Analysis Endpoint(s) :	TEAE	we -
Categories:	Relationship to Study Dr	ug [Related, Not Related]
	Intensity	[Mild, Moderate, Severe]
Analytical Method(s) :	The following summaries	s will be provided.
	(1) Overview of Treatme	ent-Emergent Adverse Events
	1) All Treatment-E number and perc	mergent Adverse Events (number of events, entage of subjects)
	2) Relationship of drug (number of	Treatment-Emergent Adverse Events to study events, number and percentage of subjects)
	3) Intensity of Trea events, number a	tment-Emergent Adverse Events (number of and percentage of subjects)
	4) Preatment-Emer discontinuation ( subjects)	gent Adverse Events leading to study drug (number of events, number and percentage of
nor	5) Serious Treatme events, number a	nt-Emergent Adverse Events (number of and percentage of subjects)
da. For	<ol> <li>Relationship of s to study drug (nu subjects)</li> </ol>	serious Treatment-Emergent Adverse Events umber of events, number and percentage of
of the	<ol> <li>Serious Treatme drug discontinua percentage of su</li> </ol>	nt-Emergent Adverse Events leading to study ation (number of events, number and bjects)
3	8) Treatment-Emer (number of even	gent Adverse Events resulting in death ts, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- rems of Use Summaries for 2) and 6) ٠ 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.

Displays of Treatment-Emergent Adverse events 6.8.1.2

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.	
, or	TEAEs will be coded using the using SOC and PT.	e MedDRA and will be summarized
leda. For	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.	
et at	(1) Treatment-Emergent Adve Preferred Term	erse Events by System Organ Class and
6	(2) Treatment-Emergent Adve	erse Events by System Organ Class
	(3) Treatment-Emergent Adve	erse Events by Preferred Term
	(4) Drug-Related Treatment-E Organ Class and Preferred	Emergent Adverse Events by System 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 Property of Takeda. For nom 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

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	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 I	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.
	<ol> <li>Pretreatment Events by System Organ Class and Preferred Term</li> <li>Serious Pretreatment Events by System Organ Class and Preferred Term</li> </ol>
	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.
  - 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 PlotsPlots over time for each subject will be presented.

Statistical	Anarysis I lan 2.0	101/0/2020
		<ul> <li>(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.</li> </ul>
6.8.2.2	Urinalysis	OPILE
Analysis	s Set:	Safety Analysis Set
Analysis	s 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.
Analytic	cal 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
		<ol> <li>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.</li> </ol>
		(2) Case Plots Plots over time for each subject will be presented.
	Fornor	(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.
of at	30a.	(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

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Analysis Endpoint(s) :	Systolic Blood Pressure	Diastolic Blood Pressure			
	Heart Rate	Body Temperature			
	Weight	Height			
	BMI	Respiration Rate			
Visit:	Using the visits (Baselin Section 9.2.2.	ne to Week 26) of the visit window defined in			
Analytical Method(s) :	For each endpoint, sum	maries (1) and (2) will be provided.			
	(1) Summary of Vital S Baseline by Visit Descriptive statistic baseline (each post- each visit.	Signs, Weight and Height, and Change from es for observed values and changes from baseline visit - Baseline) will be provided for			
	(2) Case Plots Plots over time for	each subject will be presented.			
6.8.4 ECGs		N O.			
Analysis Set:	Safety Analysis Set				
Analysis Endpoint(s) :	Heart Rate				
	RR Interval				
	PR Interval				
	QRS Interval				
	QT Interval				
	QTcF Interval				
- FOR IN	Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]			
Visit:	Using the visits (Baselin Section 9.2.2.	ne to Week 26) of the visit window defined in			
Analytical Method(s) :	For each endpoint other (1) and (2) will be provi	than 12-lead ECG interpretations, summaries ided.			
Ser.	For ECG interpretation,	summary (3) will be provided.			
Prox	(1) Summary of ECG I Descriptive statistic	Parameters and Change from Baseline by Visit es for observed values and changes from			

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

,0

- (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)** the

Analysis Set: Safety Analysis Set

Analysis Endpoint(s) : TEAE

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

## 6.9 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

### **Pharmacokinetic Analysis** 6.9.1

## 6.9.1.1 Plasma Concentrations

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

Visit:

Cohort:

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

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

Using the visits of the visit window defined in Section 9.2.2.2

## 6.10 Other Analyses

6.10.1 Analyses	for	Overall	Supplemental	Cohort
-----------------	-----	---------	--------------	--------

**Overall Supplemental Cohort** 

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

## 6.10.2 **Analyses for All Cohorts Combined**

Cohort: All Cohorts Combined

	1 450 00 01 07
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- ... 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 state of the second data https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

# subject to CHANGES TO PROTOCOL PLANNED ANALYSES 8.0

commerci

There was no change to the protocol planned analyses.

#### 9.0 **APPENDIX**

## Changes From the Previous Version of the SAP 9.1

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

Section

Property

Before the change

Not applicable.

After the change

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

lect to the applicable 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 Adecompensation [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.

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- ims of Use 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) ٠ 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  $\leq$  dose level  $\leq 225 \ \mu g/kg$ , then dose level category = 150  $\mu g/kg$ ; if 225  $\mu g/kg \leq$ dose level  $< 375 \,\mu\text{g/kg}$ , then dose level  $> \text{category} = 300 \,\mu\text{g/kg}$ ; if 375  $\mu\text{g/kg} \le \text{dose level}$  $< 525 \ \mu\text{g/kg}$ , then dose level category = 450  $\mu\text{g/kg}$ ; if 525  $\mu\text{g/kg} \leq -$  dose level  $\leq -$  Max. then dose level category =  $600 \mu g/kg$ .

- Total Drug Exposure (µg/kg): Sum of {number of study drugs taken \* dose level received •  $(\mu g/kg)$ .
- 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.  $\geq$
- **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 Cl, 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.</p>
  - For p-values use 3 decimal places.
  - Presentation of p-values display p-values that would round to 0.000 as <0.001.</p>
- 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.</p>
  - 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

to the applicable terms of Use 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]

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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, d subject to 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]

 $[Min \le -.. < 7, 7 \le -. \le Max]$ 

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

TAK-625-3002

licable terms of Use Page 42 of 59 **Statistical Analysis Plan 2.0** Added additional endpoints. Section Before the change Analysis Endpoint(s): • • • subject to the • • • After the change Analysis Endpoint(s): . . .

Reason for the change CONSIGNATION Section 6.7.3.3 Responder Analysis Before the change Added new exploratory endpoints when protocol had been amended.

After the change

Analysis Set:, ITT



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<= - < <u>9, 9</u>< <u>18</u>< - <=Max]

After the change

Subgroup(s): Age, [Min<= -- <=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.

icable terms of Use 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.

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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. omm

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

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 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.

 Values 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 detect of the lower limit date (rounded to 1.1).

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.

1

Table 9.8 Visit Window of PK

	Visit	Schedulo Da (da	ed Study ay ys)	Time Interval (days) Study Day	Scheduled Study Time	Study Time (hours)
	Pre-dose at Week 10	Study Day:	71	71	Study Time 0 (hour):	-5.0 ~ 0.0
	2.5 Hours after Morning Dose at Week 10	Study Day:	71	71	Study Time 2.5 (hour):	1.5 ~ 3.5
	Pre-dose at Week 14	<u>Study</u> <u>Day:</u>	<u>99</u>	<u>99 – 183</u>	<u>Study</u> <u>Time</u> <u>0</u> (hour):	<u>-5.0 ~</u> <u>0.0</u>
oroperty	0.5 Hours after Morning Dose at Week 14 ~ 26	<u>Study</u> <u>Day:</u>	<u>99</u>	<u>99 - 183</u>	<u>Study</u> <u>Time</u> <u>0.5</u> (hour):	<u>0.0 ~ 1.0</u>
X	After the change					

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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. <u>Values less than the lower limit of</u> <u>quantification will be treated as zero when calculating the descriptive statistics.</u>

Visit	Schedul D (da	ed Study ay ays)	Time Interval (days) Study Day	Scheduled Study	Study Time (hours)
Pre-dose at Week 10	Study Day:	71	<u>57-85</u>	Study Time 0 (hour):	-5.0 ~ 0.0
2.5 Hours after Morning Dose at Week 10	Study Day:	71	<u>57 - 85</u>	Study Time 2.5 (hour):	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";

<u>else if</u>

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

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<u>( medication end year = TAK-625 start year and</u>	. V <sup>9</sup>
. < medication end month < TAK-625 start month) or	Ó
( medication end year $=$ TAK-625 start year and	rms
medication end month = TAK-625 start month and	$\checkmark^{\odot}$
. < medication end date < TAK-625 start date ) then "(2) Concomitant	Medication"
else "(3) Concomitant Medication";	iicat
Reason for the change	0001
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.

- 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

<u>For ItchRO scores</u>, 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.

## 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.

Reason for the change

Added new exploratory endpoints when protocol had been amended. use off

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

of USE

Reason for the change

en and en and se onwand s 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.

## Data Handling Conventions 9.2

## С **Definition of Study Days** 9.2.1

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.
- Property 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 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.

<b>T</b> 7' '4	Scheduled Study Day	Time Inter	val (days)
VISIT	(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 - <mark>8</mark> 5	< 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 9.1 Visit Window of sBA, sBA subspecies, C4, Serum Storage Sa	mple
---	------

Cable 9.2Visit WindowShiratori seve	of Vital Signs, Weight and erity scores for pruritus	Height, Clinician	Scratch Scale,
Vicit	Scheduled Study Day	Time Inter	val (days)
VISIt	(days)	Study Day	Follow-up Day
Baseline (Week 0)	Study Day: 1	-42 - 1	2010
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

## Visit Window of Vital Signs, Weight and Height, Clinician Scratch Scale, Table 9.2 Shiratari severity scores for pruritus

Table 9.3	Urinalysis,	Cholestasis Biomarko	ers (FGF19)

<b>T</b> T' '/	Scheduled Study Day	Time Inter	val (days)
Visit	(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

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8	т	~ <b>h</b>		•	
Λ.		яn	Ie	У.	4

## Lipid Panel, Lipid Soluble Vitamins

	OWEEK 10	Stady Day: 127	100 - 155	< 15
	Week 26	Study Day: 183	<u> 156 – 197</u>	< 15
by.	Table 9.4 Lipid Panel, L	ipid Soluble Vitamins		
$\sim$		-		
		Scheduled Study Day	Time Inter	val (days)
Proper	Visit	Scheduled Study Day (days)	Time Inter Study Day	val (days) Follow-up Day
Prope.	Visit Baseline (Week 0)	Scheduled Study Day (days) Study Day: 1	Time Inter Study Day -42 – 1	val (days) Follow-up Day

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Table 9.4 Lipid Panel, L	ipid Soluble Vitamins			é V
77:.:4	Scheduled Study Day	Time Inter	val (days)	19
VISIt	(days)	Study Day	Follow-up Day	
Week 6	Study Day: 43	2-57	< 15	
Week 10	Study Day: 71	58 - 85	÷C₹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	<b>1</b> 20 – 197	< 15	

#### Lipid Panel, Lipid Soluble Vitamins Table 9.4

## Table 9.5

Table 9.5 CBC, Coagula	tion, Chemistry Panel	SUD,	
X7:-:4	Scheduled Study Day	Time Inter	val (days)
V ISII	(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

Visit Window of ECGs, AFP

	Week 26	Study Day: 183	170 - 197	< 15
	L'an			
	Table 9.6 Visit Window	of ECGs, AFP		
er c	<b>T</b> 7.14	Scheduled Study Day	Time Inter	val (days)
00	VISIT	(days)	Study Day	Follow-up Day
2	Baseline (Week 0)	Study Day: 1	-42 - 1	

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Table 9.6 Visit Window	of ECGs, AFP			é V
37:-:4	Scheduled Study Day	Time Inte	rval (days)	Nº IS
VISIU	(days)	Study Day	Follow-up Day	
Week 10	Study Day: 71	2 - 127	<18	
Week 26	Study Day: 183	128 - 197	15	

#### Visit Window of ECGs, AFP Table 9.6



PK Samples 9.2.2.2

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 Property quantification will be treated as zero when calculating the descriptive statistics.

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

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#### Table 9.8 Visit Window of PK

#### 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 Property of Takedai missing. The restriction is not set for baseline average ItchRO scores.

Vicit	Scheduled Study Day	Time Inter	val (days)
VISIT	(days)	Study Day	Follow-up Day
Baseline (Week 0)	Study Day: -1	-281	
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

Visit Window of Average ItchRO Score Table 9.9

#### 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 HISTORX") then "(1) Prior Medication";

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

else if

- (. < medication end year, CTAK-625 start year) or
- = TAK-625 start year and ( medication end year
- . < 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";

"(3) Concomitant Medication"; else Property

In runary 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 and a versue method.

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**

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.

- 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.

<ul> <li>9.3.3 Responder Endpoints</li> <li>Subjects who experience an sBA control: subjects with a reduction to &lt;102 μMol/L, or a reduction of &gt;75% or normalization) from baseline through Week 26</li> </ul>	TA. Sta	K-625-3002 Page 57 of 5 tistical Analysis Plan 2.0 10Nov202	$\frac{9}{3}$
• Subjects who experience an sBA control: subjects with a reduction to $<102 \mu$ Mol/L, or a reduction of $>75\%$ or normalization) from baseline through Week 26	9.3	.3 Responder Endpoints	, USO
reduction of 2 7576, or normalization from baseline through week 20	•	Subjects who experience an sBA control: subjects with a reduction to <102 $\mu$ Mol/L, or a reduction of >75%, or normalization) from baseline through Week 26	m <sup>S</sup> O1

### **Responder Endpoints** 9.3.3

Property



## Z-scores 9.3.5

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 zscores. For subjects at least 24 months of age, the CDC growth charts will be used to derive zscores.

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

9.3.6 Lists of Laboratory Tests					
Hematology (CBC with	<u>Chemistry</u>	<u>Lipid Panel</u>	<u>Urinalysis</u>		
<u>Differential)</u>	Albumin	Total cholesterol	рН		
Hematocrit	ALP	LDL-C (direct)	Specific gravity		
Hemoglobin	Amylase	HDL-C	Protein		
MCV, MCH, MCHC	ALT (SGPT)	TG	Glucose		
Red blood cells	AST (SGOT)		Ketones		
Platelets	Bicarbonate	<u>Cholestasis Biomarkers</u>	Bilirubin		
White blood cells	Bilirubin, direct	sBA (LC-MS)	Occult blood and cells		
WBC Differential (% and	(conjugated)	sBA subspecies	Nitrite		
absolute)	TSB	7alpha-hydroxy-4-	Urobilinogen		
Neutrophils	BUN	cholesten-3-one (C4)	Leukocyte esterase		
Eosinophils	Calcium	FGF-19	Microscopic examination		
Basophils	Chloride	Autotaxin	Oxalate		
Lymphocytes	Creatinine	<i>(b)</i>	Urinary creatinine		
Monocytes	GGT	Lipid Soluble	5		
	Glucose	Vitamins			
<u>Coagulation</u>	Lipase	25-hydroxy vitamin D			
aPTT (sec)	Phosphate	Retinol			
INR	Potassium	RBP			
PT (sec)	Sodium	Alpha-tocopherol			
	Corrected Sodium	Estimated Total Lipids			
	Total protein	Ratio of Alpha-tocopherol			
	Total sBA (enzymatic	to Estimated Total Lipids			
	assay)				
	Uric Acid				
	Measured serum				
~	Osmolality				

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## 9.3.7 **Table for AECI**

The categories of AECI will follow ones in CRF.  ${}^{\odot}$ 

## Significance Level and Confidence Coefficient 9.3.8

• Significance level: 5% (two-sided)

Confidence coefficient: 95% (two-sided)

## 9.4 **Analysis Software**

SAS (version 9.4)