STATISTICAL ANALYSIS PLAN

Study Title:	A Long-Term Safety Study of Maralixibat, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study
Name of Test Drug:	Maralixibat
Study Number:	MRX-800
Protocol Version (Date):	Protocol Version 3 (12 November 2020)
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
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Analysis Plan Author:	[redacted]

CONFIDENTIAL AND PROPRIETARY INFORMATION

I have reviewed and approve this statistical analysis plan:

Role: **Head of Biostatistics**	
[redacted]	[redacted]

Document History

Version	Date	Change(s)	Author
1.0	06-Sep-2024	Initial version	[redacted]

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List of Abbreviations

Abbreviation	Definition
7αC4	7α-hydroxyl-4-cholesten-3-one
AE	adverse event
AESI	AE of special interest
ALGS	Alagille syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APRI	AST-to-platelet ratio index
ASA	American Statistical Association
ASBTi	Apical sodium-dependent bile acid transporter inhibitor
AST	aspartate transferase
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CFMB	change from maralixibat baseline
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
CSS	Clinician Scratch Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	Electronic case report form
EMA	European Medicine Agency
EOT	end of treatment
ET	early termination
FDA	US Food and Drug Administration
FGF-19	fibroblast growth factor 19
FIB-4	fibrosis-4
GGT	gamma-glutamyl transpeptidase
HCC	hepatocellular carcinoma
HL(G)T	high-level (group) term
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
INR	international normalized ratio

Abbreviation	Definition
IRT	interactive response technology
ItchRO(Obs)	Observer-Reported Itch Reported Outcome
ItchRO(Pt)	Patient-Reported Itch Reported Outcome
ITT	intent to treat
LLOQ	lower limit of quantitation
LLT	lower level term
LOQ	limit of quantitation
LSV	lipid-soluble vitamin
MCMC	Markov-Chain Monte-Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
[redacted]	[redacted]
PCI	potentially clinically important
PEBD	partial external biliary diversion
PFIC	Progressive familial intrahepatic cholestasis
PIS	Patient Impression of Severity
PT	preferred term
Q1,Q3	first, third quartile
RBP	retinol binding protein
RSS	Royal Statistical Society
SAE	serious adverse event
SAP	statistical analysis plan
sBA	serum bile acid
SD	standard deviation
SE	standard error
SI	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TIP	target IBAT population
TRAE	treatment-related adverse event
TSB	total serum bilirubin
ULN	upper limit of normal
ULOQ	upper limit of quantitation
VBL	baseline visit
WHO	World Health Organization
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the final analysis to support the clinical study report (CSR) for Study MRX-800. This SAP is based on the study protocol amendment 3, dated 12 November 2020, and the electronic case report form (eCRF). The SAP was finalized before the final analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials ((ICH, 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA, 2018) and the Royal Statistical Society ((RSS, 2014), for statistical practice.

Any deviations from the approved protocol analyses will be documented in either Section 6.1 (efficacy) and/or Section 7.6 (safety).

1.1. Study Objectives

1.1.1. Primary Objective and Endpoints

1.1.1.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety of maralixibat in participants with cholestatic liver disease, including but not limited to Alagille syndrome (ALGS), progressive familial intrahepatic cholestasis (PFIC).

1.1.1.2. Primary Endpoints

The primary endpoints of this study are the following safety and tolerability endpoints:

- Incidence of adverse events (AEs), including serious, nonserious, related, and non-related AEs
- Change from study baseline in clinical laboratory tests (hematology, chemistry, urinalysis, serum pregnancy test, as appropriate)
- Change from study baseline in physical examination parameters (temperature, systolic and diastolic blood pressure, heart rate, respiratory rate, weight, and height assessments)
- Concomitant treatment/medication usage

Safety laboratory tests and associated units of measure that will be used for reporting are listed in Appendix 1.

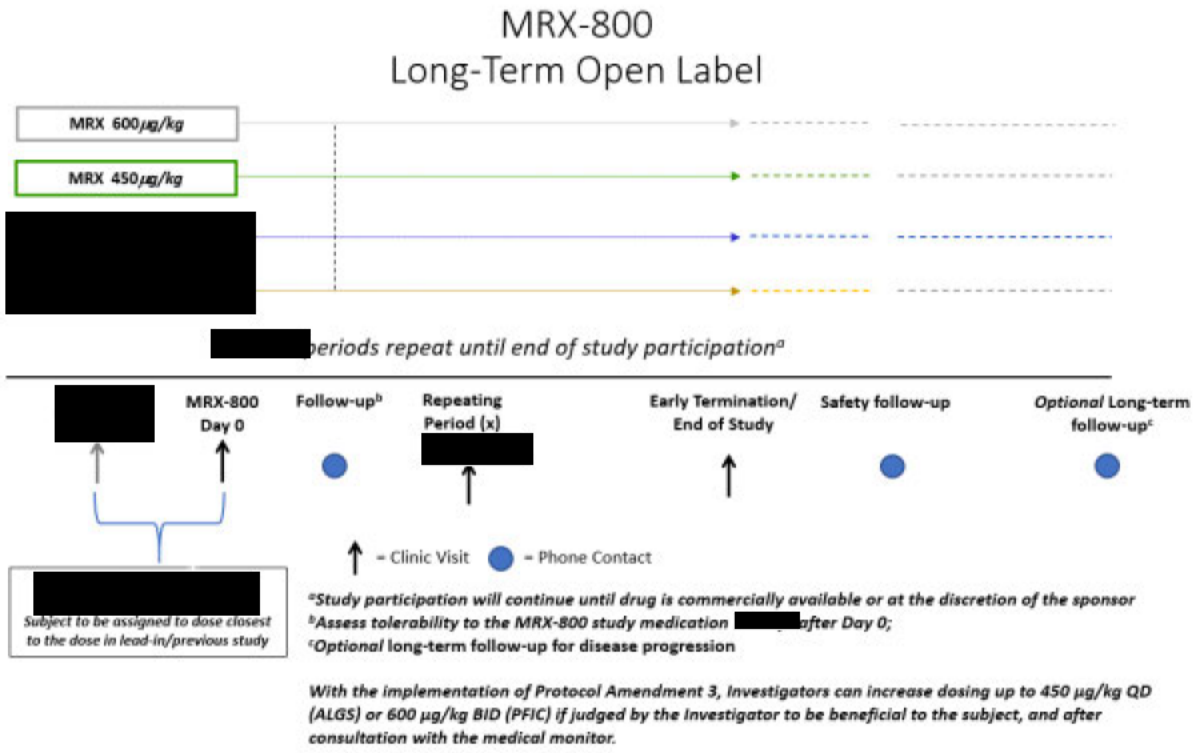
1.2. Study Design

This is a multicenter, open-label study of maralixibat in participants who have received the diagnosis of cholestatic liver disease (including but not limited to ALGS, PFIC, or biliary atresia)

who had previously participated in a maralixibat clinical study (Figure 1). Participants with other cholestatic liver diseases who have completed a maralixibat study were allowed to enroll at the discretion of the Sponsor. All participants will receive maralixibat in this study. All study participants moving to Study MRX-800 will have been on maralixibat treatment in a prior study. For participants who enroll in new, placebo-controlled studies with maralixibat, a separate, more closely monitored, open-label study or open-label extension had to have been completed by each study participant prior to enrolling in Study MRX-800.

This study will be conducted at globally, at sites in, but not limited to, North America, South America, Australia, Europe, and Asia. Regions may be added as necessary as participants complete other maralixibat studies. Only sites that have participants ongoing in a maralixibat Phase 2 or 3 study will be invited to participate.

Figure 1 Study Design



BID=twice daily; EOT=end of treatement; MRX=maralixibat; MRX-800=Study MRX-800.

1.3. Schedule of Assessments

A detailed schedule of assessments for the study, as shown in protocol amendment 3, is provided in Table 1.

Table 1 Schedule of Assessments

Procedures	Screening [a]	Treatment Period[b]		End of Treatment/ Early Termination	Safety Follow-Up	Long-term Follow Up[c]
Visit/Subject Contact #	**Screening / V0**	**Subject contact**	**[redacted] Repeating Cycle Visit**	**Visit[d]**	**Subject contact**	**Subject contact**
Study Week	[redacted]	[redacted]	[redacted]			
Study Day				[redacted]		
Window (in days)						
Informed consent/assent	X			X[c]		
Eligibility assessment	X					
Physical exam & vital signs (including height and weight)[e]	X[f]		X	X		
[redacted]			X	X		
			X	X		
Serum and Urine Pregnancy Test[i]	X (urine)		X (urine)	X (serum)		
ItchRO™ questionnaire[j]			X	X		
[redacted]			X	X		
			X	X		
			X	X		
Clinician Scratch Scale			X	X		
CBC with differential	X[f]		X	X		
Coagulation	X[f]		X	X		
Chemistry panel	X[f]		X	X		
Urinalysis	X[f]		X	X		
Lipid panel[n,o]	X[f]		X	X		
sBA collection[n]	X[f]		X	X		
Lipid-soluble vitamins[o]	X[f]		X	X		

Procedures	Screening [a]	Treatment Period[b]		End of Treatment/ Early Termination	Safety Follow-Up	Long-term Follow Up[c]
Visit/Subject Contact #	**Screening / V0**	**Subject contact**	**[redacted] Repeating Cycle Visit**	**Visit[d]**	**Subject contact**	**Subject contact**
Study Week	[redacted]					
Study Day						
Window (in days)				[redacted]		
AFP sample	X[f]		X	X		
Serum storage sample[o,p]			X	X		
Healthcare utilization	X[q]		X	X	X	
Study medication supplied[r]	X		X			
Study medication administration[s]	X	X	X			
Assess AEs	X[t]	X[u]	X	X	X	
Prior and concomitant treatments	X[t]	X[u]	X	X	X	
Disease-related event questionnaire						X[c]
Liver imaging[v]			X	X		

AFP=alpha-fetoprotein; ALGS=Alagille syndrome; BID=twice daily dosing; 7αC4=7a-hydroxy-4-cholesten-3-one; CBC=complete blood count; EOT=end of treatment; ET=early termination; FGF- 9=fibroblast growth factor-19; ItchRO™=Itch-Reported Outcome; MRI=magnetic resonance imaging; [redacted] PFIC=progressive familial intrahepatic cholestasis.

[a] Screening Visit 0/Day 0=[redacted] In certain cases where it is not possible for [redacted] MRX-800 Screening Visit 0/Day 0 [redacted] Screen failure subjects may be re-screened but only after discussing with the Medical Monitor. Re-screening may occur within [redacted]

[b] Subjects will continue treatment until the study is terminated by the sponsor.

[c] [redacted]

[d] Assessments listed under the EOT/ET Visit do not need to be repeated if the visit occurs within [redacted] of a previous clinic visit (unless otherwise specified e.g., pregnancy test).

[e] Physical examination includes specific assessments for signs of hepatomegaly, splenomegaly, edema, ascites, jaundice, and scleral icterus. Vital signs include blood pressure, heart rate, temperature, respiration rate. Height and weight will be measured by trained staff using standardized methodology, incl. calibrated stadiometer or headboard and calibrated balance, respectively.

[f] [redacted] MRX-800 Screening Visit 0/Day 0. Retests are needed if results are [redacted] prior to the MRX-800 Screening Visit 0/Day 0. Any missing exams should be performed at [redacted] other than AFP.

[g] [redacted]

[h] [redacted]

[i] Females of childbearing potential only. If available, the subject's [redacted] will be used at Screening Visit 0/Day 0. Otherwise, a urine and serum beta-human chorionic gonadotropin (β-HCG) pregnancy test will be performed. A positive urine pregnancy test result requires a subject to undergo a serum β-HCG pregnancy test. Results of the pregnancy test must be reviewed prior to dispensing study medication.

[j] Caregivers and age-appropriate subjects (only applicable for subjects with ALGS or PFIC) will complete ItchRO™ questionnaires administered as a diary BID for [redacted] after every study visit.

[k] [redacted]

[l] [redacted]

[m] This is only applicable for subjects with ALGS.

[n] Subjects are encouraged to fast at least [redacted] water intake is permitted if necessary but not recommended) prior to collection.

[o] Blood samples must be drawn before administration of vitamin supplementation.

[p] Possible analysis of FGF-19, autotaxin, 7αC4.

[q] To be done only if not captured at [redacted]

[r] If needed, study medication may be supplied via an unscheduled visit and via direct-to-patient shipments in between visits.

[s] Daily dose to be taken approximately 30 minutes before breakfast. If BID dosing, evening dose should be administered approximately 30 minutes before dinner.

[t] Only new AEs occurring after the subject provides consent or assent (as appropriate) will be collected [redacted] Ongoing concomitant treatment/medication will be manually entered into the MRX-800 CRF. AEs that were ongoing in the previous study will be copied over by the sites into the MRX-800 CRF.

[u] The Investigator or designee will contact subjects (email or phone call) during which the use of concomitant treatments and AEs will be reviewed.

[v] A liver ultrasound/MRI scan will be done starting from [redacted]

1.4. Sample Size Determination

Because this is an extension study for participants enrolled under previous protocols, the sample size is not based on statistical considerations. Participants will remain on study drug until the study is terminated by the Sponsor.

2. TYPE OF PLANNED ANALYSES

2.1. Interim Analysis

Any interim analyses will be for safety reporting. Discussion of any interim outputs are out of scope for this SAP.

2.2. Primary Analysis

No primary analyses are planned.

2.3. Final Analysis

The final analysis will be performed after all participants complete their final protocol-defined assessment, including the safety follow-up visit or contact, whichever is later, but not the optional long-term follow-up for disease progression, or have early study termination. Please refer to Table 1 for the schedule of assessments.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All study data will be presented in by-participant listings.

3.1. Analysis Set

The following analysis set is planned for this study:

Safety Analysis Set: The Safety Analysis Set includes all participants who enrolled and received at least 1 dose of maralixibat during Study MRX-800.

Membership in the analysis set will be determined prior to database lock. All efficacy and safety analysis will be based on the safety analysis set.

3.2. Baseline

Study baseline will be defined for this study as Screening/Visit 0/Day 0.

For a particular analysis variable such as a lab parameter or a vital sign test, the baseline is defined as the last non-missing observation of the analysis variable from the study the participant was previously enrolled in. If results are more than 30 days prior to the screening visit, retests are needed per protocol. In such case, the retested results are considered as baseline.

3.3. Derived Variables

Select derived variables will be rounded for presentation purposes (see Section 3.9).

Age (years) at study baseline

- The reported age in years at baseline (Study Day 0) will be used.

Age (months) at study baseline

- The reported age in years and months at baseline (Study Day 0) will be used:
  - Age (months) at baseline = (12 x Reported age in years at baseline) + Reported number of months at baseline
- Partial birth dates are imputed for analysis purposes as described in Section 3.9.

Age Group at study baseline

[redacted]

Time since original diagnosis of ALGS, PFIC2, other PFIC (months) = (date of first maralixibat dose – date of original diagnosis) / 30.4375

Change from study baseline = post-baseline value at any timepoint – value at study baseline

Change from maralixibat baseline = post-baseline value at any timepoint – value at maralixibat baseline

% Change from study baseline = 100 x change from baseline / value at study baseline

% Change from maralixibat baseline = 100 x change from baseline / value at maralixibat baseline

Treatment Duration (days) = Date of last dose of study drug on study – Date of first dose of study drug on study + 1 day

For participants who are missing the date of last dose of study drug, the last known contact date will be used in the calculation of treatment duration and study drug exposure.

Study drug Exposure (days) = Treatment duration (days) – Number of days that a participant reported missing both morning and evening doses (between the date of first and last dose)

Compliance (%) = 100 x Study drug exposure (days) / Treatment duration (days)
Study drug compliance will not be calculated for participants whose date of last study drug is unknown.

Dose (mg) = 0.001 *x* Participant's Weight on date drug dispensed (kg) *x* Dose (µg/kg)

Total Dose (mg) = $\sum$ [Number of doses taken$_i$ *x* Dose received (mg)$_i$]
where,

i = 1 to k, (k = number of time periods participant is receiving a constant dose)

Average Daily Dose (mg/day) = Total Dose (mg) / Treatment Duration (days)

Body Weight, Height and BMI Z-Scores
Height, weight, and body mass index (BMI) z-scores are based on a participant's sex and age at each scheduled visit. For participants younger than 24 months of age, the World Health Organization (WHO) growth charts will be used to derive z-scores (WHO 2000). For participants at least 24 months of age, the Centers for Disease Control and Prevention (CDC) growth charts will be used to derive z-scores (CDC 2000).

3.4. Participant Grouping

Disease groups will be classified into 2 groups for analysis: ALGS and PFIC. These disease groups, along with a total column, will be presented for all tables, listings, and figures where applicable.

3.5. Strata and Covariates

No adjustments for strata or covariates will be included for the analysis of efficacy endpoints.

3.6. Examination of Participant Subgroups

Subgrouping of participants based on disease group specified in Section 3.4 will be explored for subgroup analyses. In addition, the following subgroups may be explored:

- Age
- Sex
- Race
- Ethnicity
- Body mass index (BMI)
- Country

3.7. Adjustment for Multiplicity

No adjustments for multiplicity will be made.

3.8. Missing Data

3.8.1. Missing Adverse Event Severity/Relationship

For analysis purposes, the following rules will be applied for missing AE severity or relationship to study drug. An AE that does not have a recorded relationship to study drug value will be considered as "Related" to study drug. If the severity of an AE is missing, the severity will be reported as "Missing".

3.9. Data Handling Conventions and Transformations

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

All *p* values will be displayed in four decimals and rounded using standard scientific notation (e.g., 0.xxxx). If there is a *p* value less than 0.0001, it will be shown in tables as <0.0001.

Participant Age

The age of a participant at Study Day 0 (study baseline) will be used to determine the appropriate age category for the [redacted] and PIS. The age of a participant at screening will be used to determine the age category for the appropriate ItchRO questionnaire. The same age-appropriate instrument will be used for the duration of the study (regardless of subsequent birthdays after the baseline/screening visit).

Prior and Concomitant Treatment Definition and Data Handling

A concomitant treatment refers to all treatment, including concomitant therapies as well as herbal treatments, vitamins, behavioral treatment, non-pharmacological treatment, such as psychotherapy, taken between the dates of the first dose of study drug and the end of the participant's participation in the study.

Treatments that started before the first dose of study drug are considered prior treatments whether or not they were stopped prior to the first dose of study drug. Any treatment continuing or starting after the first dose of study drug will be considered as concomitant. If a treatment starts prior to the first dose of study drug and continues after the first dose of study drug, the medication will be considered as both prior and concomitant.

Medications that treat pruritus include ATC preferred terms of rifampicin, phenobarbital, alimemazine, brompheniramine maleate, cetirizine hydrochloride, desloratadine, dexchlorpheniramine maleate, dimetindene maleate, ketotifen fumarate, levocetirizine dihydrochloride, loratadine, mequitazine, promethazine, promethazine hydrochloride, ornithine aspartate, ursodeoxycholic acid, cholestyramine, naltrexone, naltrexone hydrochloride, and sertraline.

Concomitant treatments that are continuing from the predicate studies are copied into the study database with start dates entered as the original start date in the predicate study.

Partial Date Imputation

If partial dates are recorded, the convention for replacing missing dates for the purpose of calculating derived variables is as follows.

Partial ALGS and PFIC, Diagnosis Dates

For partial original diagnosis dates: (a) if only the day is missing, and the month and year match the first dose date, then the day is assigned the first day of the month (01); otherwise, the day assigned is 15; and (b) if both the day and month are missing, then the day/month assigned is the first day of July (01JUL), as long as the date is before the first dose date; otherwise, the day/month assigned is the first day of January (01JAN).

Partial Dates of Birth

Complete dates of birth are not reported by the investigative sites. [redacted] For partial birth dates, the convention for imputing missing dates for the purpose of statistical analysis is as follows:

Where available, the age in years and months at baseline will be used. If only age in years is reported at baseline, then 6 months will be imputed and used.

Date of Birth = Baseline Visit Date – [365.25 x (Age in years + (months/12))]

If the derived date of birth is later than the diagnosis date, the earliest complete medical history event start date, or the earliest complete reported prior/concomitant treatment start date, will be used to derive the date of birth by selecting the earliest of these 3 dates.

Lower and Upper Limit of Quantitation

In general, for quantitative laboratory values reported as "<" or "≤" the lower limit of quantitation (LLOQ), one-half of the reported value (i.e., LLOQ/2) will be used for analysis. The exception to this data treatment is for plasma maralixibat concentrations that are reported as <LLOQ, where a value of zero will be used in calculating summary statistics.

For quantitative laboratory values reported as ">" or "≥" the upper limit of quantitation (ULOQ), the reported value (i.e., ULOQ) will be used for analysis.

Laboratory Test Results

For analysis purposes, repeat laboratory test results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeat laboratory value will be used for data analysis.

The International System of Units (SI) will be used in reporting all efficacy and safety laboratory values.

Dose Used in Safety Analysis

For all safety and tolerability analyses, participants will be analyzed by the treatment received.

Treatment Duration and Exposure

For participants whose date of last study drug application is missing, for any reason, the last known contact date will be used in the calculation of treatment duration and study drug exposure. Study drug compliance will not be calculated for those participants whose date of last study drug application is unknown.

3.10. Analysis Visit Windows

Analyses of all visit-based safety and efficacy variables will be performed using the analysis visit windows defined by study day relative to the first dose of study drug as outlined below in Table 2. For participants who have study early termination, visits will be mapped to the closest next scheduled visit. Scheduled visits will be selected over unscheduled visits.

Table 2 Analysis Visit Windows

Nominal Visit	Study Day Lower Limit	Study Day Upper Limit
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

a. Only for collection of study medication dispensed, AE assessment, and prior and concomitant treatments.

3.11. Definition of Study Day

Study day will be calculated from the first dosing date of study and derived as follows:

- For post dose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, [redacted] is the day of first dose of study drug administration.

4. PARTICIPANT DISPOSITION

4.1. Participant Enrollment and Disposition

Participant disposition will include tabulations of the number and proportion of participants in the analysis population, those who completed study treatment, and those who discontinued early from the study (along with reasons for withdrawal). Percentages will be based on the number of participants in the Safety Population. The participant disposition tabulation will also include the number who were screened for eligibility, the number of screen failures, the number of participants enrolled, the number of families with siblings enrolled in the study, along with the total number of siblings, and the number of participants in the Safety Analysis Set.

The number and proportion of randomized and completed participants by country and investigative site will also be tabulated. Percentages will be based on the number of participants in the Safety Population.

Study disposition will be tabulated by disease group and overall.

Study drug accountability and compliance listings will be prepared for all participants, showing when the planned dosing schedule was not followed, along with the date and type of dosing deviation. Other disposition and study conduct information, including major protocol deviations will be listed.

4.2. Protocol Violation and Deviations

Protocol deviations will be tracked, recorded, and reviewed prior to database lock, following the Protocol Deviation Guidance Plan for this study, including:

- ICF process or signature/version issue
- Violation of inclusion/exclusion criteria
- Study/protocol procedures
- Dosing error
- Other deviation from study procedures

Other protocol deviations may be identified during the study.

Protocol deviations will be classified as “Important” or “Not Important.” An important deviation is one that poses a possible safety issue to the participant or has a potential impact on the statistical analysis of the clinical data. A non-important deviation is identified as any protocol deviation that does not meet the criteria for an important deviation. Potentially important deviations will be reviewed by the Sponsor and Premier to determine the final classification. Protocol deviations that are deemed to be “Important” and “Non-Evaluable” (i.e., a deviation that has a potential impact on the efficacy analysis) will be classified into a separate category.

Important protocol deviations may include:

- Significant and/or persistent dosing error
- A participant who did not meet criteria for assignment and did not have a waiver or dispensation by medical monitor
- Use of prohibited concomitant treatment during participation in the trial

The number and proportion of participants with important protocol violations/deviations will be tabulated by category/type and disease group in the Safety Population. These protocol violations/deviations will also be presented in a participant listing.

The final decision regarding inclusion and exclusion of participants from the analysis populations will be based on a final listing of protocol deviations prior to database lock, with input from the Clinical and Biostatistics team members and approval from the Sponsor.

Additionally, inclusion and exclusion criteria not met and reasons for screen failures will be listed.

4.3. Duration of Exposure and Adherence to Study Drug

4.3.1. Duration of Exposure to Study Drug

Total duration of exposure to study drug (days) will be defined as last dosing date - first dosing date + 1, regardless of any temporary interruptions in study drug administration, except for protocol-specified dose holds. Duration of exposure will be expressed in weeks (divided by 7) using up to 1 decimal place (e.g., 4.5 weeks).

If the last study drug dosing date is completely missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used. If the last study drug dosing date is partially missing, the closest date to the last study drug dosing date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

A participant will be assumed to have completed x weeks of study drug if he or she has dosed for the lower bound of the protocol-specified visit window. Summaries will be provided by disease group and overall for the Safety Analysis Set. Treatment exposure summaries will include total treatment duration (days), treatment exposure (days), total dose (mg), and average daily dose (mg/day).

No formal statistical testing is planned.

A listing of exposure to the study drug will be provided.

4.3.2. Adherence to Study Drug

Treatment compliance (%) will be summarized by disease group and overall. For a given day, a participant is considered compliant with treatment if any amount of study drug was administered.

[redacted]

Study drug accountability will be presented in a participant listing by disease group. Dosing details will be listed separately.

4.4. Prior and Concomitant Medications

4.4.1. Prior Medications

Prior medications are defined as any medications taken by a participant prior to the first dose of study drug.

If a medication starts prior to the first dose of study drug and continues after the first dose of study drug, it will be considered both prior and concomitant.

Prior medications will be summarized descriptively by disease group by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of participants for each indication. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be performed alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dose of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dose of study drug. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior medications will be provided in a by participant listing sorted by disease group, participant ID number, and administration date in chronological order.

4.4.2. Concomitant Medications

Concomitant medications are defined as medications taken at any time during the study after the first dose of study drug. Use of concomitant medications will be summarized by disease group by ATC drug class Level 2 and preferred name using the number and percentage of participant for each indication. A participant reporting the same medication more than once will be counted only once when calculating the number and percentage of participants who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be performed alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dose of study drug and continued to be taken after the first dose of study drug or started after the first dose of study drug but prior to or on the last dose date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dose or the last dose of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dose of study drug or a start date after the last dose of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any

medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first dose of study drug will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified.

Summaries by disease group will be based on the Safety Analysis Set. No formal statistical testing is planned.

All concomitant medications (other than per protocol study drugs) will be provided in a by-participant listing sorted by disease group, participant ID number, and administration date in chronological order.

5. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

5.1. Demographics

Summary statistics for age at baseline, sex, race, ethnicity, country, height, height z-score, weight, weight z-score, BMI, and BMI z-score will be presented by disease group and overall.

Tabulations for age group categories, defined [redacted] will also be presented. Given the small number of participants in the study, age categories may be combined for presentation and analysis [redacted]. Unless otherwise noted, age is the participant's age at the baseline visit for all evaluations and presentations.

Participants reporting more than 1 race will be counted in a "More than one race" category for purposes of tabulating summary statistics for race.

5.2. Medical History

Medical history will be collected during screening for disease-specific and general conditions (i.e., conditions not specific to the disease being studied) and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or later.

A summary of disease-specific medical history will be provided for the Safety Analysis Set.

Time since disease diagnosis (years) will be calculated by (date of informed consent of study drug – date of disease diagnosis)/365.25. Time since disease diagnosis will be summarized using summary statistics for a continuous variable. The other variables will be presented using summary statistics for a categorical variable. No formal statistical testing is planned.

General medical history data will be summarized by System Organ Class (SOC) and Preferred Term (PT).

A by-participant listing of disease-specific and general medical history will be provided by disease group and participant ID number in ascending order.

In deriving the time since disease diagnosis, all partial dates of diagnosis will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.

Partial date will not be imputed if the year is missing.

6. EFFICACY ANALYSES

6.1. Change From Protocol-Specified Efficacy Analyses

All efficacy analyses corresponding to secondary objectives in this extension study were exploratory and have been eliminated from this SAP.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

AEs will be coded using MedDRA v25.1 or later. SOC, high-level group term (HLGT), high-level term (HLT), PT, and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

AEs are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Relationship to Study Drug(s)." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes; however, by-participant data listings will show the relationship as missing.

7.1.4. Serious Adverse Events and Deaths

Treatment-emergent SAEs and SAEs related to study drug will be summarized in the same manner as AEs that led to permanent discontinuation of study drug.

Any deaths that occur during the study will be presented in a participant listing. The listing will include participant ID, participant cohort, study drug and dose received at the time of death (or the last study drug/dose received prior to death), date of death, number of days between the firstst and last dose, MedDRA PT, and relationship to study drug. SAEs captured and stored in the clinical database will be reconciled with the safety database before data finalization.

7.1.5. Adverse Events Leading to Withdrawal

AEs that led to permanent discontinuation of study drug will be tabulated by disease group and overall. By-participant listings of AEs that led to permanent discontinuation of study drug will also be presented.

7.1.6. Adverse Events of Special Interest

The following events have been defined as AESIs for participants in this study and had to be reported to the sponsor within 24 hours after awareness, irrespective of regulatory seriousness criteria or causality:

- Lipid-soluble vitamin deficiency that required study drug discontinuation.
- Liver parameter disruption that required study drug interruption and/or dose modification.

Lipid-soluble vitamin deficiencies include the following PTs:

- Vitamin A deficiency
- Vitamin A abnormal
- Vitamin A decreased
- Vitamin D deficiency
- Vitamin D abnormal
- Vitamin D decreased
- Vitamin E deficiency
- Vitamin E abnormal
- Vitamin E decreased
- Vitamin K deficiency
- Vitamin K abnormal
- Vitamin K decreased
- INR increased
- INR abnormal

Liver parameter disruption include the following PTs:

- Elevated liver enzymes
- Transaminases abnormal
- Transaminases increased
- ALT increased
- ALT abnormal
- AST increased
- AST abnormal

The incidence of TEAEs of special interest will be summarized in the same manner as AEs that led to permanent discontinuation of study drug.

7.1.7. Treatment-Emergent Adverse Events

7.1.7.1. Definition of Treatment-Emergent Adverse Events

In general, TEAEs are defined as AEs that start or deteriorate on or after the first dose of study drug and no later than [redacted] following the last dose of study drug (for participants not participating in this extension study) or reported through the [redacted] EOT visit (for participants participating in this extension study). For participants with [redacted] of study drug interruption/withdrawal, the definition of a TEAE considers both the date of the last dose prior to drug interruption and the actual last dose.

Any event that started before the first dose and worsens in either intensity or frequency or changes from non-serious to serious on or after the first dose date will also be designated as a TEAE.

For any participants who die during the study and the date of death is between the date of first dose of study drug and the date of study discontinuation (as entered by the site), inclusive, all AEs (including those resulting in death) that occur during the study will be considered as TEAEs irrespective of the last dose and will be included in the TEAE summaries.

7.1.7.2. TEAE Data Handling

If an event worsens in severity during the study, the lower grade event is marked as "Not recovered/not resolved" on the AE case report form (CRF) and an end date entered. A new event is recorded on the AE CRF with a start date that matches the end date, and the term recorded includes "Worsened" (e.g., "Worsened Headaches"). If an event becomes serious, the date that the event became serious is recorded on the AE CRF as the End Date of that AE and the Start Date of the corresponding SAE.

For those participating in this extension study, AEs that are ongoing as of the [redacted] visit are closed-out with a stop date of "ongoing.". AEs that are continuing from the predicate studies are copied into the study database with start dates entered as the original start date in the predicate study.

7.1.7.3. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to [redacted] after the date of the last dose of study drug.

An AE with completely missing onset and stop dates or with the onset date missing and a stop date later than the first dosing date of study drug will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

For the partial dates of AE onset or stop, they will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

7.1.8. Summaries of Adverse Events and Death

The number and percentage of participants who experienced the AEs described below will be provided and summarized by disease group and overall by SOC and PT unless otherwise indicated:

- TEAEs
- TEAEs of Grade 3 or higher (by SOC, PT, and maximum severity)
- Treatment-related TEAEs
- Serious TEAEs
- Serious TRAEs
- Serious treatment-related TEAEs
- TEAEs that led to discontinuation of study drug
- TEAEs that led to death
- AESIs

A brief, high-level summary of AEs described above will be provided by the number and percentage of participant who experienced the above AEs.

Multiple events will be counted only once per participant in each summary. AEs will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given participant during the study.

In addition to the above summary tables, TEAEs, TEAEs of Grade 3 or higher, serious TEAEs, TEAEs that led discontinuation of study drug, and AESIs will be summarized by PT only in descending order of total frequency within indication.

Furthermore, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment-emergent
- All AEs of Grade 3 or higher
- TRAEs
- TRAEs of Grade 3 or higher
- AESIs
- SAEs
- AEs that led to death (i.e., outcome of death)
- AEs that led to discontinuation of study drug
- AEs that led to temporary interruption of study drug
- AEs that led to dose reduction of study drug

If there are no participants who meet the criteria for any of these listings, the listing will be generated and will contain a statement, "No <*criteria*> were reported." for example, if there are no AEs that led to death on study, the statement would be "No AEs that led to death were reported.

7.2. Laboratory Evaluations

Clinical safety laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus [redacted] for participant who have permanently discontinued study drug or all available data at the time of the database snapshot for participants who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics. Hemolyzed test results will not be included in the analysis, but they will be listed in by-participant laboratory listings.

A by-participant listing for laboratory test results will be provided by participant ID number and time point in chronological order for hematology, serum chemistry, and urinalysis separately.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by disease group, and overall for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline time point
- Change from baseline at each postbaseline time point

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

The number and proportion of participants with potentially clinically important (PCI) values for select laboratory tests (Appendix 2) will be presented by study visit and disease group.

7.2.2. Shifts Relative to the Baseline Value

For all laboratory tests, shift tables will be presented by showing changes in results from baseline value (low, normal, and high) to each visit (low, normal, and high) and also to the worst postbaseline result (either low, normal, and high or low and high). A participant would have a worst postbaseline result of normal if all postbaseline results are within the normal reference range. The value of "low and high" would be used if the participant has postbaseline values that are below the normal reference range at one visit and above the normal reference range at another visit.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided for body weight, height, BMI, and vital signs (e.g., temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate at all time points outlined in the schedule of assessments) by disease group and overall as follows:

- Baseline value
- Values at each postbaseline time point
- Change from baseline at each postbaseline time point

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and vital signs measured at unscheduled visits will be included for the baseline value selection.

No formal statistical testing is planned.

Weight, height, and BMI measurements will also be summarized as a z-score for a participant's age and sex. The number and proportion of participants with PCI values for select vital signs will be presented by study visit and disease group. The PCI criteria for these vital signs are presented in Appendix 3.

A by-participant listing of vital signs will be provided by participant ID number and time point in chronological order. Body weight, height, and BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately. Since height is planned to be collected only at Screening, it will only be listed.

7.4. Electrocardiogram Results

No electrocardiogram test is planned in this study.

7.5. Other Safety Measures

7.5.1. Liver Ultrasound

Liver ultrasound (or MRI) results will be presented in by-participant listings.

7.6. Change From Protocol-Specified Safety Analyses

There are no planned changes from the protocol specified analyses.

8. PHARMACOKINETIC ANALYSES

Due to the extension nature of this study, pharmacokinetic analyses will not be conducted.

9. REFERENCES

(ASA) 2018. Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. http://www.amstat.org/about/ethicalguidelines.cfm

(ICH) 1998. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9; 1998. https://database.ich.org/sites/default/files/E9_Guideline.pdf

(RSS) 2014. The Royal Statistical Society: Code of Conduct, 2014. Available at: https://rss.org.uk/about/policy-and-guidelines/code-of-conduct/ .

10. SOFTWARE

[redacted]

APPENDICES

Appendix 1: Listing of Safety and Efficacy Laboratory Analytes

β-hCG
Serum or urine (if indicated)

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)

Clinical Chemistry
Albumin
ALP
Amylase
ALT (SGPT)
AST (SGOT)
Bilirubin, direct (conjugated)
Total serum Bilirubin (TSB)
Blood urea nitrogen (BUN)
Calcium
Chloride
Creatinine
GGT
Glucose
Lipase
Phosphate
Potassium
Sodium
Total protein
Uric Acid
Measured serum Osmolality
Total Lipids

Lipid Panel[a]
Total cholesterol
LDL-C (direct)
HDL-C
Triglycerides (TG)

Cholestasis Biomarkers[a]
Total serum bile acids (sBA)
Serum bile acid subspecies
7α-hydroxy-4-cholesten-3-one
FGF-19
Autotaxin

Lipid Soluble Vitamins[a]
25-hydroxy vitamin D
Retinol
Retinol binding protein (RBP)
α-Tocopherol

Urinalysis
pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Occult blood and cells
Nitrite
Urobilinogen
Leukocyte esterase
Microscopic examination[b]
Oxalate[c,d]
Creatinine[d]

Marker of hepatocellular carcinoma
α-fetoprotein

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; APRI=AST to platelet ratio index; AST=aspartate aminotransferase; β-hCG=beta human chorionic gonadotropin; FGF-19=fibroblast growth factor 19; FIB-4=fibrosis-4; GGT=gamma-glutamyl transferase; HDL-C=high density lipoprotein cholesterol; INR=international normalized ratio; LDL-C=low density lipoprotein cholesterol; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time; RBP=Retinol binding protein: SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=white blood cell

[a] Blood samples for the analysis of lipid panel and lipid soluble vitamins should be drawn prior to administration of vitamin supplementation. Blood samples for the analysis of cholestasis biomarkers and lipid panel should be drawn as much as possible approximately 4 hours after food or formula (water intake is permitted if necessary but not recommended). Other biomarkers [e.g., lysophosphatidic acid (LPA)] may be measured. At the discretion of the Sponsor, samples will be collected and appropriately stored for subsequent analysis, as needed.
[b] Will be performed on abnormal findings unless otherwise specified.
[c] Oxalate will be assessed at [redacted] and EOT/ET.
[d] Spot tests on creatinine and oxalate levels will be done to monitor for signs of nephrolithiasis.

A serum storage sample is collected for the analysis of cholestasis biomarkers as determined by the Sponsor.

Appendix 2: Criteria for Potentially Clinically Important Laboratory Tests

Laboratory Parameter	*SI Units*	*Conversion Factor*[a]	*Traditional Units*	*PCI Criteria*[b] *Low Values*	*PCI Criteria*[b] *High Values*
Hematology					
Hemoglobin F	g/L	0.1	g/dL	< 100	—
M				< 120	
Hematocrit F	ratio	100	%	≤ 32% and ≥3% decrease from baseline	—
M				≤ 37% and ≥3% decrease from baseline	
White cell count	10^9/L	1	10^3/μL	≤ 2.5	≥ 15
Eosinophils absolute cell count	10^9/L	1	10^3/μL	—	≥ 1.50
Neutrophils absolute cell count	10^9/L	1	10^3/μL	≤ 1.50	≥ 12.0
Lymphocyte absolute cell count	10^9/L	1	10^3/μL	≤ 0.8	≥ 4.0
Platelet count	10^9/L	1	10^3/μL	≤ 75	≥ 700
Chemistry					
Albumin	g/L	0.1	g/dL	< 28	—
Alkaline phosphatase	U/L	1	U/L	—	≥ 2 × UNL
ALT	U/L	1	U/L	—	≥ 3 × UNL
AST	U/L	1	U/L	—	≥ 3 × UNL
Blood urea nitrogen	mmol/L	2.8011	mg/dL	—	> 1.4 × UNL
Calcium	mmol/L	4.008	mg/dL	< 1.97	> 2.77
Cholesterol	mmol/L	38.6698	mg/dL	—	> 7.75
Creatinine	μmol/L	0.0113	mg/dL	—	> 1.4 × UNL
Glucose, fasting	mmol/L	18.015	mg/dL	< 3.0	> 7.6
Potassium	mmol/L	1	mEq/L	< 3.3	> 5.5
Sodium	mmol/L	1	mEq/L	< 130	> 150
Total bilirubin	μmol/L	0.0585	mg/dL	—	> 1.5 × UNL
Urinalysis					
Protein	—	—	—	—	≥ 2 +
Glucose	—	—	—	—	≥ 1 +

a Conversion factor is the multiplication factor to convert from SI units to traditional units.

b Criteria refer to SI units.

F = female, LNL = lower normal limit of laboratory reference range; M = male, PCI = potentially clinically important; SI = *Le Système International d'Unités* (International System of Units); UNL = upper normal limit of laboratory reference range.

Appendix 3: Criteria for Potentially Clinically Important Vital Signs

Parameter	***Flag***	***Criterion*** *Observed Value*
Systolic blood pressure (mmHg)	High	≥ 150
	Low	≤ 90
Diastolic blood pressure (mmHg)	High	≥ 100
	Low	≤ 50
Heart rate (bpm)	High	≥ 110
	Low	≤ 50
Body temperature (ºC)	High	≥ 38
	Low	< 35