A PHASE 3 STUDY TO EVALUATE THE EFFECTS OF CHENODEOXYCHOLIC ACID IN ADULT AND PEDIATRIC PATIENTS WITH CEREBROTENDINOUS XANTHOMATOSIS (RESTORE)

Investigational Medicinal Product:	Chenodeoxycholic Acid (CDCA)
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Statistical Analysis Plan

Protocol Number: Cheno-CTX-301

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Original Protocol:	13 November 2018
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

Abbreviation	Definition
7α12αC4	7-alpha,12-alpha-dihydroxy-4-cholesten-3-one
7αC4	7-alpha-hydroxy-4-cholesten-3-one
AEOI	Adverse events of interest
AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC_{ss}	Area under the plasma concentration-time curve at steady state
BLQ	Below the limit of quantification
BSFS	Bristol Stool Form Scale
CDCA	Chenodeoxycholic acid
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression of Severity
CI(s)	Confidence interval(s)
CL/F	Apparent total clearance of the drug from plasma after oral administration
$C_{max,ss}$	Maximum (peak) steady-state plasma drug concentration during a dosage interval
$C_{min,ss}$	Minimum steady-state plasma drug concentration during a dosage interval
CRF(s)	Case report form(s)
CTX	Cerebrotendinous xanthomatosis
DB	Double-blind
DMC	Data monitoring committee
EAS	Enrolled Analysis Set
ECG	Electrocardiogram
EEG	Electroencephalogram
EOS	End of study
EOT	End of treatment
ET	Early termination
FAS	Full Analysis Set

FCS	Fully Conditional Specification
gCDCA	GlycoChenodeoxycholic acid
IRT	Interactive response technology
IxRS	Interactive voice/Web response system
LLOQ	Lower limit of quantification
LS	Least squares
MAR	Missing at random
MAX	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MIN	Minimum
NIFAS	Newly-Initiated Full Analysis Set
OL	Open-label
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PPAS	Per Protocol Analysis Set
PPKAS	Pediatric Pharmacokinetic Analysis Set
PSAS	Pediatric Safety Analysis Set
PTAS	Pooled TEAE Analysis Set
Q1	First quartile
Q3	Third quartile
RI	Run-in
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SD	Standard deviation
SE(s)	Standard error(s)
tCDCA	TauroChenodeoxycholic acid
TEAE(s)	Treatment emergent adverse event(s)
TEFAS	Treatment-Experienced Full Analysis Set
TID	Three times daily

$t_{max,ss}$	Time to reach maximum (peak) plasma concentration following drug administration at steady state
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
W	Week
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of efficacy and safety of chenodeoxycholic acid (CDCA) in patients with cerebrotendinous xanthomatosis (CTX). Background information is provided for the overall study design and objectives. The reader is referred to the study protocol Cheno-CTX-301 Amendment 6 (04 April 2023) and case report forms (CRFs) for details of study conduct and data collection.

The proposed methods and approaches to the data analysis should be viewed as flexible. If the data suggest and warrant it, deviations from this statistical analysis plan (SAP) will be considered. However, any deviations from this SAP must be substantiated by sound and convincing statistical rationale and documented in the clinical study report.

Where appropriate, this document will provide sample computer (SAS®) codes to aid understanding of the statistical methods and help statistical analysts (programmers) to implement the statistical methods. However, the actual computer codes may be slightly different to reflect the actual dataset structure.

2 STUDY OBJECTIVES

The purpose of this study is to investigate the efficacy and safety of CDCA in patients with CTX in comparison with placebo.

2.1 Efficacy Objective

- Determine the effects of CDCA, compared with placebo, on biomarkers and clinical symptoms of CTX in adult patients with CTX.

2.2 Safety Objective

- Assess the safety and tolerability of CDCA in adult and pediatric patients.

2.3 Exploratory Objectives

- Characterize the relationship among biomarkers in adult and pediatric patients.
- Characterize steady-state pharmacokinetics (PK) of CDCA and 2 conjugated forms of CDCA, GlycoChenodeoxycholic Acid (gCDCA) and TauroChenodeoxycholic Acid (tCDCA) in adult patients.
- Characterize the relationship between dose and PK concentration among pediatric patients.
- Assess biomarkers and health status among pediatric patients treated with CDCA.

3 STUDY OVERVIEW

3.1 Overall Study Design

This study is made up of 2 designs: 1) a randomized, double-blind (DB), crossover study design among patients ≥16 years of age at Screening (adult cohort), and 2) an open-label (OL), dose-titration and maintenance study design among pediatric patients ≥1 month and <16 years of age at Screening (pediatric cohort).

3.1.1 Adult Cohort

Patients in the adult cohort will participate in a randomized, double-blind, placebo-controlled, 2-period × 2-treatment crossover study with rescue medication to assess the efficacy and safety of CDCA in the treatment of CTX. Approximately 12 male and/or female CDCA-naïve or CDCA-treated patients ≥16 years of age at Screening with CTX meeting all inclusion criteria and none of the exclusion criteria and whose clinical symptoms are stable during the open-label run-in period (OL1) are planned to be randomized in the study.

At least 6 of the patients randomized in the study will be treatment-experienced (i.e. those who have been on a stable dose of CDCA for at least 2 months prior to the run-in period). Patients who are either CDCA-naïve or those with less than 2 months of treatment prior to the run-in period are considered newly-initiated patients.

The study design is summarized in Figure 1.

Patients will be screened at Visit 1 and those who satisfy all the inclusion and none of the exclusion criteria will participate in the 8-week OL1 to establish reliable baseline measurements for biomarkers and other efficacy assessments. Patients who fail screening may be rescreened as needed.

Adult cohort patients will receive 250 mg open-label CDCA three times daily (TID) during the OL periods of the study (OL1 and OL2). During the double-blind periods (DB1 and DB2), adult cohort patients will receive either blinded CDCA 250 mg TID or matching placebo TID.

Following the OL1 period, patients will be reassessed for eligibility before randomization (Day 1). To be randomized, patients are required to have tolerated CDCA and not have developed any condition that, in the judgment of the Investigator, warranted discontinuation of CDCA treatment. Adult cohort patients will be randomized on Day 1 at a 1:1 ratio to one of two treatment sequences (AB or BA) to enter a 4-week DB period (DB1), an 8-week OL period (OL2), and then a second 4-week DB period (DB2).

Blinded- or open-label 250 mg CDCA TID rescue medication will be provided during the DB periods, if needed, based on blinded biomarkers (blinded rescue) and/or clinical CTX-related symptoms (open-label rescue). Patients who require blinded and/or open-label CDCA rescue medication in a given period will remain on the rescue medication for the remainder of the

respective DB period. Patients who require rescue medication during DB1 but otherwise remain eligible should continue to OL2 and then to DB2.

After the last dose of study medication, patients may transition to treatment for CTX per the guidance of the Investigator or prescribing physician. A safety follow-up phone call will be conducted for all patients 30 (±7) days after last dose of study medication.

4-Week DB1: On Day 1, patients will be randomized to treatment sequence AB or BA. Patients randomized to sequence AB will receive blinded 250 mg CDCA TID for 4 weeks or until rescue medication criteria are triggered; patients randomized to sequence BA will receive placebo TID for 4 weeks or until rescue medication criteria are triggered. Should rescue medication criteria be met, patients will receive 250 mg CDCA TID until the end of DB1. Patients will return to the clinic on Day 8, and weekly thereafter for the remaining 3 weeks.

8-Week OL2: Upon completion of DB1, patients will receive open-label 250 mg CDCA TID for 8 weeks and return to the clinic for bi-weekly scheduled visits.

4-Week DB2: At Week 12, patients who were randomized to sequence AB will crossover into DB2 and receive placebo treatment TID for 4 weeks or until rescue medication criteria are triggered; patients who were randomized to sequence BA will receive blinded 250 mg CDCA TID treatment for 4 weeks or until rescue medication criteria are triggered. Should rescue medication criteria be met, patients will receive 250 mg CDCA TID until the end of DB2. Patients will return to the clinic on Day 92 (7 days after first day of DB2 period), and weekly thereafter for the remaining 3 weeks.

3.1.2 Extension of an Open-Label Period as a Result of COVID-19

An adult cohort patient's participation in an OL period (OL1 or OL2) may be extended to delay the start of a DB withdrawal period (DB1 or DB2) if study and/or site operations are disrupted as a result of the COVID-19 pandemic. The decision to postpone the start of a DB period will be at the discretion of both the Investigator and Medical Monitor. If it is decided to extend an OL period, the patient will return to the study site once a month from the Visit 4 (OL1) or Visit 12 (OL2) date or last dispensation of OL study medication during the respective OL period. During these extension visits, the Investigator will ensure patient safety monitoring and dispensation of additional OL study medication is performed. Efficacy assessments during the extension visits are optional. See Table 3 for the Schedule of Assessments.

Patients will continue to receive 250 mg open-label CDCA TID during the extension periods. Details within the clinical study protocol regarding study medication in the OL1 and OL2 periods are applicable for the extension periods. A patient's total duration on treatment may extend beyond 24 weeks if an extension visit is required because of COVID-19.

A patient may proceed with the start of a DB withdrawal period when the Investigator and Medical Monitor agree that the impact to site and/or study operations because of COVID-19 has

stabilized. The Investigator and Medical Monitor will consider the site's ability to perform study visits without interruption and the timely reporting of necessary study results. A patient will resume the patient schedule as detailed in Table 1 when starting a DB period.

If a patient completes 2 or more extension visits in 1 OL period, the patient must complete a study visit 2 weeks prior to the start of a DB period to complete all safety and efficacy assessments that were otherwise required during a visit in the OL period.

The modified study design is summarized in Figure 2.

3.1.3 Pediatric Cohort

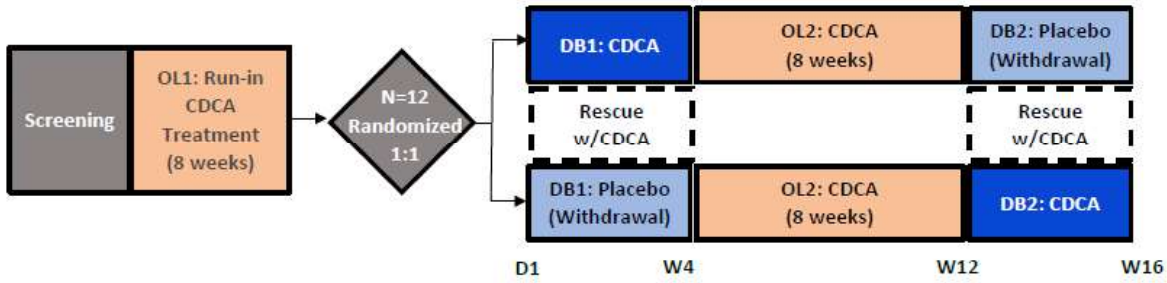
Pediatric cohort patients (≥ 1 month and <16 years at Screening) will participate in a 24-week, open-label cohort with an 8-week titration period to identify a safe and tolerable dose, and a 16-week treatment period at the safe and tolerated dose as maintenance. Patients will be screened at Visit 1 and those who satisfy all the inclusion criteria and none of the exclusion criteria will be eligible to participate in this cohort to evaluate safety, PK, and biomarkers in this population. Patients will have visits every week during the titration period and every 4 weeks during the treatment period. A safety follow-up phone call will be conducted for all patients 30 (±7) days after the last dose of study medication.

During the dose titration period, dose escalation decisions will be based on safety and tolerability. Dosing will be as follows:

- Treatment-naïve pediatric cohort patients will receive doses of 5 mg/kg/day (TID), 10 mg/kg/day (TID), or 15 mg/kg/day (TID), titrated up every 2 weeks based on safety and tolerability over a period of 8 weeks.
- Treatment-experienced pediatric cohort patients currently taking a dose ≥5 mg/kg/day of CDCA will start at their current dose and titrate up every 2 weeks to the next dose level up to 15 mg/kg/day based on safety and tolerability over a period of 8 weeks. Patients with a history demonstrating intolerance at higher doses will not be required to dose escalate.
- Pediatric cohort dosing of CDCA will not exceed an equivalent dose of 750 mg/day.
- Pediatric cohort patients who are able to take an equivalent weight-based dose of 750 mg/day and are capable of swallowing a tablet will have the option to dose with CDCA 250 mg tablets TID or the liquid suspension form of CDCA.

During the treatment period, dosing will be maintained at the dose tolerated during the titration period. After the last dose of study medication, patients may transition to treatment for CTX per the guidance of the Investigator or prescribing physician. The study design is summarized in Figure 3.

Figure 1: Study Design Diagram for Adult Cohort

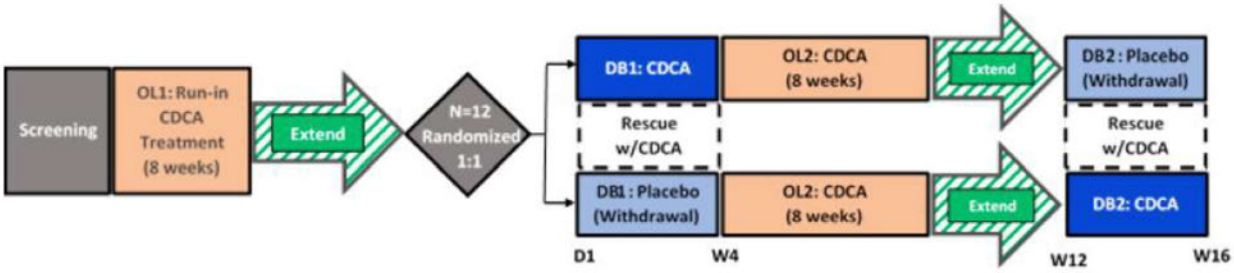


CDCA = chenodeoxycholic acid; D = day; DB1 = double-blind period 1; DB2 = double-blind period 2; OL1 = open-label period 1; OL2 = open-label period 2; W = Week.

Note 1: Patients will be contacted (via telephone call) 30 (±7) days after the last dose of study medication to ascertain patient safety.

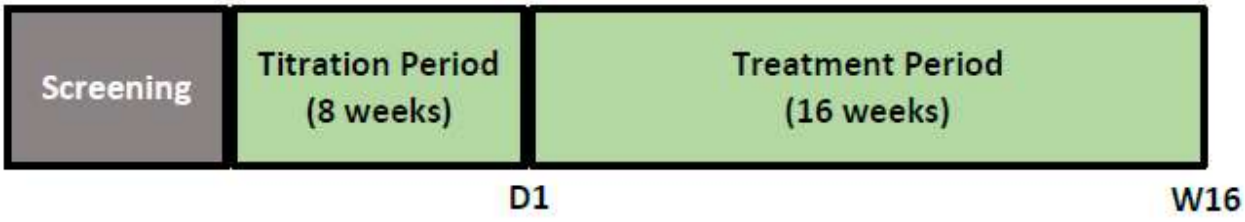
Note 2: Patients randomized to placebo will receive blinded CDCA rescue if biochemical criteria are triggered and open-label CDCA if new or worsening CTX-related symptoms trigger rescue during DB1 or DB2. Patients randomized to CDCA will continue to receive blinded CDCA rescue if triggered by biochemical criteria and will receive open-label CDCA rescue if new or worsening CTX-related symptoms are present.

Figure 2: Study Design Diagram for Extension of Open-Label Period in the Adult Cohort



CDCA = chenodeoxycholic acid; D = day; DB1 = double-blind period 1; DB2 = double-blind period 2; OL1 = open-label period 1; OL2 = open-label period 2; W = Week.

Figure 3: Study Design Diagram for Pediatric Cohort



D = day; W = Week.

3.2 Study Procedures

Study procedures and their timing are summarized in Table 1 (for the adult cohort) and Table 2 (for the pediatric cohort). Protocol waivers or exemptions are not allowed.

Study procedures related to the extension of the open-label period because of COVID-19 and their timing are summarized in Table 3.

3.2.1 Rescue Medication Criteria in the Adult Cohort

Blinded- or open-label 250 mg CDCA TID rescue medication will be provided during the DB periods, if needed, based on blinded biomarkers (blinded rescue) and/or clinical CTX-related symptoms (open-label rescue). Patients who require blinded and/or open-label CDCA rescue medication in a given period will remain on the rescue medication for the remainder of the respective DB period. Patients who require rescue during DB1 but otherwise remain eligible should continue to OL2 and then to DB2.

Blinded CDCA will be provided to patients who meet the following criterion: increase of 10 times the baseline value for a given period (i.e., Visit 6 and 14) in urine 23S-pentol. Blinded CDCA will be assigned through the Interactive Voice/Web Response System (IxRS) at the next scheduled in-clinic visit. Values entered in the IxRS system will be the geometric mean of the urine 23S-pentol results from each of the first morning void samples provided by the patient per visit time point. If the urine 23S-pentol value is below the level of quantification (BLQ), the lowest value in the analytical range (i.e., the lower limit of quantification [LLOQ]) will be used either to calculate the geometric mean or entered into the IxRS system. The Investigator and patient will remain blinded to biomarker data, treatment assignment, and if blinded rescue medication criteria are met.

Patients receiving either blinded CDCA or blinded placebo during the DB period will be rescued with open-label CDCA at the discretion of the Investigator if they present with new or worsening CTX-related symptoms relative to their respective pre-treatment assessments as defined in the protocol. The Investigator is responsible for evaluating patients to determine if they meet the criteria for rescue medication at each follow-up visit during DB1 and DB2.

The specific reasons contributing to the Investigator decision and supportive data will be collected in the database. All assessments should continue as indicated in Table 1.

3.2.2 Randomization and Blinding for the Adult Cohort

Adult cohort patients will be randomized on Day 1 (Visit 6) at a 1:1 ratio to 1 of 2 treatment sequences (AB or BA). Patients randomized to sequence AB will receive blinded CDCA TID for 4 weeks or until open-label rescue medication criteria are triggered; patients randomized to sequence BA will receive placebo TID for 4 weeks or until either the blinded and/or open-label rescue medication criteria are triggered.

The patient's treatment allocation will remain blinded to all parties involved with the study throughout its course, with the exception of the Data Monitoring Committee (DMC) (refer to 3.2.4), study medication supply, the serious adverse event (SAE) reporting contact, unblinded study monitor and the independent statistical team(s) supporting the DMC. The randomization schedule for treatment allocation will be securely maintained and will not be disclosed until after database lock. Only for emergency unblinding, randomization codes and corresponding treatment assignments will be made available to the Investigator through the interactive response technology (IRT) system.

3.2.3 Replacement

In general, patients are encouraged to remain in the study until they complete the study. A patient who permanently discontinues from the study will complete the Early Termination (ET) assessments listed in Table 1 or Table 2 as close as possible to the patient's last dose of study medication or as soon as possible for those patients who had previously completed an end of treatment (EOT) visit. The visit data, including the primary reason for premature discontinuation from the study, will be recorded on the ET electronic CRF.

Patients discontinuing from the study will not be replaced.

3.2.4 Unblinded DMC

An unblinded DMC will monitor accumulating data, including biomarkers (urine and plasma bile alcohols, plasma cholestanol, plasma 7αC4 and plasma 7α12αC4). The DMC will review efficacy, clinical outcomes, and safety results to potentially stop the study early based on the overall benefit-risk assessment, including the risk of irreversible disease progression among those receiving placebo. The scope of the DMC's review will be further defined within the DMC Charter.

3.3 Study Enrollment and Duration

3.3.1 Number of Patients

Approximately 12 patients ≥16 years of age at Screening are planned to be randomized in the adult cohort. Pediatric patients ≥1 month and <16 years at Screening will be enrolled separately in the pediatric cohort.

3.3.2 Duration of Study

The adult cohort will be approximately 24 to 28 weeks in duration, including an up to 4-week screening period; an 8-week OL run-in period (OL1); two 4-week DB treatment periods (DB1 and DB2); and an 8-week OL treatment period (OL2) in between DB1 and DB2. The duration of

the adult cohort may extend beyond 28 weeks if the start of a DB period is delayed due to COVID-19.

The pediatric cohort will be approximately 24 to 28 weeks in duration, including an up to 4-week screening period; an 8-week, OL dose titration period; and a 16-week, OL treatment period at the identified safe and tolerated dose as maintenance.

If genetic results are still pending after 28 days, the screening window for both cohorts may be extended up to 2 additional weeks, with approval by the Medical Monitor, which will bring the maximum total duration of the study to 30 weeks.

For both cohorts, a safety follow-up phone call will be conducted 30 (±7) days after the last dose of study medication.

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint for the Adult Cohort

- Change from baseline in $\log_e$-transformed urine 23S-pentol at the end of each DB treatment period

4.2 Key Secondary Efficacy Endpoints for the Adult Cohort

- Proportion of patients requiring rescue medication during the DB periods
- Percent change from baseline in plasma cholestanol levels at the end of each DB treatment period
- Percent change from baseline in plasma 7αC4 at the end of each DB treatment period

4.3 Other Secondary Efficacy Endpoints for the Adult Cohort

- Change from baseline in plasma cholestanol to cholesterol ratio during the DB periods
- Percent change from baseline in plasma 7α12αC4 at the end of each DB treatment period
- Proportion of patients with negative net change in symptoms and manifestations reported in the diary during the DB periods

4.4 Safety Endpoints for Both Adult and Pediatric Cohorts

- Change from baseline in body weight, vital signs, physical examinations, electroencephalogram (EEG), 12-lead electrocardiogram (ECG), clinical laboratory parameters (hematology, chemistry, coagulation [adult cohort only], lipid profile [including cholesterol]) and urinalysis laboratory parameters at each visit where parameters are collected

- Incidence of treatment-emergent adverse events (TEAEs), including SAEs, adverse events (AEs) leading to discontinuation of study medication, and AEs of interest (AEOI)

4.5 Exploratory Endpoints for both Adult and Pediatric Cohorts

4.5.1 Adult Cohort

- Percent change from baseline in plasma bile alcohol at the end of each DB treatment period
- Steady-state PK parameters (AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$, $t_{max,ss}$, CL/F) of 3 bile acids that include CDCA, gCDCA, tCDCA and total CDCA (summed CDCA, gCDCA, and tCDCA)
- Relationships among biomarkers (urine and plasma bile alcohols, plasma cholestanol, plasma 7αC4 and plasma 7α12αC4)
- Relationships between PK exposure parameters (AUC_{ss}, $C_{max,ss}$ or $C_{min,ss}$) and changes in biomarker levels (urine and plasma bile alcohols, plasma cholestanol, plasma 7αC4 and plasma 7α12αC4)
- Relationships between PK exposure parameters (AUC_{ss}, $C_{max,ss}$ or $C_{min,ss}$) and safety endpoints
- Change in disease severity as assessed by the Clinician Global Impression of Change (CGI-C) during each DB treatment period
- Change in health status questionnaire

4.5.2 Pediatric Cohort

- Relationships among biomarkers (urine and plasma bile alcohols, plasma cholestanol, plasma 7αC4 and plasma 7α12αC4)
- Steady-state PK concentration of CDCA, gCDCA, tCDCA and total CDCA (summed CDCA, gCDCA and tCDCA)
- Mean biomarker levels (urine and plasma bile alcohols, plasma cholestanol, plasma 7αC4 and plasma 7α12αC4)
- Change in disease severity as assessed by the CGI-C during the treatment period
- Change in health status questionnaire
- Change in developmental milestones

5 STATISTICAL ANALYSIS CONSIDERATIONS

5.1 Sample Size Justification and Power Analysis for Adult Cohort

Sample size calculations were performed assuming an interim analysis (when approximately ½ of adult patients completed the study) and a final analysis (when all adult patients completed the study) using a group sequential design. Therefore, sample size and power calculations assumed 2-sided nominal $\alpha = 0.0125$ at the interim analysis and 2-sided nominal $\alpha = 0.0436$ at the final analysis. Subsequent to the sample size calculations, the interim analysis was removed from the design and only one (final) analysis will be performed when all adult patients complete the study. The single final analysis will be performed using 2-sided nominal $\alpha = 0.05$. The references to $\alpha = 0.0436$ in the sample size and power calculations reported below are retained to reflect the assumption at the time of study design. The power at the planned study size (approximately 12 patients) using 2- sided nominal $\alpha = 0.05$ is higher than the power reported below using 2-sided nominal $\alpha = 0.0436$.

The hypothesis to be tested is H_0: $\Delta = 0$ against H_a: $\Delta \neq 0$, where Δ is the true paired treatment difference between CDCA and placebo for the change from baseline in $\log_e$-transformed urine 23S-pentol. The planned sample size is expected to provide at least 90% power at the final analysis (approximately 12 patients; two sided nominal $\alpha = 0.0436$).

For the sample size calculation, it is assumed that the true average paired treatment difference between CDCA and placebo in change from baseline in the $\log_e$-transformed urine 23S-pentol is -2.4 with a standard deviation no higher than 1.15. In a meta-analysis of the literature data from eleven CTX patients receiving CDCA treatment, the mean reduction from baseline in $\log_e$-transformed urine 23S-pentol was 3.1 with a 1.15 SD. The assumed 2.4 difference between CDCA and placebo is 2 standard errors (SEs) less than the observed 3.1 reduction.

For the proportion of patients requiring rescue treatment (secondary endpoint), the planned sample size of approximately 12 patients at the final analysis is expected to provide at least 85% power with 2-sided nominal $\alpha = 0.0436$. This assumes that 85% of patients (approximately 10/12) on placebo and 15% of patients (approximately 2/12) on CDCA will need rescue treatment, with a discordance of 80%, based on McNemar's test.

5.2 Analysis Sets

The following analysis sets will be defined for the study.

5.2.1 Adult Cohort

Enrolled Analysis Set (EAS): All adult cohort patients who signed informed consent and take at least one dose in the open-label run-in period. This will be used to assess patient characteristics, disposition during the run-in period, and overall safety presentation during the study.

Full Analysis Set (FAS): All adult cohort patients who are randomized and take at least one dose of randomized study medication will be included in the FAS. Patients in the FAS will be analyzed according to randomized treatment assignment. All efficacy analyses during the DB treatment periods will be based on the FAS.

- **Treatment-Experienced Full Analysis Set (TEFAS)**: All adult cohort patients in the FAS who had been on CDCA for at least 2 months prior to the OL run-in period.
- **Newly-Initiated Full Analysis Set (NIFAS)**: All adult cohort patients in the FAS who are either treatment-naïve or had been on CDCA for less than 2 months prior to the OL run-in period.

Per Protocol Analysis Set (PPAS): The PPAS is a subset of the FAS containing adult cohort patients who meet study eligibility requirements, have at least one efficacy measurement in the DB2 treatment period, and have no protocol deviations that might impact the assessment of efficacy measurements. Patients will be analyzed according to randomized treatment sequence assignment. The PPAS will be used for sensitivity analyses relating to efficacy. The type of protocol deviations governing exclusion from the PPAS will be determined prior to breaking the blind and are detailed in this SAP.

Safety Analysis Set (SAS): All adult cohort patients who are randomized and take at least one dose of randomized therapy will be included in the SAS. The SAS will be used for safety analyses during the DB periods and will be based upon actual study medication received.

Pharmacokinetic Analysis Set (PKAS): All adult cohort patients in the EAS with evaluable PK samples will be included in the PKAS. The PKAS will be used for summaries of PK concentration and assessment of PK parameters.

5.2.2 Pediatric Cohort

Pediatric Safety Analysis Set (PSAS): All pediatric cohort patients whose parent/legal guardian signed informed consent and received at least one dose of study medication. This will be used to assess patient characteristics, disposition, biomarkers, health status, and overall safety presentation for pediatric cohort patients.

Pediatric Pharmacokinetic Analysis Set (PPKAS): All pediatric cohort patients in the PSAS with evaluable PK samples will be included in the PPKAS. The PPKAS will be used for summaries of PK concentration.

5.2.3 Adult and Pediatric Cohorts

Pooled TEAE Analysis Set (PTAS): All adult cohort patients in the EAS and all pediatric cohort patients in the PSAS. This analysis set will be used to summarize AEs pooled from both cohorts.

5.3 Data Handling

5.3.1 Reference Date and Study Day

Visit day within the protocol schedule of assessments is described based on the date of first dose in DB1 for adult patients and date of first dose in treatment period for pediatric patients (Figure 1, Figure 2, and Figure 3). For all summaries by visit specified in this SAP, the protocol specified visit label and visit day will be used (Appendix Table 1). The mapping of unscheduled assessments to scheduled visits is discussed in 5.3.2.

However, not all adult patients may reach DB1 and/or not all pediatric patients may reach the treatment period. In order to support study datasets and listings, a study day must be derived based on a single reference date that will be consistently available for all patients as follows:

- Adult cohort: the first dose date in OL1
- Pediatric cohort: the first dose date in Titration Period

Thus, study day used in listings and study datasets presents the day of study events relative to the first dose in the study, not relative to the date of first dose in DB1 for adult patients or date of first dose in treatment period for pediatric patients as presented in the protocol schedule of assessments.

- Study day 1 in listings and study datasets is defined as the reference date.
- Subsequent Study Days (i.e. when the date of event is on or after the reference date) are defined as = [(date of event – reference date) + 1].
- Preceding Study Days (i.e. when the date of event is before the reference date) are defined as = [(date of event – reference date)].
- Thus, by definition, there is no Study Day = 0.

5.3.2 Handling of Multiple Observations (For both Cohorts)

A patient may have multiple scheduled or unscheduled visits that are associated with a protocol defined visit (nominal visit). Each unscheduled visit will be assigned a nominal visit number following the visit number of the associated scheduled visit (e.g., unscheduled visit number 2.1 is assigned to an unscheduled visit associated with protocol scheduled visit 2). If a patient has a scheduled visit, the assessment obtained at the scheduled visit will be used for data summary and analysis. Otherwise, if no scheduled visit assessment exists but at least one unscheduled visit assessment is available within a visit window of ±3 days (e.g., unscheduled visit 2.1 and 2.2 exist but not the scheduled visit 2), then the data at the latest unscheduled visit within the protocol visit window will be used for data summary and analysis.

Any unscheduled visits that cannot be attributed to a scheduled visit will not be included in statistical summary or analysis but will be presented in data listings. Since all visits during

extension of OL period in the adult cohort are planned as unscheduled, results from extension visits will be listed only.

For biomarker and lab data, if multiple measurements are recorded for the same time point (e.g. if the same blood sample is analyzed twice and recorded in the clinical database as two distinguished entries), the re-assayed data (the repeated one) will be included in data summary and analysis. All measurements will be presented in data listings.

5.3.3 Baseline and Change from Baseline

In general, the baseline values are defined as in 5.3.3.1 and 5.3.3.2 unless specified otherwise. The change from baseline value is defined as post-baseline value minus baseline value. The percent change from baseline value is defined as (post-baseline value minus baseline value) / baseline value × 100.

5.3.3.1 Adult Cohort

Efficacy Endpoints: The baseline values for DB1 are the last measurements prior to dose on Day 1. The baseline values for DB2 are the last measurements prior to dose on Day 85 (the beginning of DB2 period). Additional baseline for "during the study", defined as the last measurements prior to dose on Day -56 (the beginning of OL1 period), will also be applied when analyzing the efficacy endpoints.

Safety Endpoints: The baseline values will be defined separately for the two sets of analyses described in 6.3.3.1. The baseline values for "during the DB periods" analyses are defined the same as above. The baseline values for "during the study" analyses are the last measurements prior to dose on Day -56 (the beginning of OL1 period).

5.3.3.2 Pediatric Cohort

All Endpoints: The baseline values for the study are the last measurements prior to dose on Visit 2 (the beginning of Titration period).

5.3.4 Handling of Safety Results beyond the Limit of Quantification (For both Cohorts)

Any safety laboratory tests with results given as '< xx' or '> xx' in the database will be imputed with the absolute value of the number without the sign (e.g., < 2.5 will be imputed as 2.5) for statistical summary and analysis.

5.3.5 Handling of Biomarker Results Above or Below the Limit of Quantification (For both Cohorts)

Any biomarker results (urine 23S-pentol, plasma cholestanol, plasma 7αC4, plasma 7α12αC4, and plasma tetrol glucuronide) reported as BLQ in the database will be imputed with the LLOQ

for statistical summary and analysis. Any biomarker results reported as above the upper limit of quantification (ULOQ) in the database will be imputed with the upper limit of quantification for statistical summary and analysis.

5.3.6 Imputation of Incomplete Dates (For both Cohorts)

In cases of incomplete dates for AEs or non-study medications, the missing component(s) will be assumed as the most conservative value(s) possible. For example, the imputation rule is to conservatively capture AEs with missing start dates as TEAEs:

- If "day" is the only missing field, impute the "day" as the first dose date (the beginning of OL1 or Titration Start) if their "month" and "year" are the same; otherwise, the first day of the non-missing month.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as the first dose date if their "year" are the same; otherwise, January 1 of the non-missing year.
- If "day", "month", and "year" are all missing, to be conservative, the event will be assumed to occur on the same day as the first dose date.

In addition, the imputation rule is to conservatively assign TEAEs with partial dates for adult patients to a DB period if it's unclear whether the event began in a DB period or open-label period.

Non-study medications with missing or partial dates will be imputed similarly.

Dates imputation will only be used for computational purposes (e.g., treatment-emergent status or identifying concomitant medications). Actual data values as they appear in the clinical database will be shown in data listings.

5.3.7 PK Parameters Calculation (For Adult Cohort)

Steady-state PK parameters (AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$, $t_{max,ss}$, CL/F) of CDCA, gCDCA, tCDCA and total CDCA will be estimated using non-compartmental analysis if feasible. The calculation will be performed by LabCorp, Inc. Summary of PK concentration and PK parameters is outside the scope of this SAP. A separate analysis plan will be generated to describe the summary methodology for these endpoints.

5.4 Statistical Methods

5.4.1 Statistical Notation and Presentation

For descriptive statistical summaries, mean, sample size (n), standard deviation (SD), SE, median, the first quartile (Q1), the third quartile (Q3), minimum (MIN) and maximum (MAX)

will be calculated for continuous variables. For parameters analyzed in the $\log_e$-scale such as urine 23S-pentol, geometric mean, SE and %CV will also be presented.

Categorical variables will be summarized by count, percentage, or shift tables (if applicable).

Min, max, Q1 and Q3 values will be presented to the precision of the original value. Means and medians will be rounded to one decimal place greater than the precision of the original value. SDs/SEs and 95% confidence intervals (CIs) will be rounded to two decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place and will be based on nonmissing data, unless otherwise specified. Percentages that are ≥99.95% or <0.05% will be reported as >99.9% or <0.1%. P-values will be presented with four decimal places and values less than 0.0001 will be presented as <0.0001.

The by-patient listings, including data at scheduled and unscheduled visits, will be sorted by treatment sequence, patient number, study visit, and then by date/time of the records.

5.4.2 Statistical Hypothesis

The null (H_0) hypothesis and the alternative (H_a) hypothesis to be tested for the primary efficacy endpoint are that

$$H_0: \Delta = 0 \text{ versus } H_a: \Delta \neq 0$$

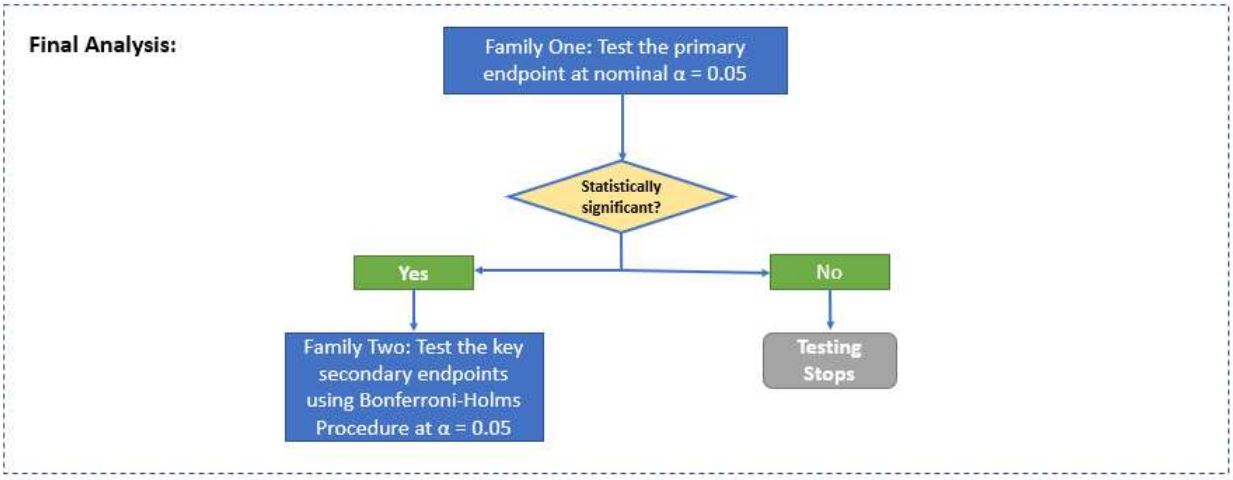
where Δ is the true paired treatment difference between CDCA and placebo for the change from baseline in $\log_e$-transformed urine 23S-pentol in the adult cohort.

5.4.3 Multiple Comparison

Multiple comparison procedure will be implemented to strongly control the family-wise type 1 errors across the primary endpoint and the key secondary efficacy endpoints. The first family of hypotheses consists of urine 23S-pentol primary endpoint. The second family of hypotheses consist of the key secondary efficacy endpoints of proportion requiring rescue medication, percent change from baseline plasma cholestanol, and percent change from baseline plasma 7αC4 (in no particular order). The schematic of the multiple comparison procedure is presented in Figure 4.

The primary endpoint of urine 23S-pentol will be tested at an $\alpha = 0.05$. If the test is significant, the Family One is rejected and the entire $\alpha = 0.05$ is preserved and then passed onto the Family Two of hypotheses (i.e. key secondary endpoints) for testing at the final analysis. Otherwise, there is no remaining α to be passed onto Family Two, and therefore, the key secondary endpoints will not be formally tested, and nominal p-values will be reported instead.

Figure 4 : The Multiple Comparison Procedure



The Bonferroni-Holms procedure will be used to control the Type 1 errors for the Family Two of hypotheses at an overall $\alpha = 0.05$. The procedure is described as follows: Let $P_{(1)} \leq P_{(2)} \leq P_{(3)}$ denote the ordered unadjusted p-values with associated null hypotheses $H_{(1)}$, $H_{(2)}$, $H_{(3)}$ for the three key secondary efficacy endpoints described in 4.2 and 6.2.2. Then we have the following stepwise procedure:

- If $P_{(1)} \leq \alpha / 3$, reject $H_{(1)}$ and continue; else stop
- If $P_{(2)} \leq \alpha / 2$, reject $H_{(2)}$ and continue; else stop
- If $P_{(3)} \leq \alpha$, reject $H_{(3)}$

All other secondary efficacy endpoints will be analyzed at the nominal 0.05 significance level.

5.4.4 Interim Analysis

No interim analysis will be conducted for this study.

6 STATISTICAL ANALYSIS

6.1 Study Patients

6.1.1 Analysis Population

Counts and percentages of patients in each analysis population will be summarized by treatment sequence and overall for the adult cohort and overall for the pediatric cohort.

6.1.2 Patient Eligibility

Patient eligibility (inclusion and exclusion criteria failures) for adults and pediatric patients will be provided in separate data listings for the EAS and the PSAS.

6.1.3 Patient Disposition

Patient disposition will be presented for adults and pediatric patients. Counts and percentages of patients who are randomized, completed, or discontinued from the study or study treatment, as well as the discontinuation reasons, will be summarized by treatment sequence and overall for the EAS and overall for the PSAS. Counts and percentages of patients completing key study milestones (OL1, DB1, OL2, DB2 for the adult cohort; titration and treatment periods for the pediatric cohort) will also be presented.

6.1.4 Demographic Characteristics

Demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, BMI, CTX diagnosis history and ophthalmology exam results will be summarized descriptively by treatment sequence and overall for the EAS, FAS, TEFAS, NIFAS and overall for the PSAS.

6.1.5 Medical History

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or later and will be summarized descriptively by treatment sequence, System Organ Class and Preferred Term for the EAS. CTX Medical History will be summarized descriptively by treatment sequence and categories provided on CRF for the EAS.

Medical History for pediatric patients will be listed for the PSAS.

6.1.6 Study Treatment Administration

Study drug administration and dosing information will be presented in a listing for the EAS and PSAS.

Treatment compliance (e.g. percent of planned tablets received) will be summarized by treatment group and treatment period (separately for on-study and DB) for the EAS. Percent of planned tablets received is calculated as the total number of tablets received in a treatment period divided by the planned tablets the patient should have received during the same treatment period (excluding dose interruption period) while still actively enrolled. The total number of tablets received will be calculated from the total number of tablets dispensed minus the total number of tablets returned for each patient.

6.1.7 Protocol Deviations

Protocol deviations will be listed for the EAS and PSAS. All protocol deviations will be reviewed by clinical and statistical personnel prior to database lock. The type of protocol deviations governing exclusion from the PPAS will be determined prior to breaking the blind and are detailed here.

Evaluation of patients' protocol deviations will be based on the following:

- Compliance of study entry criteria (inclusion and exclusion)
- Receipt of the randomized treatment
- Adequate study medication exposure (no extended dosing interruptions)
- Adequate treatment compliance based on prescribed dose level (within 80% to 120%)
- No prohibited concomitant medications or therapies during the study
- No accidental or intentional un-blinding at the investigational site
- No other major protocol deviations that may affect efficacy or safety conclusions, may include:
  - Non-withdrawal though at least one withdrawal criterion was met
  - Extensive visit window violations
  - Extensive missing visits
  - Non-adherence to study procedures
  - Inadequate handling of study medication

6.1.8 Concomitant Medications

The World Health Organization Drug Dictionary (WHO-DD) (B3 March 2019 or later) will be used to categorize verbatim descriptions of non-study medications into the Anatomic Therapeutic Chemical (ATC) Classification System. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and trade name.

6.1.8.1 Adult Cohort

Concomitant medications are non-study medications that have been used starting from OL1 throughout the study. Prior concomitant medications are medications that start prior to dose on Day -56 (the beginning of OL1) and continue after the first dose on Day -56. New concomitant medications are medications that start after receiving the first dose on Day -56.

The number and percentage of patients receiving any concomitant medications will be summarized by treatment group, treatment period (separately for on-study and DB), and ATC classification (ATC level 2 and level 4) for the EAS. A concomitant medication will be attributed to a specific treatment period that the medication starts or is still ongoing.

Pre-treatment medications that start and stop prior to receiving the first dose on Day -56 will be provided in data listing.

6.1.8.2 Pediatric Cohort

All non-study medications data that are collected will be provided in a listing.

6.2 Analysis of Efficacy

The efficacy endpoints will be analyzed primarily on the FAS and on the PPAS which will serve as sensitivity analyses.

6.2.1 Analysis of Primary Efficacy Endpoint of Urine 23S-Pentol

Urine 23S-pentol will be determined using first morning void urine samples and will be calculated as the geometric mean of 3 first morning void urine samples collected within 5 days prior to each visit at which urine 23S-pentol is assessed. The baseline value for DB1 is the calculated geometric mean of samples for Day 1. The baseline value for DB2 is the calculated geometric mean of samples for Day 85. Measurements obtained after initiation of rescue medication will be considered "missing" for purposes of the primary analysis. In the event only 1 sample or 2 samples are collected within 5 days prior to an assessment visit, the value of the sample or the geometric mean of 2 samples will be used instead, respectively. In the event when the value of a sample is BLQ, the value will be set to the LLOQ.

The paired t-test comparing CDCA with placebo will be conducted on the change from baseline to the last non-missing observation in $\log_e$-transformed urine 23S-pentol of each DB period. Specifically, the paired difference will be calculated between CDCA and placebo in the change from baseline to the last non-missing observation in $\log_e$-transformed urine 23S-pentol for each patient, ignoring the randomized order of receiving the treatment. Log-transformation is performed due to the anticipated wide range of urine 23S-pentol levels among CTX patients. A sensitivity analysis using paired t-test on FAS with missing 23S-pentol values imputed will also be performed; refer to 6.5 for details.

Additionally, the changes from baseline in $\log_e$-transformed urine 23S-pentol during the DB treatment periods will be analyzed via a mixed effects model with treatment, sequence, period, period baseline value, nominal time (in days within period; categorical), and treatment-by-time interaction as fixed effects, and patients as random effect. The model will be fitted with an unstructured covariance matrix. If convergence issues arise, a heterogeneous first order auto-regressive structure will be used. If convergence issues still arise, a first order auto-regressive structure will be used. The least squares (LS) means difference between CDCA and placebo randomized treatment-by-time evaluated at 4 weeks, its confidence interval (two-sided 95%) and the p-value will be calculated. P-values of the other fixed effects will also be provided. Estimates and CIs will also be converted to percentages via the following transformation: [exp(least squares mean change from baseline in $\log_e$-transformed urine 23S-pentol) – 1] x 100

The analysis results using the mixed effects model will be considered supportive.

The actual values and changes from baseline in urine 23S-pentol for each DB treatment period will also be summarized descriptively by treatment. Similar descriptive analysis using the study baseline (i.e. the calculated geometric mean of samples for Day -56) instead of the DB period baseline will be performed on urine 23S-pentol collected during OL and DB periods. Figures of actual values and changes from baseline will also be presented.

The SAS® sample code for the mixed effects model:

```
proc mixed data = bile;
class trtp (ref="Placebo") trtseqpn aperiodc days usubjid;
model chg = trtp trtseqpn aperiodc base days trtp*days;
repeated days / subject = usubjid type = UN;
lsmeans trtp*days /cl alpha = 0.05 pdiff;

run;
```

6.2.2 Analysis of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints will be tested using the Bonferroni-Holms procedure described in 5.4.3.

6.2.2.1 Proportion of Patients requiring Rescue Medication

The proportion of patients requiring rescue treatment and the corresponding exact 95% CI will be calculated and presented using Clopper-Pearson method for each treatment. Patients who require blinded and/or open-label CDCA rescue during the DB periods will be considered to have met the event (i.e. require rescue medication) for the primary analysis.

SAS® sample code for the Clopper-Pearson method:

```
data clop_ci;
set rescue;
p=round ((x/n),.001);
if p=0 then CI_LOW=0;
if p=1 then CI_HIGH=1;
if p ne 0 then CI_LOW=round((1-betainv(.975,(n-x+1),x)),.00001);
if p ne 1 then CI_HIGH=round((1-betainv(.025,(n-x),x+1)),.00001);

run;
```

The probability of observing contingency tables of rescue data with equal or more extreme values (exact p-values) will be calculated using Prescott's method (Prescott, 1981). The method will be implemented in SAS® using the algorithm and notations (Figure 5) in "Analyzing Binary Outcome Data from a Crossover Design Study using the SAS® System" by Anna Pictor (2003). The "No Preference" group in Figure 5 is defined as those who require rescue in both periods or those who do not require rescue in either period. Rejection of the null hypothesis for no association suggests there is a difference between two treatments.

Figure 5: The Algorithm and Notations by Anna Pictor

Sequence	Prefer First Period	No Preference	Prefer Second Period	Total for all Preferences
CDCA - Placebo	d	e	f	r_1
Placebo - CDCA	g	h	k	r_2
Total for both Sequences	s_1	s_2	s_3	N

SAS® sample code for the Prescott's method:

```
data tab;
d = 0;
f = 0;
r1 = 20;
r2 = 20;
s1 = 9;
s2 = 21;
s3 = 10;
n = 40;
diff = 5;

e = r1-d-f;
g = s1-d;
h = s2-e;
k = s3-f;

do while (e ge 0 and g ge 0 and h ge 0 and k ge 0);
      do while (e ge 0 and g ge 0 and h ge 0 and k ge 0);
      if d-f ge diff or d-f le -diff then output;
      f+1;
      e = r1-d-f;
      g = s1-d;
      h = s2-e;
      k = s3-f;
      end;
f=0;
d+1;
e = r1-d-f;
g = s1-d;
h = s2-e;
k = s3-f;
end;
run;

data ppres;
set tab;
c_d = comb(s1,d);
c_e = comb(s2,e);
```

```
c_f = comb(s3,f);
c_r1 = comb(n,r1);
product = c_d*c_e*c_f;
sum_p + product;
p_two_sided = sum_p/c_r1;
run;
```

6.2.2.2 Percent Change from baseline in Plasma Cholestanol

Since cholestanol is expected to require longer treatment with CDCA to show meaningful changes, the primary analysis (as described below) for cholestanol will be conducted on the TEFAS to mitigate against the potential impact of the short duration of the treatment run-in period prior to the DB period. The baseline values and measurements obtained after initiation of rescue medication will be handled in the same manner as for the primary efficacy endpoint.

The paired t-test comparing CDCA with placebo will be conducted on the percent change from baseline to the last non-missing measurement of each DB period in the same manner as for the analysis of the primary endpoint. A sensitivity analysis using paired t-test on TEFAS with missing cholestanol levels imputed will also be performed; refer to 6.5 for details.

Additionally, the percent change from baseline in plasma cholestanol levels during the DB treatment periods will be analyzed in the same manner as for the analysis of the primary endpoint via a mixed effects model with treatment, sequence, period, period baseline value, nominal time (in days within period; categorical), and treatment-by-time interaction as fixed effects, and patients as random effect. The model will be fitted with an unstructured covariance matrix. If convergence issues arise, a heterogeneous first order auto-regressive structure will be used. If convergence issues still arise, a first order auto-regressive structure will be used. The LS means difference between CDCA and placebo randomized treatment-by-time evaluated at 4 weeks, its p-value will be calculated. P-values of the other fixed effects will also be provided. Estimates and CIs will also be converted to percentages via the following transformation:
[exp(least squares mean change from baseline in $\log_e$-transformed plasma cholestanol) – 1] x 100

The analysis results using the mixed effects model will be considered supportive.

The actual values, actual change, and percent change from baseline in plasma cholestanol levels for each DB treatment period will also be summarized descriptively by treatment. Similar descriptive analysis using the study baseline (i.e. the last measurement prior to dose on Day -56) instead of the DB period baseline will be conducted on plasma cholestanol collected during OL and DB periods. Figures of actual values and changes from baseline will also be presented.

6.2.2.3 Percent Change from baseline in Plasma 7αC4

Percent change from baseline in plasma 7αC4 levels will be analyzed in a similar way as in 6.2.2.2. The primary analysis will be based on the FAS.

6.2.3 Analysis of Other Secondary Efficacy Endpoints

All other secondary efficacy endpoints will be analyzed at the nominal 0.05 significance level at the final analysis.

6.2.3.1 Change from baseline in Plasma Cholestanol to Cholesterol Ratio

Change from baseline in plasma cholestanol to cholesterol ratio will be analyzed in a similar way as in 6.2.2.3.

6.2.3.2 Percent Change from baseline in Plasma 7α12αC4

Percent change from baseline in plasma 7α12αC4 will be analyzed in a similar way as in 6.2.2.3.

6.2.3.3 Proportion of Patients with Negative Net Change in Symptoms and Manifestations reported in the Diary

The proportion of patients with negative net change in symptoms (described below) or manifestations reported in the diary during the DB period is a composite endpoint and will be analyzed as a binary efficacy endpoint using the same approach described for the proportion of patients requiring rescue medication.

For each symptom, the value for each planned visit (i.e. Day 1 [baseline], Weeks 1, 2, 3, and 4, for DB1; Day 85 [baseline], Weeks 13, 14, 15, and 16, for DB2) will be based on the results reported in the diary during the 7 days preceding the visit. Data obtained after initiation of rescue treatment will be excluded from the calculations. The following parameters will contribute to the composite endpoints (i.e. bowel function, seizures, tremors, and manifestations) calculated at the planned visits for each patient:

- Bowel function:
    - the proportion of bowel movements with Bristol Stool Form Scale (BSFS) scores of 1 (severe constipation), 2 (mild constipation), 6 (mild diarrhea), or 7 (severe diarrhea);
    - the average BSFS score of all reported bowel movements
- Seizures:
    - the rate of seizure per day (i.e. total number of seizures / total days with diary data);
    - the average duration of seizures;
    - the average severity of seizures (1 for mild; 2 for moderate; 3 for severe; 4 for very severe)
- Tremors:

  - the proportion of days with tremors (i.e. number of days with tremors / total days with diary data);
  - the average number of body parts with tremors;
  - the average severity of all tremors reported (1 for mild; 2 for moderate; 3 for severe; 4 for very severe)

- Manifestations:
  - the proportion of days with the specific manifestation (i.e. number of days with the manifestation / total days with diary data);
  - the weighted (2 for most bothersome manifestations, 1 for other manifestations) average impact or discomfort/distress score (0 to 4, ranging from no impact or discomfort/distress to very severe impact or discomfort/distress)

For each parameter above, the change from baseline score will be calculated as the difference between the value for a specific visit during the DB period and the corresponding baseline visit (i.e. post-baseline – baseline visit). The sign of the change will be noted as -1, 0, or +1 if it is greater than 0, equal to 0, or less than 0, respectively. Patients are considered to have a negative net change in a symptom or manifestations if there are more negative changes than positive changes across the contributed parameters and visits.

The count and proportion of patients with negative net change in each composite endpoint will be summarized by treatment and visit; and by treatment at the end of double-blind period (DB1 or DB2).

6.3 Analysis of Safety Endpoints

Descriptive statistics will be used to summarize the safety data by treatment group or sequence among adult patients and by overall among pediatric patients. For the adult cohort, EAS will be used for on-study summary, and SAS will be used for DB periods summary. PSAS will be used for the pediatric cohort summary. For DB periods summary, measurements obtained after initiation of rescue medication will be considered "missing".

6.3.1 Extent of Exposure

Total number of days on CDCA per patient will be summarized descriptively for the EAS and PSAS. Additionally, the number of days on CDCA and placebo during the DB period will be summarized for the SAS.

6.3.2 AEs

An AE is any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study medication, whether or not considered

related to the study medication. The patient will be evaluated for new AEs and the status of existing AEs at each study visit, including screening or washout periods, or at any time contact is made with the patient outside of a scheduled visit.

6.3.2.1 Adult Cohort

TEAEs will be defined as those that start from OL1 throughout the study, or existing AEs that worsen during or after OL1. AEs prior to OL1 will be classified as pre-treatment. An AE will be attributed to a specific treatment period that the event occurs. All AEs will be coded using the MedDRA (Version 22.0 or later) by System Organ Class and Preferred Term.

Number and percentage of patients with TEAEs during the DB periods and on-study will be summarized separately by treatment group, system organ classification, and preferred term.

TEAEs leading to discontinuation of study medication, TEAEs related to study medication (possibly related will be grouped together with related for summary), serious TEAEs, TEAEs by severity, and TEAEs of interest during the DB periods and on-study will also be summarized separately by treatment group, system organ class, and preferred term. For each system organ class and preferred term, patients with multiple events (different severities or relationships) will be counted only once at the worst grade. TEAEs with missing severity or missing relationship will be summarized as "Not Reported".

Abnormal liver function tests that meet the below criteria will be considered TEAEs of interest:

- The abnormality represents a new elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN), with or without an elevation of total serum bilirubin >2 times ULN; or
- The abnormality represents a 2-fold increase in ALT or AST above the baseline value in patients who had elevated values prior to starting any medication.

Death and pre-treatment AEs will be listed if any.

6.3.2.2 Pediatric Cohort

TEAEs will be defined as those that start from Titration period throughout the study, or existing AEs that worsen during or after Titration period. AEs prior to Titration period will be classified as pre-treatment. All AEs will be coded using the MedDRA (Version 22.0 or later) by System Organ Class and Preferred Term.

Number and percentage of patients with TEAEs during the study will be summarized by overall, system organ classification, and preferred term.

TEAEs leading to discontinuation of study medication, TEAEs related to study medication, serious TEAEs, TEAEs by severity, and TEAEs of interest during the study will also be summarized overall, by system organ class and preferred term.

Death and pre-treatment AEs will be listed if any.

6.3.2.3 Adult and Pediatric Cohort

Targeted pooled analyses of TEAEs for the PTAS (adult patients in the EAS and pediatric patients in the PSAS) will be performed.

Number and percentage of patients with TEAEs while on-study will be summarized separately by treatment group (CDCA and overall), system organ classification, and preferred term.

TEAEs leading to discontinuation of study medication, TEAEs related to study medication (possibly related will be grouped together with related for summary), serious TEAEs, and TEAEs of interest while on-study will also be summarized separately by treatment group (CDCA and overall), system organ class, and preferred term.

6.3.3 Laboratory Evaluations

All hematology, chemistry, coagulation, lipid profile and urinalysis results will be listed. Laboratory assessments that are outside of normal ranges and/or with clinical significance will be flagged in the listings.

6.3.3.1 Adult Cohort

For central lab results, the following descriptive analyses will be performed separately on 2 sets with different baseline values: during the study and during the DB periods.

- Baseline values (refer to 5.3.3.1), values at post-baseline visits, and changes from the baseline values will be summarized for quantitative laboratory assessments by treatment group.
- Count and percentage will be summarized for laboratory assessments with categorical results (including pregnancy test) by treatment group and visit.
- Shift tables of laboratory data will be generated to summarize the normal and abnormal (abnormal high and abnormal low if applicable) status changes from baseline to the worst post-baseline during the treatment period.
- Tables that summarize the count and percentage of values outside of normal ranges for hematology, chemistry and urinalysis will also be provided.

Additionally, the count and percentage of each category as defined below will be summarized by treatment group and visit on the 2 sets.

- ALT and AST: >1 x ULN; >2 x ULN; >3 x ULN; >5 x ULN; >8 x ULN
- Alkaline phosphatase (ALP): >1 x ULN; >1.5 x ULN; >2.5 x ULN; >5 x ULN
- Total Bilirubin: >1 x ULN; >1.5 x ULN; >2 x ULN; >3 x ULN

6.3.3.2 Pediatric Cohort

For central lab results, the following descriptive analyses will be performed on the set: during the study:

- Baseline values (refer to 5.3.3.2), values at post-baseline visits, and changes from the baseline values will be summarized descriptively for quantitative laboratory assessments by overall.
- Count and percentage will be summarized for laboratory assessments with categorical results (including pregnancy test) by overall and visit.
- Shift tables of laboratory data will be generated to summarize the normal and abnormal (abnormal high and abnormal low if applicable) status changes from baseline to the worst post-baseline.
- Tables that summarize the count and percentage of values outside of normal ranges for hematology, chemistry and urinalysis will also be provided.

Additionally, the count and percentage of each category as defined below will be summarized by overall and visit.

- ALT and AST: >1 x ULN; >2 x ULN; >3 x ULN; >5 x ULN; >8 x ULN
- ALP: >1 x ULN; >1.5 x ULN; >2.5 x ULN; >5 x ULN
- Total Bilirubin: >1 x ULN; >1.5 x ULN; >2 x ULN; >3 x ULN

6.3.4 Vital Signs and Body Weight

For vital signs (blood pressure, heart rate, respiratory rate and oral temperature) and body weight, baseline values, post-baseline values, and changes from baseline values will be summarized descriptively by treatment group for the adult cohort, and by overall for the pediatric cohort. For each cohort, the analysis will be performed on the sets as for the lab analysis.

6.3.5 EEG and 12-Lead ECG

Shift tables of EEG and ECG data will be generated to summarize the assessment interpretation changes from baseline to the worst post-baseline during the treatment period by treatment group for the adult cohort, and by overall for the pediatric cohort. For each cohort, the analysis will be performed on the same sets as for the lab analysis.

6.3.6 Physical Examination

Physical examination results will be listed for both cohorts.

6.4 Analysis of Exploratory Endpoints

6.4.1 Adult Cohort

Percent change from baseline in plasma bile alcohol (tetrol glucuronide) will be analyzed in a similar way as in 6.2.2.3.

For each pair of biomarkers (e.g. urine 23S-pentol vs. plasma cholestanol), pooled changes from DB period baseline to each post-baseline nominal visit (in days within period) grouped by treatment will be presented by scatter plot along with Pearson's correlation coefficient in the original and $\log_e$ scales. Pooled changes from DB period baseline to the worst post-baseline during the period (either DB1 or DB2) grouped by treatment will be plotted the same.

Changes from baseline in biomarker (urine and plasma bile alcohols, plasma cholestanol, plasma 7αC4, or plasma 7α12αC4) value at Run-In Week 6 (RIW6; Visit 5) vs. PK exposure parameter (AUC_{ss}, $C_{max,ss}$ or $C_{min,ss}$) of CDCA, gCDCA, tCDCA and total CDCA at RIW6 per patient will be presented by scatter plot along with Pearson's correlation coefficient.

The event count of TEAEs in OL1 vs. PK exposure parameter of CDCA at RIW6 per patient will also be plotted with Pearson's correlation coefficient.

The event count of TEAEs of interest in OL1 vs. PK exposure parameter of CDCA at RIW6 per patient will be plotted the same.

The Clinician Global Impression of Severity (CGI-S) measures the severity of the patient's disease using a global, 7-point scale. The CGI-C is a global, 7-point scale used to assess how much the patient's illness has improved or worsened relative to the patient's condition since baseline. The score ranges from 1 (very much improved) to 7 (very much worse). The number and percentage of patients for each CGI-S score and each CGI-C score during DB treatment periods will be summarized by treatment group and visit.

Patients will complete a visual analog scale by rating their overall health status over the past week from 0 to 100. The actual values and changes from baseline in health status scores during DB treatment periods will be summarized descriptively by treatment group and visit.

6.4.2 Pediatric Cohort

Biomarker levels (urine and plasma bile alcohols, plasma cholestanol, plasma 7αC4 and plasma 7α12αC4) and their changes from baseline will be summarized descriptively by overall and study visit.

For each pair of biomarkers (e.g. urine 23S-pentol vs. plasma cholestanol), changes from baseline to the worst post-baseline during the study will be presented by scatter plot along with Pearson's correlation coefficient in the original and $\log_e$ scales.

The number and percentage of patients for each CGI-S score and each CGI-C score collected during Treatment Period will be summarized by overall and visit.

The actual values and changes from baseline in health status scores will be summarized descriptively by overall and visit.

Assessment of motor developmental milestones will be done at Titration Start (baseline) and W16/EOT/EOS/ET (Table 2). The count and percentage of patients with any post-baseline changes to previous milestones assessed will be summarized by overall and visit.

6.5 Handling of Missing Data (For both Cohorts)

6.5.1 Imputation Rules for Analysis Sets

FAS (or TEFAS if applicable): Measurements of urine 23S-pentol, cholestanol, plasma 7αC4, plasma 7α12αC4, and cholesterol obtained after initiation of rescue medication will be considered "missing" for purposes of the primary analyses. Imputation of missing urine 23S-pentol, plasma bile alcohol, cholestanol, plasma 7αC4, plasma 7α12αC4, and cholesterol values will be performed using a multiple imputation (MI) method under the assumption of missing at random (MAR) separately for each treatment group. The efficacy endpoints analyses using the imputed values will serve as sensitivity analyses, whereas the efficacy endpoints analyses without using the imputation will be treated as the primary analyses; refer to 6.2 for details.

PPAS: No imputation of missing data will be performed for the efficacy endpoints.

SAS: No imputation of missing data will be performed for the safety endpoints.

PKAS: No imputation of missing data will be performed for the PK endpoints.

PSAS: No imputation of missing data will be performed for any endpoints.

PPKAS: No imputation of missing data will be performed for the PK endpoints.

6.5.2 MI under MAR assumption

MI is a general approach to the problem of missing data that aims to account for uncertainty associated with imputing the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. MAR approach assumes that any systematic difference between the missing values and the observed values can be explained by differences in observed data. The use of MI under MAR assumption provides unbiased estimation of the parameters and allows to evaluate the uncertainty of parameters' estimation due to the presence of missing data.

Fully Conditional Specification (FCS) regression methods will be used to impute missing biomarker values for the efficacy endpoints. The imputation will be performed on the scale in which the variables are analyzed (eg, natural log scale for urine bile alcohol). The imputed data

sets will then be analyzed according to 6.2, and analysis results will be synthesized using the MIANALYZE procedure of SAS®. In order to prevent a power falloff due to choosing the number of imputations too small, 25 imputations will be performed (Graham, John W. et al. 2007). Imputation will be performed separately by treatment. If imputation by treatment is not possible (due to, for example, insufficient observations to fit the regression models), then treatment may be added as a class variable in the regression model. SAS® sample code for the whole process is given as below:

```
*Create a Sample dataset;
data temp;
do trt = 'Placebo', 'Cheno';
      do subject = 1 to 12;
      bile1 = rannor(1);
      bile2 = rannor(2);
      bile3 = rannor(3);
      bile4 = rannor(4);
      bile5 = rannor(5);
      missing1 = ranuni(1);
      missing2 = ranuni(2);
      missing3 = ranuni(3);
      missing4 = ranuni(4);
      missing5 = ranuni(5);
      output;
      end;
end;
run;

data temp (drop=missing1 missing2 missing3 missing4 missing5);
set temp;
if missing1 > 0.95 then bile1 =.;
if missing2 > 0.9 then bile2 =.;
if missing3 > 0.85 then bile3 =.;
if missing4 > 0.8 then bile4 =.;
if missing5 > 0.75 then bile5 =.;
run;

*Multiple Imputation using PROC MI;
proc sort data=temp;
by trt;
run;

proc mi data=temp nimpute=25 seed=123 out=bile;
by trt;
fcs reg(bile5/details);
var bile1 bile2 bile3 bile4 bile5;
run;

data bile_pl (keep=_imputation_ subject chg rename=(chg=chg_pl)) bile_cheno
(keep=_imputation_ subject chg rename=(chg=chg_cheno));
set bile;
chg = bile5 - bile1;
if trt = 'Placebo' then output bile_pl;
else output bile_cheno;
run;
```

```
data bile_new;
merge bile_pl bile_cheno;
by _imputation_ subject;
run;

*Analysis of completed data sets;
ods trace on;
proc ttest data=bile_new plots=none;
by _imputation_;
paired chg_pl*chg_cheno;
ods output Statistics = stats;
run;
ods trace off;

*Synthesize analysis results;
proc mianalyze data = stats;
modeleffects mean;
stderr stderr;
ods output parameterestimates = stats_syn;
run;
```

6.6 Statistical Software

All statistical analyses will be performed using SAS® version 9.4.

7 REFERENCES

Graham, John W., Allison E. Olchowski, and Tamika D. Gilreath. "How many imputations are really needed? Some practical clarifications of multiple imputation theory." Prevention science 8.3 (2007): 206-213.

Prescott, R. J. "The comparison of success rates in cross-over trials in the presence of an order effect." Journal of the Royal Statistical Society: Series C (Applied Statistics) 30.1 (1981): 9-15.

Pictor, Anna. "Analyzing Binary Outcome Date from a Crossover Design Study using the SAS® System." SAS VIEWS 2003. https://www.lexjansen.com/views/2003/statpharm/st02.pdf.

8 APPENDIX

Table 1: Schedule of Assessments for Adult Cohort

	V1	V2	V3-5	V6	V7	V8	V9	V10	V11-13	V14	V15	V16	V17	V18
		OL1		DB1					OL2	DB2				
		RIW1, First day	RIW2[a] RIW4[a] RIW6[b]		W1	W2	W3	W4/EOT1[c]	W6[a], 8[a], 10[a]	W12	W13	W14	W15	W16/ EOT2[c] EOS ET
Week/Day	S	D -56	D -42 D -28 D -14	D1	D8	D15	D22	D29	D43, D57, D71	D85	D92	D99	D106	D113
Visit Window	≤28 days prior to start of OL1	±1 day	±1 day		±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day
Informed Consent/Assent	X													
Inclusion/Exclusion	X			X										
Genetic Testing for CTX[d]	X													
Serologic test for Hep B, Hep C, HIV	X													
Medical History	X													
CTX Medical History[e]	X													
Prior Medication	X													
Demographics	X													
Pregnancy Test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X
Health Status During Prior Week		X		X	X	X	X	X		X	X	X	X	X
CGI-S				X						X				
CGI-C					X	X	X	X			X	X	X	X[g]

	V1	V2	V3-5	V6	V7	V8	V9	V10	V11-13	V14	V15	V16	V17	V18
		OL1		DB1					OL2	DB2				
Week/Day	S	RIW1, First day D -56	RIW2[a] RIW4[a] RIW6[b] D -42 D -28 D -14	D1	W1 D8	W2 D15	W3 D22	W4/EOT1[c] D29	W6[a], 8[a], 10[a] D43, D57, D71	W12 D85	W13 D92	W14 D99	W15 D106	W16/ EOT2[c] EOS ET D113
Visit Window	≤28 days prior to start of OL1	±1 day	±1 day		±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day
Ophthalmology Exam[h]		X												X
Physical Examination (including body weight)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluate OL Rescue Medication Criteria[j]					X	X	X	X		X	X	X	X	X
Vital Signs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Diary[l]	X[m]		X[n]	X	X	X	X	X		X	X	X	X	X
Urine 23S-pentol (3 first morning voids)[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for Cholestanol, 7αC4, 7α12αC4, and Plasma Bile Alcohol	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments (including coagulation [INR and PT[p]] and LFTs)[q]	X[r]	X[s]	X	X[s]	X	X	X	X[s]	X	X[s]	X	X	X	X[s]
Pharmacokinetic Blood Sample Collection[b]			X[b]											
Adverse Events[t]		Collected continuously												

	V1	V2	V3-5	V6	V7	V8	V9	V10	V11-13	V14	V15	V16	V17	V18
		OL1		DB1					OL2	DB2				
		RIW1, First day	RIW2[a] RIW4[a] RIW6[b]		W1	W2	W3	W4/EOT1[c]	W6[a], 8[a], 10[a]	W12	W13	W14	W15	W16/ EOT2[c] EOS ET
Week/Day	S	D -56	D -42 D -28 D -14	D1	D8	D15	D22	D29	D43, D57, D71	D85	D92	D99	D106	D113
Visit Window	≤28 days prior to start of OL1	±1 day	±1 day		±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day
EEG[u]		X		X		X		X		X		X		X
12-Lead ECG	X			X		X		X				X		X
Randomization				X										
Study Medication Administration[v]		X	X	X	X	X	X	X	X	X	X	X	X	
Dispense DB Study Medication				X	X	X	X			X	X	X	X	
Dispense OL Study Medication		X	X[w]					X	X[w]					
Medication Accountability			X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; BCVA = best-corrected visual acuity; CDCA = Chenodeoxycholic acid; CGI-C = Clinician Global Impression of Change; CGI-S = Clinician Global Impression of Severity; CTX = cerebrotendinous xanthomatosis; D = day; DB = double-blind; DB1 = double-blind period 1; DB2 = double-blind period 2; ECG = electrocardiogram; EEG = electroencephalogram; EOS = end of study; EOT = end of treatment; ET = Early Termination; Hep B = hepatitis B virus surface antigen; Hep C = hepatitis C; HIV = human immunodeficiency virus; INR = international normalized ratio; LFT = liver function test; OL = open label; OL1 =open-label period 1; OL2 = open-label period 2; PK = pharmacokinetics; PT = prothrombin time; PRO = Patient-reported outcomes; RI = Run-in; S = Screening; TID = three times a day; V = visit; W = week; WOCBP = women of childbearing potential.

Note 1: Laboratory samples required at Screening may be collected across multiple days to reduce blood volume drawn on a single day. Screening laboratory results must be received before Visit 2. If genetic results are still pending after 28 days, the screening window may be extended up to 2 additional weeks, with approval by the Medical Monitor. If a patient's screening window is extended, the patient is not required to repeat screening assessments. Laboratory assessments for all other visits should be collected prior to the first daily dose of CDCA.

Note 2: Patients will be contacted (via telephone call) 30 (±7) days after the last dose of study medication to ascertain patient safety (see Section 6.6.2 and Section 6.8 for details).

[a] Assessments for Visits 3, 4, 11, 12, and 13 may be conducted by a home health vendor at an alternative site than the Investigator's site.

[b] PK blood draws will be collected at Visit 5. PK samples will be collected predose and at 0.5, 1, 2, 3, 6, and 8 hours postdose. Patients will need to hold the first dose of study medication for on-site administration to facilitate the correct timing of the blood draw for the PK analysis. PK samples will only be obtained from patients who are on 750 mg (250 mg TID). A standardized low-fat meal will be provided 45-60 minutes prior to the first study medication dose and should be completed within 30 minutes of starting the meal. Predose blood sample for plasma PK will be drawn within 15-30 minutes post completion of the meal. After the first study medication dose, the 0.5 hours post dose draw has a ±5-minute window. The 1, 2, and 3-hour post dose draws have a ±10-minute window. An optional small snack may be offered and completed within 30 minutes of the post 3-hour timepoint. The 6-hour post dose draw has a ±15-minute window. A second standardized low-fat meal is provided 45 to 60 minutes prior to the 8-hour timepoint and the meal will be completed within 30 minutes of starting the meal. The 8-hour PK draw will be taken 15-30 minutes after the completion of the meal.

[c] If open-label rescue medication criteria are triggered prior to Visits 10 or 18, all assessments must be conducted prior to administration of open-label treatment.

[d] If prior genetic confirmation of CTX is not available, blood will be drawn at Visit 1 for gene sequencing. No patient with negative genetic sequencing will be randomized.

[e] CTX medical history should include a complete list of CTX-related symptoms present at the time of Screening.

[f] Serum pregnancy tests will be performed at Screening for WOCBP. Urine pregnancy tests will be performed at all other visits. A positive urine pregnancy test will be confirmed by a serum test. All WOCBP must have a negative pregnancy test (urine, with positive results confirmed by serum) at every visit.

[g] The CGI-C needs to be completed at this visit if a patient leaves the study early during DB1 or DB2.

[h] Ophthalmology exam includes BCVA and cataracts. The ophthalmology exam has a window of ±1 day to accommodate being conducted by a separate specialist.

[i] At Screening, the physical examination is a full physical examination; at subsequent visits, the physical examination can be an abbreviated exam. Height will be measured at Screening, baseline (Visit 6/Day 1), and EOS for adult cohort patients. Physical examinations will include assessment of the following body systems: abdomen; cardiovascular; ear, nose, and throat; eyes; hair and skin; lymph nodes; mental status; musculoskeletal; neurological; and respiratory.

[j] The Investigator will assess if a patient requires OL rescue medication at each visit of a DB period including Visits 10 and 18 when OL medication is dispensed per protocol. If OL rescue medication is required, the Investigator must complete and submit a Clinical Progression Requiring Rescue Form (Appendix 5). If OL rescue medication is not required, the rescue form must be submitted at the completion of each DB period (ie, Visit 10 and Visit 18).

[k] Vital signs will always be measured prior to having blood drawn for laboratory evaluations.

[l] All adult cohort patients (regardless of their history of CDCA use) and/or their parent/legal guardian will be asked to complete the daily and per-event PRO diaries for bowel function and seizures during the 7 days prior to Visit 4 (OL1), Visit 6 (DB1), Visit 14 (DB2), and throughout the duration of each double-blind period. Reminders regarding the completion of the PRO diary will be sent to patients and/or patient's parent/legal guardian at times specified in the Study Manual. Diaries will be reviewed for compliance at each visit that it is required. If the review of the PRO diary indicates that the patient or the patient's parent/legal guardian is not sufficiently compliant with completion of the diary as described in the Study Manual, the patient or the patient's parent/legal guardian will be retrained on how to complete the diary.

[m] Distribution and training on use of diary only.

[n] Patients who are treatment-naïve or have been treated with CDCA for ≤2 months prior to Screening will also complete the daily and per-event PRO diaries for bowel function and seizures during the 7 days prior to Visit 3 and Visit 5 (OL1). Diaries will also be reviewed for compliance at these visits.

[o] First morning void on 3 mornings within 5 days prior to the visit will be collected and brought to the site visit. For the Screening visit, the patient may bring these urine samples to the site after the Screening visit and before the first day of the OL1 period.

[p] Collected only from patients on anticoagulants at all visits, except Visits 7, 9, 15, and 17.

[q] A list of clinical laboratory assessments is provided in Appendix 3.

[r] Blood draw for thyroid stimulating hormone will only be collected at Screening.
[s] Fasting blood draws for the assessment of lipid parameters will be collected at Visits 2, 6, 10 (EOT1), 14, and 18 (EOT2/EOS/ET).
[t] It is anticipated that some patients will have a worsening of the underlying condition of the disease, such as increasing diarrhea. Any such conditions considered by the Investigator to be worsening of the underlying condition should be reported as AEs. Investigators should also report such AEs as part of the clinical rescue assessment as appropriate (Section 12.4).
[u] EEG has a window of ±1 day to accommodate being conducted by a separate specialist.
[v] Patients will need to hold the first dose of study medication for on-site administration.
[w] In OL1 and OL2, open-label study medication is dispensed at Visit 4 and Visit 12, respectively.

Table 2: Schedule of Assessments for Pediatric Cohort

	V1	V2	V3[a], 5[a], 7[a], 9[a]	V4, 6, 8	V10	V12[a], 14[a], 16[a]	V11, 13, 15, 17	V18
		Titration Period				Treatment Period		
Week	**Screening**	**Titration Start**	**Titration W1, 3, 5, 7**	**Titration W2, 4, 6**	**Treatment Start Day 1[b]**	**W4, 8, 12**	**W2, 6, 10, 14**	**W16 EOT EOS ET**
Visit Window	≤28 days prior to Titration start	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day
Informed Consent/Assent	X							
Inclusion/Exclusion	X							
Genetic Testing for CTX[c]	X							
Serologic test for Hep B, Hep C, HIV	X							
Medical History	X							
CTX Medical History[d]	X							
Prior Medication	X							
Demographics	X							
Pregnancy Test[e]	X	X	X	X	X	X		X
Concomitant Medication	X	X	X	X	X	X		X
Health Status During Prior Week		X		X	X	X		X
CGI-S					X			
CGI-C						X		X[f]
Motor Developmental Milestones[g]		X						X
Ophthalmology Exam[h]		X						X
Physical Examination (including body weight)[i]	X	X		X	X	X		X
Vital Signs[j]	X	X	X	X	X	X		X

	V1	V2	V3[a], 5[a], 7[a], 9[a]	V4, 6, 8	V10	V12[a], 14[a], 16[a]	V11, 13, 15, 17	V18
		Titration Period				Treatment Period		
Week	**Screening**	**Titration Start**	**Titration W1, 3, 5, 7**	**Titration W2, 4, 6**	**Treatment Start Day 1[b]**	**W4, 8, 12**	**W2, 6, 10, 14**	**W16 EOT EOS ET**
Visit Window	≤28 days prior to Titration start	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day	±1 day
Patient Diary[k]	X[l]			X	X	X		X
Urine 23S-pentol (3 first morning voids)[m]	X	X	X	X	X	X		X
Urinalysis Assessments	X	X	X	X	X	X		X
Blood draw for Cholestanol, 7αC4, 7α12αC4, and Plasma Bile Alcohol	X	X		X	X	X		X
Laboratory Assessments (including LFTs)[n, o]	X[p]	X		X	X	X		X
AST, ALT, Bilirubin			X					
Pharmacokinetic Blood Sample Collection[q]		X[q]		X[q]		X[q]		
Adverse Events[r]			Collected continuously					
EEG[s]		X			X	X[t]		X
12-Lead ECG	X			X				X
Study Medication Administration[u]		X	X	X	X	X	X	
Dispense Study Medication		X		X	X	X	X[v]	
Medication Accountability			X	X	X	X		X

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; BCVA = best-corrected visual acuity; CDCA = chenodeoxycholic acid; CGI-C = Clinician Global Impression of Change; CGI-S = Clinician Global Impression of Severity; CTX = cerebrotendinous xanthomatosis; ECG = electrocardiogram; EEG = electroencephalogram; EOS = end of study; EOT = end of treatment; ET = Early Termination; Hep B = hepatitis B virus surface antigen; Hep C = hepatitis C; HIV = human immunodeficiency virus; LFT = liver function test; PK = pharmacokinetics; PRO = Patient-reported outcomes; S = Screening; V = visit; W = week; WOCBP = women of childbearing potential.

Note 1: Laboratory samples required at Screening may be collected across multiple days to reduce blood volume drawn on a single day. Screening laboratory results must be received before Titration Period W1. If genetic results are still pending after 28 days, the screening window may be extended up to 2 additional weeks, with approval by the Medical Monitor. If a patient's screening window is extended, the patient is not required to repeat screening assessments. Laboratory assessments for all other visits should be collected prior to the first daily dose of CDCA.
Note 2: Patients will be contacted (via telephone call) 30 (±7) days after the last dose of study medication to ascertain patient safety (see Section 6.6.2 and Section 6.8 for details).

[a] Assessments for Visits 3, 5, 7, 9, 12, 14, and 16 may be conducted by a home health vendor at an alternative site than the Investigator's site. However, the EEG assessment at Visit 14 must be conducted on site.

[b] Patients will need to hold the first dose of study medication for on-site administration.

[c] If prior genetic confirmation of CTX is not available, blood will be drawn at Visit 1 for gene sequencing. No patient with negative genetic sequencing will be enrolled.

[d] CTX medical history should include a complete list of CTX-related symptoms present at the time of Screening.

[e] Serum pregnancy tests will be performed at Screening for WOCBP. Urine pregnancy tests will be performed at all other visits. A positive urine pregnancy test will be confirmed by a serum test. All WOCBP must have a negative pregnancy test (urine, with positive results confirmed by serum) at every visit.

[f] The CGI-C needs to be completed at this visit if a patient leaves the study early during the treatment period.

[g] Note that after the baseline assessment at Titration start, there will be a trigger question to ask if there have been any changes to previous milestones assessed (either new milestone met or a regression).

[h] Ophthalmology exam includes BCVA and cataracts. The ophthalmology exam has a window of ±1 day to accommodate being conducted by a separate specialist.

[i] At Screening, the physical examination is a full physical examination; at subsequent visits, the physical examination can be an abbreviated exam. Height, weight, and head circumference will be measured at all visits for pediatric cohort patients to be able to determine Failure to Thrive. Physical examinations will include assessment of the following body systems: abdomen; cardiovascular; ear, nose, and throat; eyes; hair and skin; lymph nodes; mental status; musculoskeletal; neurological; and respiratory.

[j] Vital signs will always be measured prior to having blood drawn for laboratory evaluations.

[k] All pediatric cohort patients (regardless of their history of CDCA use) and/or their parent/legal guardian will be asked to complete the daily and per-event PRO diaries for bowel function and seizures during the 7 days prior to Visits 4, 10, 14, and 18. Reminders regarding the completion of the PRO diary will be sent to patients and/or patient's parent/legal guardian at times specified in the Study Manual. Diaries will be reviewed for compliance at Visits 4, 10, 14, and 18. If the review of the PRO diary indicates that the patient or the patient's parent/legal guardian is not sufficiently compliant with completion of the diary as described in the Study Manual, the patient or the patient's parent/legal guardian will be retrained on how to complete the diary.

[l] Distribution and training on diary only.

[m] First morning void on 3 mornings within 5 days prior to the visit will be collected and brought to the site visit. For the Screening visit, the patient may bring these urine samples to the site after the Screening visit and before the first day of the Titration period.

[n] Laboratory tests will be conducted at a central laboratory. During the titration period of the pediatric cohort, testing at a local laboratory is permitted to facilitate titration review if there are delays to central laboratory reporting (eg, lost or hemolyzed blood sample). A list of clinical laboratory assessments is provided in Appendix 3.

[o] Fasting blood draws for the assessment of lipid parameters will be collected at Visits 2 (Titration Start), 8 (Titration Week 6), 12 (Week 4), 16 (Week 12), 18 (Week 16/EOT/EOS/ET).

[p] Blood draw for thyroid stimulating hormone will only be collected at Screening.

[q] Blood sample for plasma PK will be drawn within 1 hour prior to study medication administration. PK samples will be collected predose (t0), and at 1 and 3 hours postdose at Visit 2 (Titration Start). PK samples will be collected at Visits 4, 6, or 8 only if there is a dose change. Additional PK samples will be collected at Visit 12 if a steady dose has been maintained for ≥1 month prior to the visit. If a steady dose was not maintained for ≥1 month prior to Visit 12, PK sample collection may be delayed to Visit 14. If a steady dose was not maintained for ≥1 month prior to Visit 14, PK sample collection may be delayed and will occur at Visit 16. Patients will need to hold first daily dose of study medication for on-site administration to facilitate the correct timing of the blood draw for the PK analysis. A standardized low-fat meal will be provided 45-60 minutes prior to dosing and should be completed within 30 minutes of starting the meal. Predose blood sample for plasma PK will be drawn within 15-30 minutes post completion of the meal. After the first study medication dose, the 0.5 hours post dose draw has a ±5-minute window. The 1, 2, and 3 hour post dose draws have a ±10-minute window.

[r] Adverse event information should be collected by Investigators throughout the study, regardless of where the visit takes place (ie, on-site or homecare).

[s] EEG has a window of ±1 day to accommodate being conducted by a separate specialist.

[t] EEG will be performed only at Visit 14.

[u] Treatment Day 1 occurs one week after Visit 9 (Titration Week 7).

[v] Study medication may be shipped directly to the patient or made available for dispensation at the site.

Table 3: Schedule of Assessments during the Extension of the Open-label Periods in the Adult Cohort

Visit	OL1-A[a]	OL1-B [a, b]	OL2-A[a]	OL2-B[a, b]
Visit #	Unscheduled	Unscheduled	Unscheduled	Unscheduled
Visit Frequency	Every 28 (±3) days from Visit 4 or last dispensation of OL study medication in the OL1 Period	14 (±2) days prior to the start of DB1	Every 28 days (±3) from Visit 12 or last dispensation of OL study medication in OL2 Period	14 (±2) days prior to the start of DB2
Pregnancy Test *(WOCBP only)*[c]	X	X	X	X
Concomitant Medications	X	X	X	X
Physical Examination (including body weight)	O	X	O	X
Vital Signs[d]	O	X	O	X
Urine 23S-pentol (3 first morning voids)[e,f]	O	X	O	X
Urinalysis Assessments[e]	X	X	X	X
Blood draw for Cholestanol, 7αC4, 7α12αC4, and Plasma Bile Alcohol[e]	O	X	O	X
Laboratory Assessments (including coagulation [INR and PT] and LFTs)[e,g,h]	X	X	X	X
Adverse Events[i]	X	X	X	X
On-Site Study Medication Administration[j]	X	X	X	X
Dispense OL Study Medication	X		X	
Medication Accountability	X	X	X	X

Abbreviations: CDCA = chenodeoxycholic acid; DB1 = double-blind period 1; DB2 = double-blind period 2; INR = international normalized ratio; LFT = liver function test; O = optional assessment; OL = open label; OL1 = open-label period 1; OL2 = open-label period 2; PT = prothrombin time; WOCBP = women of childbearing potential; X = required assessment.

[a] Assessments may be conducted by a home health vendor at an alternative site than the Investigator's site.

[b] OL1-B and OL2-B visits are required if a patient completes ≥2 OL1-A or OL2-A visits, respectively.

[c] Urine pregnancy tests will be performed for each WOCBP at all visits in the extension period. A positive urine pregnancy test will be confirmed by a serum test. All WOCBP must have a negative pregnancy test (urine, with positive results confirmed by serum) at every visit.

[d] Vital signs will always be measured prior to having blood drawn for laboratory evaluations.

[e] Laboratory assessments should be collected prior to the first daily dose of CDCA.

[f] First morning void on 3 mornings within 5 days prior to the visit will be collected and brought to the site visit.

[g] Collected only from patients on anticoagulants.

[h] A list of clinical laboratory assessments is provided in Appendix 3.

[i] It is anticipated that some patients will have a worsening of the underlying condition of the disease, such as increasing diarrhea. Any such conditions considered by the Investigator to be worsening of the underlying condition should be reported as adverse events. Investigators should also report such adverse events as part of the clinical rescue assessment as appropriate (Section 12.4).

[j] Patients will need to hold the first dose of study medication for on-site administration.

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