Statistical Analysis Plan

Protocol Number: 018CTXX15001

AN OBSERVATIONAL, MULTICENTER STUDY OF THE PREVALENCE OF CEREBROTENDINOUS XANTHOMATOSIS (CTX) IN PATIENT POPULATIONS DIAGNOSED WITH EARLY-ONSET IDIOPATHIC BILATERAL CATARACTS

Original Protocol: 18 May 2015
Amendment 1: 08 July 2015
Amendment 2: 13 December 2016

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May-28-2021 | 1:59:15 PM EDT
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Version: Final

Date: February 26, 2016 (SAP version 1.0)
April 26, 2021 (SAP version 2.0)
May 28, 2021 (SAP version Final)

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Jun-07-2021 | 1:15:40 AM PDT
86F210734B4F48C3A9F848A9078A910D

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LIST OF TABLES

List of Abbreviations

AE	Adverse Event
CDCA	Chenodeoxycholic Acid
CRFs	Case Report Forms
CSR	Clinical Study Report
CTX	Cerebrotendinous Xanthomatosis
DMC	Data Monitoring Committee
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TOC	Table of Content
WHO	World Health Organization

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used to assess the prevalence of cerebrotendinous xanthomatosis (CTX) in patient populations diagnosed with early-onset idiopathic bilateral cataracts. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol, 018CTXX15001 dated 13 December 2016, and case report forms (CRFs) for details of study conduct and data collection.

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

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To calculate the prevalence of CTX in a patient population diagnosed between the ages of 2 and 21 years old (inclusive) with early-onset idiopathic bilateral cataracts.

2.1.2 Secondary Objective

To assess other manifestations of CTX within patients presenting with idiopathic bilateral cataracts.

2.2 Endpoints

- Proportion of patients with positive CTX test based on
  - Elevated plasma cholestanol level ≥ 0.4 mg/dL (4 μg/mL) or
  - Positive urine bile alcohol results among those with urine sample
- Proportion of patients with confirmed CTX based on genetic testing for mutations associated with CTX among those with non-missing plasma cholestanol or urine bile alcohol results
- Proportion of patients with confirmed CTX based on genetic testing for mutations associated with CTX among those with elevated plasma cholestanol levels or positive urine bile alcohol results
- Plasma cholestanol, plasma cholesterol, and urine bile alcohol levels

- Incidence of serious adverse events (SAEs) associated with study procedures (i.e. a blood draw)

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is an observational, multicenter study to determine the prevalence of CTX in patient populations diagnosed or treated for early-onset idiopathic bilateral cataracts, identified through a chart review of patients who were seen at each study site prior to that site's initiation or by entering care at the site while the site is participating in the trial. Approximately 500 patients are to be enrolled in this study.

Participation will be limited to persons between the ages of 2 to 21 years old (inclusive) at the time of diagnosis with idiopathic bilateral cataracts. For specific inclusion/exclusion criteria, please refer to the study protocol, 018CTXX15001.

Participation in the study is limited to one or more study visit(s) for collection of study data, including a blood draw and urine sample (if provided). These procedures will typically be completed in a single visit, but additional visits are permitted if a blood sample is not obtained or a replacement blood sample is required for any reason. The length of a patient's participation will be from the time the informed consent form is signed until results of the CTX testing have been obtained and reported to the patient. Study participation for patients who have normal test results for plasma cholestanol and urine bile alcohol (if urine sample is provided) will be complete after reporting of these test results to the patient. Study participation for patients who require genetic testing will be complete after reporting of these test results to the patient. For a complete schedule of events, please refer to 9.1.

3.2 Treatments

No treatments will be administered during this observational study.

4 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

As an observational study, there are no statistical hypotheses regarding treatment effects. Rather, displays and comparisons of patient data will primarily utilize descriptive statistics, as noted below.

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by presenting the number of patients and percentage for each category.

Minimum and maximum 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. Standard deviation and 95% confidence intervals 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.

All summary tables will be based on pooled data across centers. By-patient listings, including data collected at all visits, will be sorted by patient number, study visit, and then by date/time of the records.

Analyses will be performed using SAS® version 9.4.

4.1 Analysis Sets

All patients who signed the informed consent will be included in the Screened Set. All patients who signed the informed consent and whose eligibility was established will be included in the Enrolled Set. All screened patients who undergo invasive study procedures (i.e. a blood draw) will be included in the Safety Set.

4.2 Assessment Windows

The study schedule of events appears in 9.1. Study patients are expected to attend a single clinic visit, during which all study procedures will be performed. No analysis windows are planned regarding data collected in the study.

4.3 Handling of Multiple Lab Observations

If multiple lab records exist at a collection time point, the repeated record will be used for data summary.

4.4 Handling of Missing or Invalid Data

Missing data will remain missing. Missing data including partial dates will not be imputed. Data points that appear to be invalid will be queried for correction or confirmation by the clinical site.

4.5 Interim Analysis

No interim analysis is planned. There is no Data Monitoring Committee (DMC) for this study.

4.6 Determination of Sample Size

Approximately 500 patients will be enrolled in the study. Because this is an observational, non-interventional study, no power calculation has been performed. The study size is considered to be appropriate to investigate the prevalence of CTX among patients diagnosed or treated for early-onset idiopathic bilateral cataracts.

5 STUDY PATIENTS

5.1 Analysis Sets

The number and percentage of patients in each analysis set will be summarized. The data will also be listed.

5.2 Subject Eligibility

Subject eligibility for the study (inclusion and exclusion criteria failures) will be listed for the Screened Set.

5.3 Disposition of Patients

Patient disposition will be presented for the Screened Set. The number and percentage of patients who complete or discontinue the study, as well as the discontinuation reasons, will be provided. In addition, the number of patients who have plasma samples, urine samples, or genetic tests will be summarized.

A patient listing for study disposition will be provided for the Screened Set.

5.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, and ethnicity) will be analyzed using the Enrolled Set. Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be reported for continuous variables, whereas counts and percentages will be reported for categorical variables. A listing of demographics will be provided.

5.5 Medical History

A targeted medical history is collected for all patients enrolled in the study. It includes any history of, or current manifestation of, signs and symptoms commonly associated with CTX. Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The number and percentage of patients with each medical condition will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the Enrolled Set.

All medical history data (including family history) will be listed.

5.6 Prior and Concomitant Medications

Concomitant medications and therapies the patient has taken in the week prior to enrollment will be recorded during the study visit(s). Concomitant medications will be coded using WHODrug Global B3 released in March 2021. Each verbatim term 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 chemical substance (ATC level 5).

The number and percentage of patients using concomitant medications will be summarized by ATC level 2 and preferred term using the Enrolled Set.

All prior and concomitant medication data will also be listed.

5.7 CTX Testing Analyses

Results of CTX testing (plasma cholestanol, plasma cholesterol, urine bile alcohol, and genetic testing) will be summarized using the Enrolled Set when data are available. Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be reported for continuous variables. Frequency counts and percentages will be reported for categorical variables. A listing of CTX testing data will also be provided.

Additionally, the prevalence of CTX will be examined on the basis of the following percentages, reported together with 95% confidence intervals:

1. Patients with a plasma cholestanol level ≥ 0.4 mg/dL (4 µg/mL).
2. Patients with a positive test for urine bile alcohol.
3. Patients with a plasma cholestanol level ≥ 0.4 mg/dL (4 µg/mL) or a positive test for urine bile alcohol.
4. Patients with a positive genetic test for CTX.
5. Patients with a positive genetic test for CTX among those with elevated plasma cholestanol level or positive urine bile alcohol result.

For criteria 1 and 2, denominator of the percentage will be based on the number of patients with non-missing results. For criteria 3 and 4, denominator of the percentage will be based on the number of patients with either plasma cholestanol or urine bile alcohol results reported. Two-sided 95% confidence intervals will be calculated using the exact Clopper-Pearson method.

SAS® sample code for the Clopper-Pearson method:

```
data clop_ci;
set lb;
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;
```

Table 1 lists the mapped genetic testing results that will be used for summary.

Table 1: Genetic Testing Results

Mapped Genetic Testing Result	Reported Genetic Testing Result
Positive	Positive
	Likely positive
Negative	Inconclusive
	Negative
	No mutations identified
	No biochemical evidence of CTX
	No mutations were identified
	No mutations found

6 SAFETY ANALYSIS

Safety analysis will be based on the Safety Set. The only planned safety analysis is procedure-related or possibly related AEs.

6.1 Adverse Events

An AE is any untoward medical occurrence associated with the performance of a study procedure in a clinical investigation patient. A procedure-related AE is an AE occurring during a clinical study that is considered by the investigator or the medical monitor (or designee) to be related to a research procedure. For example, a procedure-related AE may be an untoward event related to a medical procedure required by the protocol (i.e. a blood draw in the case of this study).

Only SAEs determined by the investigator to be possibly related or related to study procedures are planned to be recorded for this study; however, all procedure-related or possibly related AEs will be analyzed if collected. All AEs will be coded using MedDRA version 24.0.

An overall summary of procedure-related or possibly related AEs will be provided, which includes:

- The number and percentage of patients experiencing a procedure-related or possibly related AE;
- The number and percentage of patients experiencing a procedure-related or possibly related AE by greatest severity;
- The number and percentage of patients experiencing a procedure-related or possibly related AE leading to study withdrawal;
- The number and percentage of patients experiencing a procedure-related or possibly related AE resulting in death.

Additionally, the number and percentage of patients experiencing a procedure-related or possibly related AE will be summarized by SOC and PT.

Data of procedure-related or possibly related AEs will also be listed.

7 CHANGES TO THE PLANNED ANALYSES FROM THE PREVIOUS SAP

The current SAP is based on the study protocol amendment 2, dated 13DEC2016; whereas the previous SAP (version 1.0, dated 26FEB2016) uses the protocol amendment 1, dated 08JUL2015.

While study endpoints and general statistical methods stay the same between the two versions of SAP, more details have been added on both in the current version, and updates have been made to reflect the changes in the latest protocol. Appendix **Error! Reference source not found.** provides a summary of key changes to the planned analyses from the previous SAP.

8 TABLE OF CONTENT (TOC) FOR OUTPUTS

Table 2: TOC for Tables and Listings

Output Type	Output Name	Analysis Set
Table	Analysis Sets	Screened Set
Table	Patient Disposition	Screened Set
Table	Demographics and Baseline Characteristics	Enrolled Set
Table	CTX Medical History	Enrolled Set
Table	Concomitant Medications	Enrolled Set
Table	CTX Testing Results	Enrolled Set
Table	Prevalence of CTX	Enrolled Set
Table	Overall Summary of Procedure-related or possibly related AEs	Safety Set
Table	Procedure-related or possibly related AEs by SOC and PT	Safety Set
Listing	Analysis Sets	Screened Set
Listing	Subject Eligibility	Screened Set
Listing	Patient Disposition	Screened Set
Listing	Demographics and Baseline Characteristics	Enrolled Set
Listing	CTX Medical History	Enrolled Set
Listing	Family History	Enrolled Set
Listing	Concomitant Medications	Enrolled Set
Listing	CTX Testing Results	Enrolled Set

Listing	Procedure-related or possibly related AEs	Safety Set

9 APPENDIX

9.1 Schedule of Events

	Screening/Enrollment	**CTX Testing (if Necessary)**
Confirm Study Eligibility	X	
Obtain Informed Consent	X	
Demographics	X	
Targeted Medical History[1]	X	
Concomitant Medications/Therapies[2]	X	
Blood draw for Plasma Cholestanol testing and Genetic testing[3]	X	
Urine collection for Bile Alcohol testing (if urine sample is provided)[4]	X	
Serious Adverse Events related to procedures	X	
Genetic Testing for CTX[5]		X
Photographic Documentation of Cataracts[6]		X
Follow-Up Notification of Results	X[7]	X[8]
Study Discontinuation	X[7]	X[8]

[1] History of or current manifestations of signs and symptoms commonly associated with CTX.
[2] Concomitant medications and therapies during the week prior to enrollment will be collected.
[3] Blood draw may be collected in conjunction with other scheduled treatments during medical care that is separate from the clinical study.
[4] Urine sample (if provided) may be collected in conjunction with other scheduled treatments during medical care that is separate from the clinical study.

[5] Will be completed if patient plasma cholestanol level is ≥0.4 mg/dL (4μg/mL) or urine bile alcohol is positive (if urine sample is provided).
[6] If available, collected for patients who have been diagnosed with CTX.
[7] For those patients with *normal results* for plasma cholestanol <0.4 mg/dL (4 μg/mL) and urine bile alcohol is negative (if urine sample is provided), participation ends after tests results have been communicated to the patient and study discontinuation page is completed.
[8] For those patients who *require genetic testing*, participation ends after reporting of test results to the patient, and study discontinuation page is completed.

9.2 Key Changes to the Planned Analyses from the Previous SAP

Section	SAP Version 1.0	Current SAP
Primary Objective	Patient population diagnosed up to age 21	Patient population diagnosed between the ages of 2 and 21 years old (inclusive)

Other Endpoints	CTX testing will be done using plasma cholestanol and urine bile alcohol levels (if urine sample is provided) for all study participants. Genetic testing for mutations associated with CTX will be done for all study participants with elevated plasma cholestanol levels or positive urine bile alcohol results (if urine sample is provided).	• Proportion of patients with positive CTX test based on
		  ○ Elevated plasma cholestanol level ≥ 0.4 mg/dL (4 µg/mL) or
		  ○ Positive urine bile alcohol results among those with urine sample
		• Proportion of patients with confirmed CTX based on genetic testing for mutations associated with CTX among those with non-missing plasma cholestanol or urine bile alcohol results.
		• Proportion of patients with confirmed CTX based on genetic testing for mutations associated with CTX among those with elevated plasma cholestanol levels or positive urine bile alcohol results.
		• Plasma cholestanol, plasma cholesterol, and urine bile alcohol levels.

Study Design	Participation in the study is limited to one clinic visit.	Participation in the study is limited to one or more study visit(s) for collection of study data, including a blood draw

		and urine sample (if provided). These procedures will typically be completed in a single visit, but additional visits are permitted if a blood sample is not obtained or a replacement blood sample is required for any reason.
General Considerations for Data Analysis	No description on the precision of the summary	Minimum and maximum 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. Standard deviation and 95% confidence intervals 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.
Analyses Sets	All patients will be included in the analysis dataset. All study patients who undergo invasive study procedures (i.e. a single blood draw) will be included in the safety dataset.	All patients who signed the informed consent will be included in the Screened Set. All patients who signed the informed consent and whose eligibility was established will be included in the Enrolled Set. All enrolled patients who undergo invasive study procedures (i.e. a blood draw) will be included in the Safety Set.
Handling of Multiple Lab Observations	No description	If multiple lab records exist at a collection time point, the repeated record will be used for data summary.
Analysis Sets	No description	The number and percentage of patients in each analysis set will be summarized. The data will also be listed.

Subject Eligibility	No description	Subject eligibility for the study (inclusion and exclusion criteria failures) will be listed for the Screened Set.
Disposition of Patients	A table of counts of all safety patients who complete the study will be provided. Reasons for not completing study as planned will be tabulated. A patient listing for early discontinuations and reasons for discontinuation will be provided for the safety analysis set. The number of patients with evaluable CTX testing data based on plasma cholestanol levels, urine bile alcohol levels, and genetic testing will also be summarized.	Patient disposition will be presented for the Enrolled Set. The number and percentage of patients who complete or discontinue the study, as well as the discontinuation reasons, will be provided. In addition, the number of patients who have plasma samples, urine samples, or genetic tests will be summarized. A patient listing for study disposition will be provided for the Enrolled Set.
Demographics and Baseline Characteristics	Demographics and baseline characteristics (age/age categories, sex, race, ethnicity, and baseline characteristics) will be analyzed using the safety analysis set.	Demographics and baseline characteristics (age, sex, race, and ethnicity) will be analyzed using the Enrolled Set.
Medical History	A targeted CTX specific medical history will be collected for all patients enrolled in the study. It includes any history of or current manifestation of signs and symptoms commonly associated with CTX. Medical history terms will not be coded. Information collected from the targeted CTX specific	A targeted medical history is collected for all patients enrolled in the study. It includes any history of, or current manifestation of, signs and symptoms commonly associated with CTX. Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The number and percentage of patients with each medical condition will be summarized

	medical history such as, ophthalmological disorders other than cataracts, xanthomas, etc. will be summarized in the same fashion as the demographics. Should coding of medical history term be required at a later date, all medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 (or higher). The number and percent of patients with each medical condition and surgical procedure will be presented for each SOC and PT for the safety analyses set. All medical history data will also be listed.	by System Organ Class (SOC) and Preferred Term (PT) for the Enrolled Set. All medical history data (including family history) will be listed.
Prior and Concomitant Medications	Concomitant medications and therapies the patient has taken in the week prior to enrollment will be recorded during the single study visit. Concomitant medications will be coded using World Health Organization (WHO) drug classifications. The number and percent of safety patients using concomitant medications will be tabulated by drug class and by preferred name using the safety analysis set. All prior and concomitant medication data will be listed, sorted by investigative site and patient number, start	Concomitant medications and therapies the patient has taken in the week prior to enrollment will be recorded during the study visit(s). Concomitant medications will be coded using WHODrug Global B3 released in March 2021. Each verbatim term 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 chemical substance (ATC level 5).

	and stop date. Information listed will include medication, indication, dose, unit, frequency and route of administration.	The number and percentage of patients using concomitant medications will be summarized by ATC level 2 and preferred term using the Enrolled Set. All prior and concomitant medication data will also be listed.
CTX Testing Analyses	Results of CTX testing (plasma cholestanol level, urine bile alcohol results (if urine sample is provided), and genetic testing) will be summarized using all patients with evaluable data for each assessment. Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be reported for continuous variables. Frequency counts and percentages will be reported for categorical variables. A listing of CTX testing data will also be provided. Specifically, the prevalence of CTX will be examined on the basis of the following percentages, reported together with 95% confidence intervals: 1. Patients with a plasma cholestanol level $\geqslant$ 0.4 mg/dL (4 mcg/mL). 2. Patients with a plasma cholestanol level $\geqslant$ 0.4 mg/dL (4 mcg/mL) and a positive test for urine bile alcohol.	Results of CTX testing (plasma cholestanol, plasma cholesterol, urine bile alcohol, and genetic testing) will be summarized using the Enrolled Set when data are available. Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be reported for continuous variables. Frequency counts and percentages will be reported for categorical variables. A listing of CTX testing data will also be provided. Additionally, the prevalence of CTX will be examined on the basis of the following percentages, reported together with 95% confidence intervals: 1. Patients with a plasma cholestanol level $\geq$ 0.4 mg/dL (4 μg/mL). 2. Patients with a positive test for urine bile alcohol. 3. Patients with a plasma cholestanol level $\geq$ 0.4 mg/dL (4 μg/mL) or a positive test for urine bile alcohol. 4. Patients with a positive genetic test for CTX.

	3. Patients with a plasma cholestanol level ⩾ 0.4 mg/dL (4 mcg/mL), a positive test for urine bile alcohol, and a positive genetic test for CTX.
	
	Two-sided 95% confidence intervals will be calculated using the Newcombe-Wilson score method.
		5. Patients with a positive genetic test for CTX among those with elevated plasma cholestanol level or positive urine bile alcohol result.
		
		For criteria 1 and 2, denominator of the percentage will be based on the number of patients with non-missing results. For criteria 3 and 4, denominator of the percentage will be based on the number of patients with either plasma cholestanol or urine bile alcohol results reported. Two-sided 95% confidence intervals will be calculated using the exact Clopper-Pearson method.
		
		SAS® sample code for the Clopper-Pearson method:
		
		`data clop_ci;`
		`set lb;`
		`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;`
		
		Table 1 lists the mapped genetic testing results that will be used for summary.