OBSERVATIONAL CLINICAL STUDY PROTOCOL

An Observational, Multicenter Study of the Prevalence of Cerebrotendinous Xanthomatosis (CTX) in Patient Populations Diagnosed with Early-Onset Idiopathic Bilateral Cataracts

Protocol Number: **018CTXX15001**

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Amendment 2: 13 December 2016

Sponsor:	Retrophin, Inc. 12255 El Camino Real, Suite 250 San Diego, CA 92130 USA
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This protocol was designed and will be conducted, recorded, and reported in accordance with the principles of GCP as stated in the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use and any applicable national and regional laws. I have read and agree to abide by the requirements of this protocol.
Investigator Signature Date
Investigator Name (please print or type)

Signature Page for Sponsor's Representative

I have reviewed and approved Amendment 2 to the protocol entitled, "An Observational, Multicenter Study of the Prevalence of Cerebrotendinous Xanthomatosis (CTX) in Patient Populations Diagnosed with Early-Onset Idiopathic Bilateral Cataracts"

13 December 2016

Randall Marshall, MD — Date
Executive Medical Director, Retrophin, Inc.

1 SYNOPSIS

NAME OF COMPANY
Retrophin, Inc.
12255 El Camino Real, Suite 250
San Diego, CA 92130
USA
NAME OF FINISHED PRODUCT
Not Applicable
NAME OF ACTIVE INGREDIENT
Not Applicable

TITLE:

An Observational, Multicenter Study of the Prevalence of Cerebrotendinous Xanthomatosis (CTX) in Patient Populations Diagnosed with Early-Onset Idiopathic Bilateral Cataracts

PROTOCOL NO.:

018CTXX15001

INVESTIGATOR STUDY SITES:

This multi-center study will involve approximately 50 study sites in the United States.

OBJECTIVES:

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

Secondary Objective:

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

METHODOLOGY:

This is an observational, multicenter study to determine the prevalence of CTX in patient populations diagnosed with early-onset idiopathic bilateral cataracts. Patients who are potentially eligible for study participation will be 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.

NUMBER OF PATIENTS:

Approximately 500 patients will be enrolled in this study.

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

A patient must meet all of the following criteria to be eligible for this study.

1. The patient and/or their parent/legal guardian is willing and able to provide signed informed consent and the patient, if <18 years of age, is willing to provide assent if deemed able to do so. If the patient is ≥ 18 years of age but has diminished capacity to provide informed consent, their parent/legal guardian is willing and able to provide signed informed consent and the patient is willing to provide assent, if deemed able to do so.
2. The patient has a diagnosis of idiopathic bilateral cataracts.

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Not Applicable

3. The patient is between the ages of 2 to 21 years old (inclusive) at the time of diagnosis with idiopathic bilateral cataracts.

Exclusion Criteria:

A patient who meets any of the following criteria will be excluded from this study.

1. The patient has a diagnosis of cataracts with known etiology other than CTX.
2. The patient has a diagnosis of CTX.
3. The patient has cataracts caused by cataractogenic treatments.
4. The patient has taken or is currently taking cholic acid or chenodeoxycholic acid.
5. The patient has received an investigational product in an interventional clinical trial in the past 30 days.
6. The patient and/or their parent/legal guardian, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

DOSE/ROUTE/REGIMEN (TEST ARTICLE):

Not applicable – this is an observational study

REFERENCE TREATMENT:

Not applicable

CRITERIA FOR EVALUATION:

The plasma cholestanol levels and/or urine bile alcohol results (if urine sample is provided) will be used to determine whether genetic testing is indicated. Genetic testing, if indicated, will be used to determine the prevalence of CTX.

STATISTICAL METHODS:

Power and Sample Size:

Approximately 500 patients will be enrolled in the study. Because this is an observational 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.

Analysis Sets:

All study patients for whom results of cholestanol or urine bile alcohol testing (if urine sample is provided) are available will be included in the analysis dataset. All study patients who undergo study procedures (i.e., a blood draw) will be included in the safety dataset.

Demographics and Baseline Characteristics:

Descriptive statistics will be used.

Efficacy:

There are no efficacy endpoints in this descriptive, observational study.

NAME OF COMPANY Retrophin, Inc. 12255 El Camino Real, Suite 250 San Diego, CA 92130 USA **NAME OF FINISHED PRODUCT** Not Applicable **NAME OF ACTIVE INGREDIENT** Not Applicable
Safety: Serious Adverse Events associated with study procedures (i.e., a blood draw) will be listed. **CTX Testing:** Plasma cholestanol levels, urine bile alcohol results (if urine sample is provided), and results of genetic testing for CTX will be summarized using descriptive statistics.

2 TABLE OF CONTENTS

2.1 List of Abbreviations

AE	Adverse Event
CDCA	Chenodeoxycholic Acid
CTX	Cerebrotendinous Xanthomatosis
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
FDA	The United States Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PI	Principal Investigator
SAE	Serious Adverse Event
SOPs	Standard Operating Procedures
US	United States
WHO	World Health Organization

3 INTRODUCTION

Genetic basis of cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive disease caused by mutations in the cytochrome P450 *CYP27A1* gene that result in production of a defective sterol 27-hydroxylase enzyme. Physiologically, the CYP27 enzyme is present in mitochondria and involved in bile acid synthesis. If normal, it functions by introducing a hydroxyl group in the C27 position, as the first step in shortening the steroid side chain of 7α-hydroxylated intermediates or other substrates such as cholesterol. In CTX patients, reduced bile acid synthesis causes decreased inhibition of cholesterol 7α-hydroxylase activity and increased formation of 7α-hydroxy-4-cholesten-3-one, which accumulates and leads to production of cholestanol and abnormal 25-hydroxylated bile alcohols.

The upregulation of both cholesterol and cholestanol synthesis leads to an accumulation of cholesterol in cholestanol-containing xanthomas in a variety of body tissues over time. This is the chief pathophysiologic mechanism responsible for many of the symptoms associated with CTX.[1]

Verrips et al [2] reported on genotypes and genotype/phenotype correlation in 58 CTX patients they studied and 67 patients reported in published literature (total of 125 patients from 74 unrelated families). Among these patients there were 37 different mutations in the *CYP27A1* gene: 16 were missense mutations; 3 were deletions; 1 was an insertion; 8 were splice site mutations; 6 were nonsense mutations; and 3 mutations were in the last nucleotides of exons. Fifteen of the 37 mutations (41%) were located in the region of exons 6-8 of the *CYP27A1* gene. Striking phenotypic heterogeneity was observed, even within families. A genotype-phenotype correlation analysis was done for 79 homozygous patients from 45 families harboring 23 different mutations, but no genotype-phenotype correlation could be established. The authors concluded that a given mutation may result in the same or different CTX phenotypes, and that mutations at different sites of the *CYP27A1* gene may likewise result in the same or different phenotypes.

Symptoms of cerebrotendinous xanthomatosis

CTX is typically a highly progressive disease, with case reports of symptoms that first appear at any time from birth through adulthood and then worsen over time. There are a wide variety of clinical symptoms and considerable morbidity in CTX patients, with disabling effects in many body systems and a high burden of illness. The most common manifestations reported are gait

disturbance, cataracts, decreased intelligence, dementia, impaired reflexes, pyramidal and cerebellar signs, dysarthria, epilepsy, neuropathy, ataxia, muscle atrophy, foot deformities, chronic diarrhea, and xanthomas, particularly of the Achilles tendon. Psychiatric, nervous system, and musculoskeletal manifestations predominate.[3, 4] The natural history of CTX has not been thoroughly studied, but case reports for several hundred patients have been published. Based on these case reports and the published review articles about CTX, the symptoms that occur earliest in children with CTX are chronic diarrhea, developmental delay, behavioral disorders, seizures, and cataracts.

Prevalence of cerebrotendinous xanthomatosis

Published articles generally state that the actual prevalence of CTX is unknown, with many patients thought to be unidentified; but the prevalence is widely assumed to be rare. Three publications have presented attempts to estimate the prevalence of CTX in specific ethnic groups.

Berginer and Abeliovich [5] noted that there had been 6 individuals from 3 Jewish families of Moroccan origin diagnosed with CTX over a 5-year period in the Beer-Sheba region of Israel. Because approximately 70,000 Jews of Moroccan origin lived in this region, the authors reported a CTX frequency of 6/70,000 for this community. Whether this represents a good estimate of prevalence for this ethnic group generally or how it compares to prevalence in other ethnic groups is not known.

Lorincz et al [6] used a genetic analysis of a CTX patient with German-English ancestry with consanguineous parents (second cousins) and her family members to estimate the prevalence of CTX. Molecular genetic analysis was performed using DNA extracted from peripheral blood leukocytes of the patient, her family members, and 115 white volunteer controls of European ancestry. The CYP27A1 exon from each sample was amplified by polymerase chain reaction. Sequencing of the amplified DNA resulted in the identification of a single homozygous substitution of thymidine for cytosine at complementary DNA position 1384 for the patient. Sequence analysis of DNA from both parents showed that they were both heterozygous, cytosine/ thymidine, at the same position. Unexpectedly, one control patient who was heterozygous for the same mutation at position 1384 was identified. Haplotype analysis of DNA from the heterozygous control patient was not performed, but there was no known familial relationship to the patient. The observed frequency of the mutation calculated for the control group was 8.7×10^{-3}. The prevalence of CTX due to this one homozygous mutation was

estimated at 1.9 per 100,000. The overall prevalence of CTX due to all known mutations was estimated to be "several-fold" higher, approximately 3 to 5 per 100,000.

Pilo-de-la-Fuente et al [7] reported on data for all patients diagnosed with CTX between 1992 and 2008 at any of the main reference centers for genetic diagnosis of CTX in Spain. CTX diagnosis was based on clinical features and mutational analysis with one exception, a patient diagnosed in 1992 for whom DNA was not available. Twenty-five CTX patients, from 19 families were identified. The authors estimated a minimum prevalence of 1/1,800,000 individuals in Spain.

Diagnosis of cerebrotendinous xanthomatosis

Suspicion of CTX is typically based on clinical symptoms, most often including chronic diarrhea with infantile onset, bilateral cataracts in children, and the appearance of xanthomas on the Achilles tendons, extensor tendons of the elbows and hands or patellar tendons, often by the third decade of life.[8] Biochemical abnormalities that indicate likely CTX are elevated bile and plasma cholestanol levels, increased ratio of serum cholestanol/cholesterol, increased urinary excretion of bile alcohol glucuronides and diminished biliary concentrations of chenodeoxycholic acid (CDCA).[9, 10] In clinical practice, elevated plasma cholestanol and urine bile alcohol are used as tests for probable CTX, with the diagnosis confirmed by a finding of mutation in the *CY 27A1* gene on chromosome 2q35-qter.[8, 11]

Treatment of cerebrotendinous xanthomatosis

CDCA has long been considered to be the standard of care for the condition. CDCA treatment is effective in preventing adverse clinical manifestations of the disease from occurring or progressing if the treatment is administered early enough.[12] Though the extent of published evidence is limited, available clinical studies and case reports suggest that the ability of CDCA treatment to reverse existing adverse clinical manifestations is mixed, with some manifestations being at least partially reversed and others stabilizing. Initiation of CDCA treatment as early as possible is universally recommended by experts, before irreversible damage has occurred.[13] There are also published reports of cholic acid being used instead of CDCA.[14, 15, 27] Recently, cholic acid has been approved for the treatment of bile acid synthesis disorders, including CTX [27].

Other treatments that have been reported to be combined with CDCA treatment in clinical practice are: Vitamin D, Vitamin E, anti-seizure medications, L-dopa-carbidopa, anti-psychotic medications, anxiolytics, anti-depressants and statins.[16-23] In a small number of reported

cases, statins were given without CDCA.[22, 24] Apheresis treatment has also reported in a small number of cases, in combination with CDCA or alone.[7, 25, 26]

Because idiopathic bilateral cataracts occur at an early age in many children with CTX, biomarker testing of these children presents an opportunity for diagnosing children with CTX. Since initiation of treatment as early as possible may prevent or reverse the development of debilitating symptoms of CTX, the opportunity to use contact with health care providers in connection with pediatric cataract evaluation and treatment is a promising avenue for disease detection and prevention.[12]

3.1 Summary of Potential Risks

This is an observational study with no drugs or treatments that could have associated risks. Drawing blood for diagnostic testing by venipuncture is an invasive procedure that may occasionally be associated with adverse events such as pain, bleeding, syncope, ecchymosis or infection.

3.2 Summary of Potential Benefits

Patients in this study will not experience personal benefits from study participation in this non-treatment, prevalence study. However, patients with CTX who are identified through participation in the study may seek medical care for CTX as a result of the diagnosis made during study participation. Study participants who test positive for CTX will be informed of the diagnosis by the Investigator and advised to seek appropriate medical evaluation and care.

4 STUDY OBJECTIVES

The primary objective of this study is 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.

The secondary objective of this study is to assess other manifestations of CTX within patients presenting with idiopathic bilateral cataracts.

5 INVESTIGATIONAL PLAN

5.1 Endpoints

5.1.1 Efficacy Endpoints

This study has no treatments and no efficacy endpoints.

5.1.2 Safety Endpoints

Only serious adverse events (SAEs) associated with study procedures (i.e., a blood draw) will be recorded.

5.1.3 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). Genetic testing will be performed at a Clinical Laboratory Improvement Amendment (CLIA) certified laboratory. The results of testing for plasma cholestanol and urine bile alcohol (if urine sample is provided), and genetic testing (when indicated) will be reported to the Investigator at each clinical site. The results of plasma total cholesterol (fasting or nonfasting, if > 190 mg/dL) may also be reported to the Investigator. Samples will be retained only for the duration of testing of plasma cholestanol, urine bile alcohol (if urine sample is provided), plasma total cholesterol (if applicable) and genetic testing (when indicated). Samples will not be used for future, presently unidentified research.

5.2 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.

5.2.1 Site of Study Procedures

Study procedures may be completed at investigational sites, either during a visit for the clinical study, or in conjunction with other scheduled visits separate from the clinical study. Alternatively, study procedures may be completed during a visit at an alternate location (such as but not limited to a home, daycare or workplace) provided by personnel from a home health care company licensed and authorized to perform these procedures.

5.2.2 Completion of a Patient's Participation in the Study and Overall Study Completion

5.2.2.1 Completion of a Patient's Participation in the Study

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 blood draw and urine sample (if provided) may be collected in conjunction with other scheduled treatments separate from the clinical study. 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. The Investigator will contact the patient to share the results of the plasma cholestanol, urine bile alcohol, plasma total cholesterol (if applicable) and genetic testing for example, via a follow-up phone call. For those participants who require genetic testing, the Investigator will provide a referral for appropriate follow-up care, if clinically indicated, to the patient or patient's parent or guardian. Genetic counseling will not be provided per the study.

5.2.2.2 Premature Patient Discontinuation from the Study

Patients are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor.

5.2.2.3 Overall Study Completion

The study will be considered to be complete when CTX testing, including cholestanol, urine bile alcohol (if urine sample is provided) and genetic testing (if indicated), has been completed and recorded for all patients, and patients have been informed of the testing results.

5.3 Discussion of 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. The number of patients to be enrolled in this study is considered appropriate for such a study. Because this is an observational study, no power calculation has been performed.

6 PATIENT POPULATION AND SELECTION

6.1 Inclusion Criteria

A patient must meet all of the following criteria to be eligible for this study.

1. The patient and/or their parent/legal guardian is willing and able to provide signed informed consent and the patient, if <18 years of age, is willing to provide assent if deemed able to do so. If the patient is ≥18 years of age but has diminished capacity to provide informed consent, their parent/legal guardian is willing and able to provide signed informed consent and the patient is willing to provide assent, if deemed able to do so.
2. The patient has a diagnosis of idiopathic bilateral cataracts.
3. The patient is between the ages of 2 to 21 years old (inclusive) at the time of diagnosis with idiopathic bilateral cataracts.

6.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from this study.

1. The patient has a diagnosis of cataracts with known etiology other than CTX.
2. The patient has a diagnosis of CTX
3. The patient has cataracts caused by cataractogenic treatments.
4. The patient has taken or is currently taking cholic acid or chenodeoxycholic acid.
5. The patient has received an investigational product in an interventional clinical trial in the past 30 days.
6. The patient and/or their parent/legal guardian, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

7 TREATMENTS

No treatments will be administered during this observational study.

7.1 Prior and Concomitant Medications and Therapeutic Procedures

Concomitant medications and therapies the patient has taken in the week prior to enrollment will be recorded during the study visit(s). Patients will be excluded from enrollment in the study if they have taken or are currently taking cholic acid or chenodeoxycholic acid or if they have received an investigational product in an interventional clinical trial within 30 days before enrollment. Patients excluded for receiving an investigational product may later be included in the study after the 30-day period has passed.

7.2 Method of Assigning Patients to Treatment

Not applicable.

7.3 Blinding and Randomization

Not applicable.

7.4 Treatment Compliance

Not applicable.

8 STUDY ASSESSMENTS

8.1 Study Schedule of Events

The study schedule of events appears in Appendix.

Study participants will attend a clinic visit or receive a visit at an alternate location (such as but not limited to home, daycare or workplace) during which the following procedures will be performed:

- Confirmation of study eligibility
- Informed consent
- Targeted medical history
- Collection of demographic data and concomitant medications and therapies
- Collection of blood and urine (if urine sample is provided) for testing

The blood draw and urine sample (if provided) may be collected in conjunction with other scheduled treatments separate from the clinical study.

These procedures will 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.

Written informed consent must be obtained prior to any protocol-required procedure. Remote consenting of subjects by authorized study personnel, using telephone, mail, fax or other communication means, is permitted.

8.2 Demographic and Screening Assessments

Demographic data will be collected at the study visit. No physical examination will be performed as part of the study.

A targeted 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.

8.3 Efficacy Assessments

Not applicable.

8.4 Safety Assessments

Any SAEs associated with study procedures (i.e., blood draw) will be recorded.

8.5 CTX Testing (if necessary)

Blood and urine (if urine sample is provided) will be collected during the study for testing of the plasma cholestanol and urine bile alcohol levels. The following is applicable:

- If the plasma cholestanol level is < 0.4 mg/dL (4 µg/mL) and urine bile alcohol is negative (if urine sample is provided) then no further testing is required.
- If the plasma cholestanol level is ≥ 0.4 mg/dL (4 µg/mL) or urine bile alcohol is positive (if urine sample is provided), this will prompt genetic testing.
    - If a patient is diagnosed with CTX, photographic documentation of cataracts, if available, will be obtained from the patient's clinical records for the study data files.
- The Investigator may be notified if the plasma total cholesterol level (fasting or nonfasting) is > 190 mg/dL. These results are provided for medically informative purposes only.

9 ADVERSE EVENT REPORTING

9.1 Adverse Event

For the purpose of this protocol, the following definitions and reporting requirements will apply:

An adverse event (AE) is any untoward medical occurrence associated with the performance of a study procedure in a clinical investigation patient.

AEs may include:

- Symptoms described by the patient
- Clinically significant changes in the patient's physical exam or other signs observed by the Investigator or medical staff

Definition of a Procedure-related AE:

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 (i.e., related to the fact that a patient is undergoing a procedure in the study). 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 serious procedure-related adverse events will be recorded.

9.2 Serious Adverse Event

A serious adverse event (SAE) is an AE that results in any of the following:

- Death: The patient died as the result of the event.
- Is life-threatening: An AE that places the patient, in the view of the Investigator or Sponsor, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of an existing hospitalization
- Persistent or significant disability/incapacity: An AE that results in a substantial disruption of a person's ability to conduct normal life functions.
- Congenital anomaly/birth defect: A congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the study procedure.

- Other Medically Important Serious Medical events: An AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient or patient may require medical or surgical intervention to prevent one of the outcomes listed above.

9.3 Evaluation of Adverse Events/Serious Adverse Events

SAEs will be assessed by the Investigator. Only SAEs determined by the Investigator to be possibly related or related to study procedures will be recorded. Any study-procedure-related or possibly-related SAEs ongoing after the Screening/Baseline visit will be followed until resolution.

9.3.1 Causality Assessment

For each SAE the Investigator must determine whether, based on available evidence, there is a reasonable possibility that the study procedure caused the event. Causal relationship will be classified according to the following criteria:

- Not Related: There is no suspicion of a causal relationship between the procedure and the AE.
- Unlikely Related: There is no evidence for a causal relationship between the procedure and the AE; however, such a relationship cannot be ruled out.
- Possibly Related: There is some evidence supporting the possibility of a causal relationship between the procedure and the AE.
- Related: There is strong evidence that there is a causal relationship between the procedure and the AE.

A causality assessment must be provided for each SAE recorded even if there is only limited information at the time.

Upon receipt of follow-up information, the Investigator may change his/her assessment of causality and amend the SAE report accordingly.

9.3.2 Severity

Severity indicates the intensity of the event and should not be confused with seriousness (i.e., Section 9.2), which is an event outcome applied for the purpose of event classification and regulatory reporting.

Severity Grading

The Investigator will assess the severity of all study-procedure-related SAEs as Mild, Moderate, or Severe, based on the following definitions.

Definitions:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.3.3 Outcome

Outcome describes the status of the SAE.

The Investigator will provide information regarding the patient outcome of each SAE that is judged to be possibly related or related to a study procedure.

Definitions for possible results of an SAE outcome:

- Recovered/Resolved: the event has improved or recuperated
- Recovering/Resolving: the event is improving
- Not Recovered/Not Resolved: the event has not improved or recuperated
- Recovered/Resolved with sequelae: the patient recuperated but retained pathological conditions resulting from the prior disease or injury

- Fatal: termination of life as a result of an adverse event; there should be only one AE marked with this outcome
- Unknown: not known, not observed, not recorded or refused

9.3.4 Action Taken Regarding the Investigational Product

Not applicable.

9.4 Reporting Serious Study-Procedure-Related Adverse Events

9.4.1 Initial Reporting of Serious Study-Procedure-Related Adverse Events

Study-procedure-related or possibly related SAEs should be recorded using appropriate medical terminology. When recording, it is preferable to provide a diagnosis. In the absence of a diagnosis, each sign and symptom should be captured as a unique SAE. Sufficient information should be sought to assist the Investigator both in determining the diagnosis and in making a causality assessment.

The necessity and time requirements for reporting of study-procedure-related or possibly related SAEs to the Sponsor or its designee and/or regulatory agencies are as follows:

- All SAEs related or possibly related to study procedures must be reported to the Sponsor or designee within 24 hours of the Investigator's first knowledge of the event.
- A completed Clinical Study SAE Report Form containing a detailed written description of the event along with available supporting documents (e.g., discharge summary, autopsy report, diagnostic test results, etc.) should be provided by fax or e-mail to the following address:

Safety Reporting ProPharma
E-mail: clinicalsafety@propharmagroup.com

- Additional information that is not available at the time the initial SAE Report Form was completed, must be promptly reviewed and provided to the Sponsor within 48 hours of receipt. Full supporting documentation should be solicited by the investigative site even if the SAE occurred at another institution. Such documentation may include copies of relevant patient/hospital records, discharge summaries, laboratory/test results or autopsy reports.
- If, at any time after the patient has completed participation in the study (as defined in Section 5.2.2.1), the Investigator or study staff becomes aware of an SAE that they suspect is related to the study procedures (see Section 9.3.1), then the event and any known details must be reported promptly to the Sponsor or its designee, following the reporting instructions in Section 9.4.3.

9.4.2 Follow-Up of Serious Adverse Events

All SAEs related or possibly related to study procedures will be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow up is no longer necessary.

Rules for SAE follow up apply to all patients, to the extent allowed by the patient's consent. The Investigator will ensure that follow up includes further investigations consistent with appropriate medical management to understand the nature and/or causality of the SAE. The Sponsor/designee, or regulatory authorities may also request additional information regarding an SAE at any time.

All follow-up information must be promptly reviewed by the Investigator and provided to the Sponsor within the specified timelines. Additional procedure-related SAEs may be identified during the review of follow-up information and should be processed in accordance with requirements defined throughout Section 10.

9.4.3 Reporting to Regulatory Authorities, Investigators and IRB/IECs

The Sponsor will ensure that processes are in place for provision of study-procedure-related or possibly related SAE reports to Investigators and institutional review boards (IRBs)/institutional ethics committees (IECs) as required, within the specified timelines.

The Sponsor or its designee will submit study procedure-related or possibly related SAE reports to the Investigator as required. In the US, Investigators will report study procedure-related or possibly related SAEs to their IRB in accordance with applicable standard operating procedures

and/or local reporting requirements.

Investigators must forward copies of the IRB notification to the Sponsor or its designee, when applicable.

9.5 Pregnancy Reporting

Not applicable.

10 DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

10.1 Recording of Data

Copies of pertinent records in connection with the study, including all source documents, will be made available to the Sponsor or its designee on request with due precaution towards protecting the privacy of the patient.

The Sponsor may elect to have data entered by the clinical site directly into an electronic system using electronic case report forms, eCRFs.

Data will be entered by the site into the eCRFs in the electronic data capture (EDC) system that is 21 Part 11 compliant. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made in the eCRFs must be corrected. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail, and include the reason for change. Incomplete entries or entries needing additional explanation will be highlighted or queried to the Investigator for clarification.

Adverse events may be coded with the latest version of the medical dictionary for regulatory activities (MedDRA) available at study initiation. Similarly, prior and concomitant medications and concomitant therapies may be coded using the latest version of World Health Organization (WHO) drug available at study initiation. If used, the versions employed at study start will be maintained throughout the project.

10.2 Data Quality Assurance

Study monitors will perform source document verification according to the clinical monitoring plan to ensure there are no inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of Good Clinical Practice (GCP).

10.3 Data Management

Data management will be coordinated by Retrophin or its designated representative in accordance with the study data management plan.

11 STATISTICAL METHODS AND PLANNED ANALYSES

11.1 General Considerations

This is an observational, non-interventional study.

11.2 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.

11.3 Analysis Sets

All study patients for whom data are available will be included in the analysis dataset. All study patients who undergo invasive study procedures (i.e., a blood draw) will be included in the safety dataset.

11.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics (age/age categories, sex, race, ethnicity, and baseline characteristics) will be analyzed using the safety analysis set. Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be reported. Information collected from the targeted medical history will be summarized in the same fashion as the other baseline characteristics.

11.5 Patient Accountability

Not applicable.

11.6 Study Treatment Usage and Compliance

Not applicable.

11.7 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. Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be calculated for quantitative data. Frequency counts will be compiled and rates of positive and negative tests will be calculated for classification of qualitative data.

11.8 Safety Analyses

Any SAEs related or possibly related to study procedures (i.e., a blood draw) will be listed.

11.8.1 Physical Examination and Vital Signs

Not applicable.

11.8.2 Clinical Laboratory Tests

No safety clinical laboratory tests will be conducted.

11.8.3 Adverse Events

Only SAEs related or possibly related to invasive study procedures (i.e. a blood draw) will be recorded.

11.8.4 Other Safety Assessments

Not applicable.

11.9 Other Analyses

Not applicable.

11.10 Other Statistical Issues

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the complete statistical plan, the clinical study report, or any combination of these, as appropriate.

11.10.1 Significance Levels

Not applicable.

11.10.2 Missing or Invalid Data

Missing data will remain missing and no imputation of missing data will be done. Data points that appear to be invalid will be queried for correction or confirmation by the clinical site.

11.11 Interim Analysis

No interim analysis is planned.

12 SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the International Conference on Harmonisation (ICH)/GCP guideline. These requirements are stated in the ICH Guideline Topic E6 entitled "Guideline for Good Clinical Practice."

12.1 Institutional and Ethics Review

This protocol, informed consent form, participant information sheet, and any proposed advertising material will be submitted to an appropriate ethics committee, applicable regulatory authorities, and host institution(s) for written approval (where applicable). These documents will also be submitted to and approved by the above parties for all substantial amendments to the original approved documents (where applicable). Documentation of any applicable approval(s) and the approved consent form must be received by the Sponsor or its designee prior to enrollment of patients.

12.2 Data Monitoring Committee

There will be no data monitoring committee (DMC) for this study.

12.3 Changes to the Conduct of the Study or Protocol

Any changes in the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator and the Sponsor or its designee. All protocol changes must be documented in protocol amendment(s). Protocol amendment(s) must be signed by the Investigator and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to implementation. Any changes in study conduct that result from a pending amendment will be considered protocol deviations until IRB or IEC approval is granted. Documentation of IRB or IEC approval must be returned to the Sponsor or its designee.

12.4 Investigator's Responsibilities

Refer to the Study Operation Manual for further details regarding the Investigator's responsibilities as outlined in the sections below.

12.4.1 Patient Informed Consent

Investigators must adhere to GCP, which includes ethical principles that have their origin in the Declaration of Helsinki, when developing the patient informed consent form and when obtaining consent from the patient. Written informed consent is required prior to enrollment in the study.

It is the responsibility of the Investigator to document the consent process within the source documents and obtain consent using an IRB or IEC approved consent form. Remote consenting of subjects by authorized study personnel, using telephone, mail, fax or other communication means, is permitted.

The patient and/or their parent/legal guardian must be willing and able to provide signed informed consent and the patient, if <18 years of age, is willing to provide assent if deemed able to do so. If the patient is ≥ 18 years of age but has diminished capacity to provide informed consent, their parent/legal guardian must be willing and able to provide signed informed consent and the patient is willing to provide assent, if deemed able to do so.

Confidenality will be maintained during the study. Data and information collected during this study, including information on patients' race and ethnicity, are required by government regulatory authorities and may be published but will not include any personal identity. The study will use unique study identifiers to maintain confidentiality. Any study-related records that identify patients will be kept confidential, and to the extent permitted by applicable laws and/or regulations will not be made publicbly available. Any results that are published from this study will not include a patient's personal identity.

12.4.2 Case Report Forms

Copies of pertinent records in connection with the study, including all source documents, will be made available to the Sponsor or its designee on request with due precaution towards protecting the privacy of the patient.

Data will be entered by the site into the eCRFs in the EDC system. Unless explicitly directed, blank data fields are not acceptable. Any erroneous entries made in the eCRFs must be corrected. Changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail, and include the reason for change. Incomplete entries or entries needing additional explanation will be highlighted or queried to the Investigator for clarification.

12.4.3 Record Retention

The Investigator is responsible for oversight and maintenance of the study records and patient source documents. These records must be readily available for audit or inspection.

The Investigator must retain study records for at least 2 years after completion of the clinical study. However, these documents should be retained for a longer period, if required by other applicable requirements (e.g., applicable local regulatory requirement) or by an agreement with

the Sponsor or its designee. The Investigator will contact the Sponsor or its designee prior to any record destruction.

Patient records or other source data must be kept for the maximum period of time mandated by the hospital, institution, or private practice, but not less than 15 years.

If off-site archiving is used, all records must be retrieved and made available for review at the time of an audit or regulatory authority inspection.

12.4.4 Monitoring

A representative of the Sponsor or its designee will remotely interface with and may visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with the protocol, GCP, and local regulations. A monitor, auditor, IRB and or/other regulatory authority, such as the The United States Food and Drug Administration (FDA), would have access to study-related medical documents for the purposes of the study. Non-compliance with the protocol, GCP, and local regulations will be documented and corrective actions implemented, as necessary. It is the responsibility of the Investigator to be present or available for consultation during remote or on-site monitoring visits. In order to complete remote or on-site monitoring visits, all data pertaining to a patient's participation in this clinical investigation must be made available to the monitor.

At any time prior to, during, or after completion of the clinical study, an audit may be performed by the Sponsor or its designee or a representative of a national regulatory agency may choose to inspect a study site; this includes FDA. The FDA may inspect all records related to the study. Investigators must notify the Sponsor or its designee upon notification of inspection by a representative of a national regulatory agency. A Sponsor or designee representative will be available to assist in the preparation for study site inspections. All pertinent study data must be made available for verification, audit, or inspection purposes.

12.4.5 Study or Site Termination

If the Sponsor or its designee, the Investigator, or regulatory authorities discover any conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor or its designee and the Investigator. The Sponsor or its designee has the right to terminate the participation of either an individual site or the study at any time, for any reason which may include the following:

- The incidence and severity of AEs in this or other studies indicates a potential health hazard to patients.

- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigator(s) do(es) not adhere to the protocol or applicable regulatory guidelines in conducting this study.
- Submission of knowingly false information from the study site to the Sponsor or its designee, or regulatory authorities.

In the event that the study is terminated early, the Sponsor or its designee will provide specific guidance to investigational sites regarding the end-of-study procedures.

12.4.6 Investigational Product Control

Not applicable.

12.4.7 Insurance

The Sponsor will maintain a liability insurance policy covering all clinical studies under its sponsorship, and that policy will comply with local laws and requirements. The Sponsor or its designee will provide a certificate of insurance to any IRB/IEC or regional Health Authority that may require such a document. Note that this Sponsor insurance coverage does not relieve the Investigator, the Institution, and their collaborators from each maintaining their own liability insurance policy for their clinical research activity.

12.4.8 Disclosure of Data

All details related to the disclosure and publication of study data will be addressed in the Investigator's study contract.

12.4.9 Clinical Study Report

The Sponsor or the Sponsor's designee is responsible for preparing a clinical study report. The final report is signed by the Sponsor. Study results will be provided to the Investigators.

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14 APPENDIX

Table 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 ≥0.4mg/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 participants 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 participants who *require genetic testing*, participation ends after reporting of test results to the patient, and study discontinuation page is completed.