RESTORE

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RESTORE STUDY (Cheno-CTX-301) OVERVIEW — PEDIATRIC GROUP

STUDY INTRODUCTION

Retrophin, a biopharmaceutical company that specializes in developing drugs for rare diseases, is sponsoring a global clinical study, called RESTORE, in adults, teenagers, and children who have been diagnosed with cerebrotendinous xanthomatosis (CTX). The purpose of the study is to evaluate the safety and efficacy (how well the study drug works) of chenodeoxycholic acid (an investigational bile acid replacement therapy also called chenodiol, or CDCA) in people with CTX.

CTX is a rare disease of bile acid production that is caused by a genetic defect in a single protein, or enzyme.[1,2] Normally, this enzyme helps to break down cholesterol in the body to make bile acids, such as CDCA. Bile acids are important and help with the absorption of fat and fat-soluble vitamins. When the body lacks the bile acid CDCA, abnormal (or atypical) bile acids, such as bile alcohols and cholestanol, are produced and accumulate. Patients with CTX may then have abnormalities in multiple parts of the body, including the brain, eyes, stomach, and tendons.

CDCA replacement therapy is recognized as a potential treatment for CTX[1,2]; however, it has not been approved by the US Food and Drug Administration (FDA) for use in CTX in the United States. CDCA is approved in the United States for the treatment of a certain type of gallstones.[3] For the purposes of the RESTORE study, CDCA is considered to be an investigational study drug.

In the RESTORE study, doctors want to learn how bile alcohol levels change, as measured in urine, when CDCA is used. It will also help the sponsor (Retrophin Inc.) learn more about the safety of CDCA, or what side effects, if any, occur with CDCA use.

STUDY OVERVIEW

The study has 2 groups: Pediatric and Adult. The Pediatric Group will include patients who are younger than 16 years old. The study lasts about 25 to 28 weeks (6-7 months). During this time, all patients will need to make approximately 18 trips to the study center to complete visits with the study doctor. The goal is to include about 3 patients in the Pediatric Group. For information on the Adult Group of the RESTORE study, please see the Adult study flyer.

KEY ELIGIBILITY CRITERIA

1. Male or female, at least 1 month old and less than 16 years old at the time of screening
2. Clinical diagnosis of CTX (presence of symptoms) with supporting laboratory results (for example, increased cholestanol and bile alcohols in blood or urine)
3. Male and female participants of childbearing potential must agree to use reliable birth control throughout the study

For more information, visit clinicaltrials.gov (NCT04270682) or contact medinfo@retrophin.com

PEDIATRIC GROUP

All patients in the Pediatric Group will be provided CDCA in liquid form. No **placebo** will be given. This study involves a **Screening period** (4 weeks), a **Titration/Dose Adjustment period** (8 weeks), a **Treatment period** (16 weeks), and a **Follow-up Phone Call**.

A placebo is a substance that looks like CDCA but does not contain any drug.

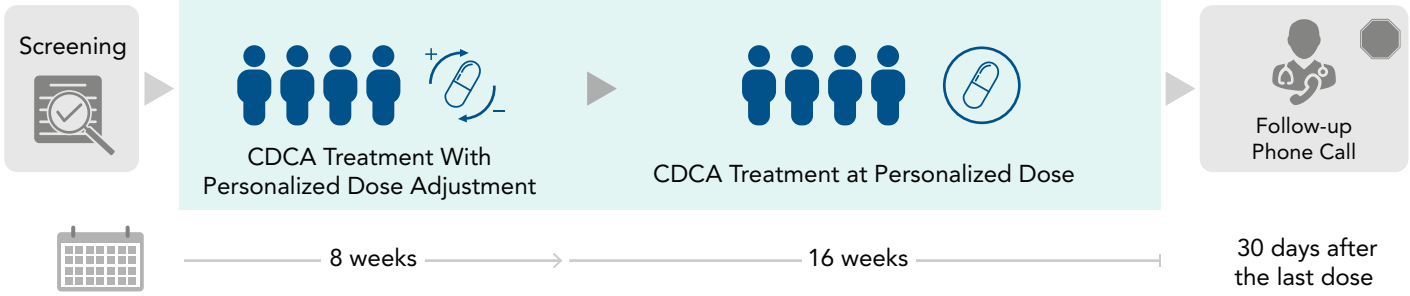

Figure. Study Design for Pediatric Group (children and teenagers under 16 years of age)

At **Screening**, your study doctor will examine your child and collect blood and urine samples to determine if this study is right for your child. If the doctor thinks your child is eligible to participate in the study and you agree, your child may then begin treatment. As shown in the Figure, the treatment includes 2 phases:

1. **Titration/Dose Adjustment**: During these 8 weeks, your doctor will provide your child with CDCA treatment in a liquid form, at a dose based on body weight and if your child has taken CDCA treatment before. Study doctor visits will occur every week for a health check and blood/urine collection, and a dose adjustment, as needed.
2. **Treatment Period**: Following the titration period, patients will take CDCA for 16 weeks at the dose the study doctor identifies to be most appropriate during the Titration/Dose Adjustment period. Visits with the study doctor will occur every 2 weeks for a health check and blood/urine collection.

Follow-up phone call: Approximately 30 days after the last dose of study drug, patients' families will receive a phone call from the study center to check up on them.

WHAT MUST PATIENTS (OR THEIR GUARDIANS) DO FOR THIS STUDY?

1. Patients must attend study doctor visits and participate in the required assessments, which may vary by visit, and include:
    a. Interviewing to assess your child's overall health
    b. Monitoring your child's vital signs (such as blood pressure)
    c. Evaluating your child's heart (by electrocardiogram, or ECG), brain function (by electroencephalogram, or EEG), and eyes (ophthalmology exam)
    d. Collecting blood and urine samples from your child
2. Patients/guardians must collect urine samples at home prior to a study visit, refrigerate the samples while at home, and then transport the urine samples to the study center for each visit
3. Patients must take study drug as directed and follow directions provided by study staff
4. Patients/guardians must complete health questionnaires at home and during doctor visits
5. Patients/guardians must complete a paper and electronic diary to record information about the study drug, at-home urine collections, changes in symptoms, and quality of life
6. Patients of childbearing potential must use appropriate birth control methods throughout participation in the study

REFERENCES: 1. Mignarri A, Gallus GN, Dotti MT, Federico A. A suspicion index for early diagnosis and treatment of cerebrotendinous xanthomatosis. *J Inherit Metab Dis.* 2014;37(3):421-429. 2. National Organization for Rare Disorders. Rare Disease Database: Cerebrotendinous xanthomatosis. https://rarediseases.org/rare-diseases/cerebrotendinous-xanthomatosis/ Accessed April 26, 2020. 3. CHENODAL [package insert]. Fort Collins, CO: Manchester Pharmaceuticals, Inc; 2009.