RESTORE

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RESTORE STUDY (Cheno-CTX-301) OVERVIEW — ADULT 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. The other study drug in RESTORE is a placebo. A placebo is a substance that looks like CDCA but does not contain any drug.

In the RESTORE study, doctors want to learn how bile alcohol levels change, as measured in the 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, appear with CDCA use.

STUDY OVERVIEW

The study has 2 groups: Pediatric and Adult. The Adult Group will include patients who are 16 years old and older. 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 12 patients in the Adult Group. For information on the Pediatric Group of the RESTORE study, please see the Pediatric study flyer.

KEY ELIGIBILITY CRITERIA

1. Male or female, at least 16 years of age 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

ADULT GROUP

For adults, this study involves a **Screening period** (4 weeks), a **Treatment period** (totaling 6 months), and a **Follow-up Phone Call**.

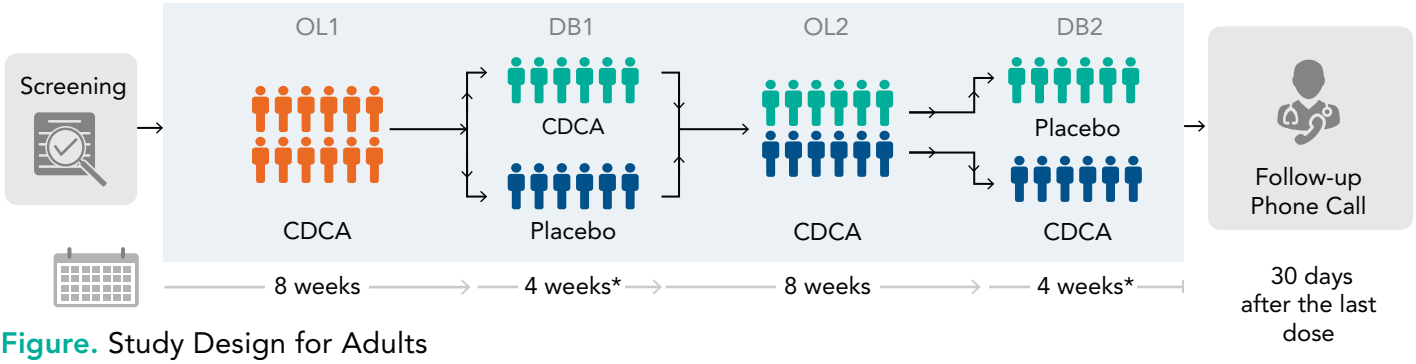

Figure. Study Design for Adults

*Rescue CDCA will be available as needed if symptoms occur or lab values are out of the expected range for patients receiving CDCA or placebo.

At **Screening**, a physical exam will be performed, and blood and urine will be collected to determine if this study is right for you. If your doctor thinks you are eligible to participate in the study and you agree, you may then begin the **Treatment period**. As shown in the Figure, the Treatment period consists of 4 phases:

1. **OL1:** All patients will take study drug by mouth 3 times daily for 8 weeks. Visits with the study doctor will occur every 2 weeks for a health check and blood/urine collection.
2. **DB1:** Following OL1, patients will be randomly assigned either to continue CDCA as before, or take placebo tablets 3 times daily for the next 4 weeks. Visits with the study doctor will occur every week for a health check and blood/urine collection.
3. **OL2:** Just as in OL1, all patients will take study drug by mouth 3 times daily for 8 weeks. Visits with the study doctor will occur every 2 weeks for a health check and blood/urine collection.
4. **DB2:** Following OL2, patients will take the alternative treatment that they did not take in DB1. This means that patients who took placebo in DB1 will now take CDCA and patients who took CDCA in DB1 will now take placebo. Visits with the study doctor will occur every week for a health check and blood/urine collection.

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

CDCA treatment will be given in a tablet form to adult patients.

OL or "open-label" means that patients and study staff are aware of which study drug each patient is taking.

DB or "double-blind" means that patients and all study staff are NOT aware which study drug (CDCA or placebo) patients are taking.

If the change in urine bile alcohols in your urine exceed a pre-set limit or you experience worsening of symptoms related to CTX, you may be switched to rescue CDCA.

WHAT MUST PATIENTS 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 you and assessing your overall health
   b. Monitoring vital signs (such as blood pressure)
   c. Evaluating heart (by electrocardiogram, or ECG), brain function (by electroencephalogram, or EEG), and eyes (ophthalmology exam)
   d. Collecting blood and urine samples
2. Patients 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 must complete health questionnaires at home and during doctor visits
5. Patients 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 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.