# LEADER 3D: Leveraging Existing Biomarker and Natural History Data to Support Drug Repurposing for a Rare Disease

## Chenodiol (Ctexli)

**Before reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource.** FDA recognizes that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. The small population affected by a rare disease presents additional considerations that must be addressed and also calls for appropriate flexibility. **Please note this case study is not intended or designed to provide specific strategies for obtaining product approval.** Rare disease drug development is not one-size-fits-all. The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and must therefore be assessed on a case-by-case basis.

## Learning Objectives

After reading this case study you will:

- Have a greater understanding of how existing biomarker data from published literature can be leveraged to support the use of a surrogate endpoint as predictive of clinical benefit when the disease pathophysiology and drug mechanism of action are well understood.
- Be aware of how natural history data from published literature can serve as confirmatory evidence by demonstrating that biomarker changes observed in a clinical trial differ from the expected natural disease progression and are consistent with clinical improvement.
- Have a greater understanding of how the 505(b)(2) regulatory pathway enables drug repurposing for rare diseases by allowing applicants to rely on published literature and FDA's previous findings of safety and effectiveness for a previously approved drug.

*To access FDA guidance documents for rare disease drug development organized by topic, please scan this QR code.*

## Case Study Summary

This case study describes the use of a biomarker and natural history data to support repurposing chenodiol for the treatment of cerebrotendinous xanthomatosis (CTX). Chenodiol is an orally administered form of the primary bile acid chenodeoxycholic acid (CDCA) that replaces the deficient bile acid in patients with CTX. It was previously approved in the U.S. to treat radiolucent gallstones[1] and had been used off-label for decades as standard of care for CTX. However, no prospective, randomized, controlled trials had been conducted to confirm chenodiol's clinical benefit for treating CTX. To pursue FDA approval, the Applicant submitted a 505(b)(2)[2] application that relied, in

### Highlights

**505(b)(2) Pathway: Leveraging Existing Evidence to Streamline Drug Development**

The chenodiol application for CTX was submitted under the 505(b)(2) regulatory pathway, which allows applicants to rely, in part, on published scientific literature and prior FDA findings of safety and/or effectiveness rather than conducting new nonclinical or clinical studies when reliance is scientifically appropriate. For CTX, this pathway allowed approval of chenodiol based on existing evidence. As it may reduce product development time and costs while maintaining FDA safety and effectiveness standards, this regulatory mechanism can be particularly important for rare disease drug development, where patient populations are small, and trial recruitment may be challenging.

[1] Chenix (Xenbilox, chenodiol) was approved in 1983 for treating radiolucent gallstones in adults. A generic version (ANDA 091019) was subsequently approved in 2009. The original NDA 018513 was later discontinued by the manufacturer for reasons unrelated to safety or effectiveness, as noted in the Federal Register on May 15, 2007.

[2] Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2))

### Key Concept: Surrogate Endpoints

For efficacy evaluation, trials may include either clinical endpoints, which directly measure how a patient feels, functions, or survives, or surrogate endpoints substituting for clinical outcomes when that surrogate endpoint can be relied upon to predict, or correlate with, clinical benefit in a context of use. Surrogate endpoints can be characterized by the level of clinical validation and include: (1) validated surrogate endpoints that predict clinical benefit; (2) reasonably likely surrogate endpoints (RLSEs); and (3) candidate surrogate endpoints. According to FDA, "validated surrogate endpoints are supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a specific clinical benefit."[3] Validated surrogate endpoints accepted by FDA as predictive of clinical benefit can be used to support traditional approval of a drug or biological product. Surrogate endpoints can be biomarkers used to substitute for clinical outcomes and used to support regulatory decisions. A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.

Please refer to Surrogate Endpoint Resources for Drug and Biologic Development and BEST (Biomarkers, EndpointS, and other Tools) Resource for more information on surrogate endpoints and biomarkers as surrogate endpoints.

part, on published literature and FDA's previous findings of the safety of chenodiol for the treatment of radiolucent gallstones. To demonstrate efficacy for traditional approval, the Applicant proposed assessment of various CTX biomarkers as primary efficacy outcomes—including plasma cholestanol and urine 23S-pentol—in a single adequate and well-controlled investigation and utilized mechanistic and natural history data from the literature as part of the confirmatory evidence package.

## Introduction to the Rare Disease: Cerebrotendinous Xanthomatosis

CTX is a rare autosomal recessive metabolic disorder caused by pathogenic variants in the *CYP27A1* gene, which results in deficiency of the mitochondrial enzyme sterol 27-hydroxylase, a key enzyme in bile acid synthesis. Deficiency of this enzyme disrupts the normal synthesis of bile acids from cholesterol in the liver, leading to reduced production of the primary bile acid CDCA, increased

### FDA Guidance Corner

Note: The FDA Guidance Corner includes excerpts of draft FDA guidance documents which, when final, will represent the Agency's current thinking on topics in the case study. For up-to date guidance documents please search Guidance Documents for Rare Disease Drug Development | FDA.

*In this case study, the Applicant submitted a 505(b)(2) new drug application (NDA) to repurpose chenodiol for CTX, relying on published literature and FDA's previous findings of safety for chenodiol. This guidance document, which, when final, will represent the Agency's current thinking, explains different abbreviated approval pathways for drug products under the Federal Food, Drug, and Cosmetic (FD&C) Act, including the 505(b)(2) pathway, and the types of information permitted to support approval under these pathways.*

*Draft Guidance for Industry Applications Covered by Section 505(b)(2)* (October 1999)

A 505(b)(2) application is an NDA described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). It is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act. This provision expressly permits FDA to rely, for approval of an NDA, on data not developed by the applicant.

Types of information an applicant can rely on:

- **Published literature**: An NDA will be a 505(b)(2) application if any of the specific information necessary for approval is obtained from literature or from another source to which the applicant does not have a right of reference, even if the applicant also conducted clinical studies to support approval. Note, however, that this does not mean any reference to published general information (e.g., about disease etiology, support for particular endpoints, methods of analysis) or to general knowledge causes the application to be a 505(b)(2) application. Rather, reference should be to specific information (clinical trials, animal studies) necessary to the approval of the application.
- **The Agency's finding of safety and effectiveness for an approved drug**: An applicant should submit a 505(b)(2) application for a change in a drug when approval of the application relies on the Agency's previous finding of safety and/or effectiveness for a drug.

It is possible that an applicant could submit a 505(b)(2) application that relies both on literature and upon the Agency's finding of safety and effectiveness for a previously approved drug product (e.g., to support a new claim).

[3] Surrogate Endpoint Resources for Drug and Biologic Development

production of abnormal bile acids and alcohols, and accumulation of cholestanol, a toxic cholesterol metabolite, in various organs and tissues.

Clinical features of CTX vary widely and may include chronic diarrhea, premature cataracts, tendon xanthomas (i.e., lipid deposits), cardiovascular disease, and neurocognitive problems. Other neurological symptoms often progress over time and can include ataxia, spasticity, seizures, dementia, and psychiatric changes. CTX is associated with an increased risk of early death, with a typical life expectancy of 50–60 years, although deaths in infancy have also been reported. More than 400 cases of CTX have been reported worldwide, but recent studies suggest that the condition is likely underdiagnosed. The estimated frequency of CTX differs by region. It is most common in South Asian populations, where it occurs in approximately 1 in 36,000 to 1 in 75,600 people. In African populations, it is less common, with estimates ranging from approximately 1 in 263,000 to 1 in 468,600 people.[4] CTX also appears to affect females slightly more often than males, with women making up around 55% of reported cases.[5]

## Current Treatment Options

Prior to its FDA approval for CTX, CDCA (chenodiol) had been used off-label as bile acid replacement therapy for more than 40 years and was widely regarded as the standard of care. Cholbam (cholic acid), an FDA-approved oral bile acid for certain single-enzyme bile acid synthesis disorders, has also been used in some patients with CTX. However, it is believed to be less effective than CDCA at correcting the underlying biochemical abnormalities of CTX.

## Chenodiol Mechanism of Action

Chenodiol is an exogenous form of CDCA, one of the primary bile acids produced from cholesterol in the liver by the enzymes cholesterol 7-α-hydroxylase (CYP7A1) and sterol 27-hydroxylase (CYP27A1). CYP7A1 first converts cholesterol into the intermediate metabolite 7α-hydroxy-4-cholesten-3-one (7αC4), which is then converted into primary bile acids by CYP27A1. These bile acids are secreted into bile, stored in the gallbladder, and released into the intestine to support digestion of fats and absorption of fat-soluble vitamins. Under normal conditions, when CDCA levels rise above physiological levels, CDCA provides feedback inhibition on CYP7A1—potentially by acting as a ligand for the farnesoid X receptor (FXR)—thereby downregulating this rate-limiting enzyme and maintaining bile acid homeostasis (**Figure 1,** Left Panel).

In CTX, pathogenic variants in the *CYP27A1* gene cause deficiency of sterol 27-hydroxylase (CYP27A1), leading to reduced CDCA levels and loss of normal feedback control.

As a result, the bile acid pathway becomes overactive, producing excess 7αC4. In the absence of CYP27A1 activity, 7αC4 is diverted into abnormal metabolic pathways, forming intermediates such as 7α12αC4 and then bile alcohols like tetrol, which are ultimately converted into urine 23-S-pentol. Excess 7αC4 also contributes to the formation of cholestanol, a toxic metabolite that accumulates in tissues throughout the body, including the brain, tendons, skin, lungs, eyes, and bones, and is believed to drive many clinical manifestations of CTX. Exogenous chenodiol replenishes the bile acid pool, restores feedback inhibition, and suppresses the formation of these harmful metabolites, reducing cholestanol buildup in tissues and helping to reduce the symptoms of CTX (**Figure 1**).

## The Single Adequate and Well-Controlled Investigation

### RESTORE Study Design

The Applicant conducted a single adequate and well-controlled trial (RESTORE trial) to evaluate the efficacy of chenodiol for the treatment of CTX. The RESTORE clinical trial was a randomized, double-blind, placebo-controlled

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[4] Appadurai V. et al. (2015). Apparent underdiagnosis of Cerebrotendinous Xanthomatosis revealed by analysis of ~60,000 human exomes. Mol Genet Metab, 116(4), 298–304.

[5] Verrips A. et al. (2000). Presence of diarrhea and absence of tendon xanthomas in patients with cerebrotendinous xanthomatosis. Arch Neurol, 57(4), 520–524.

crossover study[6] in patients (aged 16 years and older) with CTX. The trial began with an 8-week open label, run-in period (OL1) during which all participants received chenodiol (Figure 2). After this period, participants were randomly assigned to one of two treatment arms:

- **Chenodiol-then-placebo Arm:** Participants received 4 weeks of chenodiol (DB1: chenodiol), followed by 8 weeks of open-label chenodiol (OL2), and then 4 weeks of placebo (i.e., withdrawal of chenodiol) (DB2: placebo).
- **Placebo-then-chenodiol Arm:** Participants received 4 weeks of placebo (DB1: placebo), followed by 8 weeks of open-label chenodiol (OL2), and then 4 weeks of chenodiol (DB2: chenodiol).

The total study duration was 24 weeks—8 weeks for the run-in period and 16 weeks for the randomized treatment phases (i.e., DB1 and DB2 phases). Participants received chenodiol at a dose of 250 mg three times daily. During each treatment phase, rescue with chenodiol was permitted in participants in whom urine 23S-pentol values increased 10 times above the baseline value. For efficacy analyses, Day 1 and Day 85 served as the baseline time points, and Day 29 and Day 113 marked the end of the 4-week (28-day) double-blind treatment phases.

***Figure 1: Mechanism of Action of Chenodiol in CTX:*** *In unaffected individuals (left panel), endogenous CDCA provides negative feedback inhibition on CYP7A1 to regulate bile acid synthesis, including its own production. In untreated CTX (middle panel), CYP27A1 deficiency caused by pathogenic variants in the CYP27A1 gene (represented by asterisk) disrupts CDCA production and impairs negative feedback regulation, leading to excess 7αC4 and in turn toxic cholestanol accumulation in the CNS and other tissues. The accumulation of cholestanol underlies CTX clinical symptoms. Treatment with exogenous chenodiol (right panel), restores the bile acid pool and CYP7A1 feedback control, thereby reducing harmful metabolites, cholestanol accumulation, and consequently CTX symptoms.*

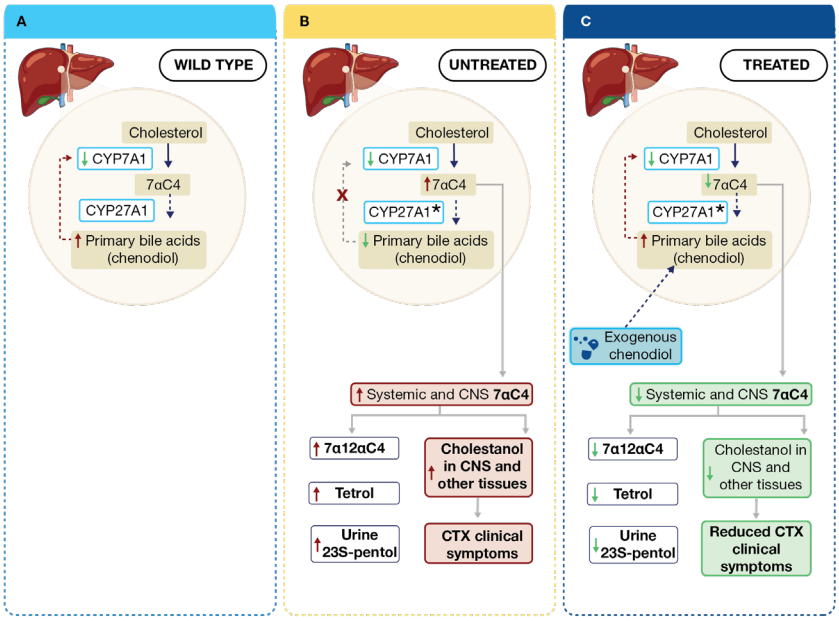
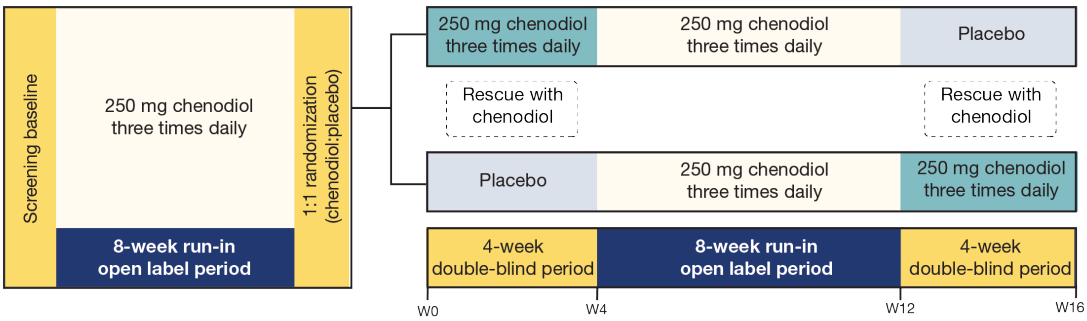



***Figure 2:*** *RESTORE Trial Design. Following an eight-week run in period, participants were randomized into either a chenodiol-placebo arm or a placebo-chenodiol arm. During each treatment phase, placebo participants received blinded chenodiol rescue if they met rescue criteria.*




[6] For more information about crossover trial designs, please refer to the LEADER 3D video on Challenges, Strategies, and Regulatory Considerations for Rare Disease Clinical Trial Design, here: https://youtu.be/KKm2hG7foQw.

## CTX Biomarkers as Efficacy Endpoints

To evaluate the efficacy of chenodiol for the treatment of CTX in the RESTORE trial, the Applicant proposed urine 23S-pentol as the primary endpoint (See **Figure 1** right panel labeled treated), measured as the change from baseline to the end of each DB treatment period, and plasma cholestanol as a secondary endpoint, measured as the percent change from baseline. However, based on published scientific evidence supporting the role of cholestanol in the pathophysiology of CTX, FDA focused primarily on changes in this key secondary endpoint, as opposed to the urine 23S-pentol primary endpoint.

## CTX Biomarker Results[7]

The RESTORE trial results demonstrated a statistically significant improvement in plasma cholestanol with chenodiol compared with placebo (**Figure 3**). Specifically, the Agency's efficacy evaluation focused on the endpoint of absolute change from baseline in the plasma cholestanol levels at the end of each DB treatment period. Chenodiol treatment also resulted in a 2.3 µg/mL (SD: 3.9) reduction in plasma cholestanol, whereas placebo resulted in a 6.2 µg/mL (SD: 5.6) increase. The resulting treatment difference was -8.5 µg/mL (95% CI: -13.2, -3.9), indicating clear reduction in plasma cholestanol with chenodiol.

Similarly, results from the double-blind periods showed a statistically significant improvement in urine 23S-pentol where substantially lower urine 23S-pentol levels were reported with chenodiol treatment (compared to placebo (**Figure 4**)). During both treatment phases levels of both cholestanol and urine 23S-pentol increased with placebo and decreased with resumption of chenodiol treatment (**Figures 3 and 4**).

***Figure 3:*** *Mean (SE) Plasma Cholestanol Demonstrating Reversible Changes with Chenodiol Initiation and Withdrawal. Solid line represents treatment with chenodiol, and dashed line represents treatment with placebo. Red line represents group who received placebo during the first double-blind period and chenodiol during the second double-blind period. Blue line represents group who received chenodiol during the first double-blind period and placebo during the second double-blind period.*
*Key: SE = standard error.*

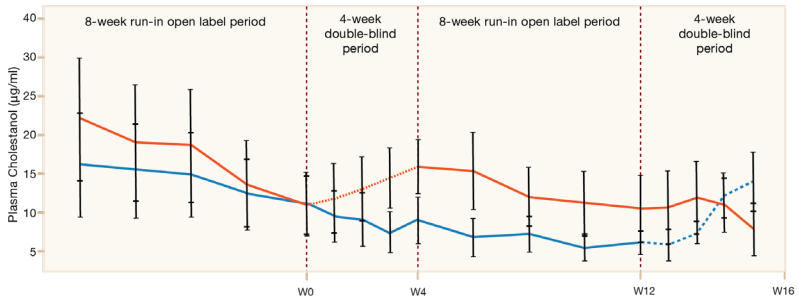
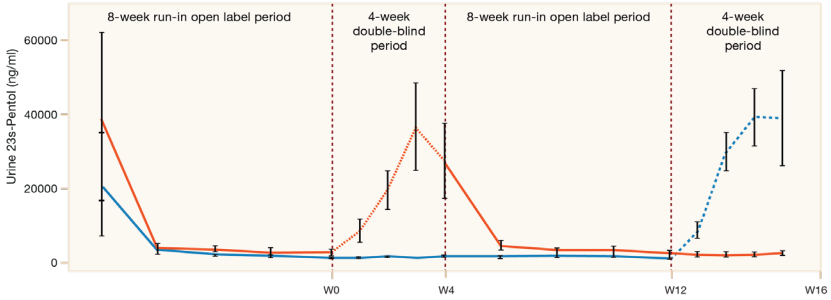



***Figure 4:*** *Mean (SE) Urine 23S-Pentol Demonstrating Reversible Changes with Chenodiol Initiation and Withdrawal. Solid line represents treatment with chenodiol, and dashed line represents treatment with placebo. Red line represents group who received placebo during the first double-blind period and chenodiol during the second double-blind period. Blue line represents group who received chenodiol during the first double-blind period and placebo during the second double-blind period.*
*Key: SE = standard error.*




## Literature Evidence for the Predictive Clinical Benefit of Cholestanol

Likely due to short trial duration, small population size, and variability in CTX manifestations, the Applicant did not report meaningful changes in clinical outcome data during the RESTORE trial. Long-term randomized trials are also difficult to conduct for a therapy that is already considered standard of care for a progressive multisystem disorder like CTX because withholding standard of care for an extended period is not considered ethical or feasible given the high risk of irreversible disease progression in untreated patients. To address these limitations of the RESTORE trial, the Applicant submitted evidence from published literature to support the conclusion that reductions in cholestanol are predictive of clinical benefit in CTX. Robust evidence from the literature indicates that cholestanol accumulates in organs

[7] Please refer to the Integrated Review on page 76 for additional information on CTX biomarker results for Chenodiol (Ctexli) – https://www.accessdata.fda.gov/drugsatfda_docs/nda/2026/219488Orig1s000MultidisciplineR.pdf

impacted by CTX, is toxic to tissue where it accumulates, and that participants treated with chenodiol experienced consistent and durable reductions of plasma cholestanol levels associated with improvement in CTX symptoms (although factors such as advanced age and advanced neurological disease may influence the degree of clinical benefit).

These findings, when considered along with the sufficiently well-understood pathophysiology of CTX and well-understood mechanism of action of chenodiol, support the trial's results and indicate that a significant reduction in plasma cholestanol predicts clinical benefit in CTX in trial participants receiving chenodiol. Therefore, FDA determined that reduction in plasma cholestanol is a surrogate endpoint predictive of clinical benefit with chenodiol and the observed effect on plasma cholestanol in the RESTORE trial contributed to substantial evidence of effectiveness. The review team assessed both the strengths and limitations of the evidence in the literature (see table, below) and determined it was sufficient to support the use of plasma cholestanol as a biomarker predictive of clinical benefit.

***Key Strengths and Limitations of the Literature to Support Cholestanol as Predictive of Clinical Benefit with Chenodiol Treatment***

| Strengths | Limitations |
|---|---|
| • Cholestanol accumulates in tissues where CTX causes structural damage and functional impairment, with high levels reported in the brain and cerebrospinal fluid of untreated patients compared with healthy controls. Chenodiol treatment reduces cholestanol levels in the CNS.[9]<br>• Cholestanol is toxic to the tissues where it accumulates, including the central and peripheral nervous systems, which are significantly affected in CTX.<br>• A nonclinical rat study demonstrated that cholestanol exposure caused a significant increase in apoptosis in cerebellar Purkinje cells, supporting the conclusion that cholestanol accumulation is toxic to affected cells.[9]<br>• Observational and retrospective studies show that plasma cholestanol is markedly elevated in untreated CTX and decreases with chenodiol therapy, with a substantial proportion of patients achieving normal levels (63% of patients in one observational study and in 46% of participants in the RESTORE trial).[10] Several observational studies and case reports also suggest that reductions in plasma cholestanol correlate with improvements in clinical outcomes such as neurocognitive impairment and diarrhea.<br>• Case reports show that plasma cholestanol levels decrease during chenodiol treatment, and that cholestanol levels rise when treatment is discontinued, accompanied by worsening neurological and imaging findings.[11,12] | • There are no consistent quantitative data showing that reducing cholestanol levels with chenodiol treatment reliably leads to improved clinical outcomes, and no information on how much plasma cholestanol must decrease to achieve positive outcomes in CTX patients. Although chenodiol reduces cholestanol in nearly all published cases, some patients still experience worsening symptoms despite these reductions. Several studies suggest that certain baseline characteristics, such as older age or more advanced neurological disease, may predict a limited response to chenodiol.<br>• In rare cases, CTX patients may have normal plasma cholestanol levels but elevated urine 23S-pentol, 7αC4, and 7α12αC4 before treatment. These patients still show typical CTX features, including tendon xanthomas, diarrhea, ataxia, and cognitive impairment. Chenodiol has improved some non-neurological symptoms (such as xanthomas and diarrhea) in these reported cases.[12]<br>• Plasma or serum cholestanol levels may not fully reflect the extent of disease in specific organs.[8,13] |

[8] Höflinger, P., et al. 2021. Metabolic profiling in serum, cerebrospinal fluid, and brain of patients with cerebrotendinous xanthomatosis. J Lipid Res 62: 100078.

[9] Inoue, K., et al. 1999. Cholestanol induces apoptosis of cerebellar neuronal cells. Biochem Biophys Res Commun 256(1): 198–203.

[10] Duell P. B., et al., 2018. Diagnosis, treatment, and clinical outcomes in 43 cases with cerebrotendinous xanthomatosis. J Clin Lipidol 12(5):1169-1178

[11] Nakamura, T., et al., 1991. Combined treatment with chenodeoxycholic acid and pravastatin improves plasma cholestanol levels associated with marked regression of tendon xanthomas in cerebrotendinous xanthomatosis. Metabolism 40(7): 741–746.

[12] Catarino, C. B., et al. 2018. Brain diffusion tensor imaging changes in cerebrotendinous xanthomatosis reversed with treatment. J Neurol 265(2): 388–393.

[13] DeBarber, A. E., et al. 2024. Genetically and clinically confirmed atypical cerebrotendinous xanthomatosis with normal cholestanol and marked elevations of bile acid precursors and bile alcohols. J Clin Lipidol 18(3): e465–e476.

## Confirmatory Evidence

The confirmatory evidence supporting the RESTORE trial results includes two major components:

- **Mechanistic data**: Literature evidence supporting the well-established pathophysiology of CTX and the known mechanism of action of chenodiol.
- **Natural history data**: Literature evidence showing that the biomarker reductions in the RESTORE trial would not be expected in untreated CTX and are consistent with symptom improvement on chenodiol.

### Literature Evidence: Mechanistic Data

The Applicant proposed that CTX has a clearly defined metabolic cause, and chenodiol's mechanism of action (described in detail in the **Chenodiol Mechanism of Action** section) directly addresses this defect. CTX results from loss of sterol 27-hydroxylase activity due to CYP27A1 mutations, which leads to dysregulated bile acid synthesis and accumulation of toxic metabolites such as cholestanol, urine 23S-pentol, 7αC4, and 7α12αC4. Chenodiol replaces missing CDCA, restores feedback inhibition of bile acid synthesis, and reduces production of these abnormal metabolites, thereby decreasing cholestanol deposition in tissues.

### Literature Evidence: Natural History Data

Because the RESTORE trial relied on biomarkers, the Applicant also provided literature showing that the biomarker changes seen with chenodiol differ from the natural course of untreated CTX. This evidence falls into four main categories:

1. Untreated CTX patients have elevated levels of cholestanol, urine 23S-pentol, 7αC4, and 7α12αC4. Observational studies consistently show that untreated CTX patients have high levels of cholestanol, 7αC4, 7α12αC4, and urine 23S-pentol.[14,15] These levels are much higher than in chenodiol-treated patients or healthy controls.
2. Long-term chenodiol treatment lowered biomarker levels and was linked to clinical improvement. In a long-term (11-year) study of five CTX patients, high baseline cholestanol normalized within two months of chenodiol treatment (750 mg/day), along with improvements in visual evoked potentials and nerve conduction.[16] In two retrospective cohort studies, chenodiol was found to reduce 23S-pentol, 7αC4, and 7α12αC4, and improved non-neurological symptoms such as tendon xanthomas and diarrhea in some cases.[7]
3. Literature reports show stopping chenodiol increases cholestanol and urine 23S-pentol, indicating reactivation of the abnormal bile acid pathway.[4,10] This is consistent with the findings that biomarkers used in the RESTORE trial rose when chenodiol was stopped.
4. Therapies that failed to rebalance the dysfunctional bile acid pathway in CTX left toxic biomarker levels unchanged or worse, mirroring those levels seen in untreated individuals. Several observational studies describe changes in urine 23S-pentol and plasma cholestanol during treatment with chenodiol compared with other therapies considered ineffective by CTX experts, including ursodeoxycholic acid (UDCA), taurocholic acid (TCA), and pravastatin. Plasma cholestanol and/or urine 23S-pentol levels increased or remained abnormal while patients received these treatments and decreased when patients were switched to chenodiol.[17] A comparative study showed that only chenodiol normalized bile acid synthesis, lowered cholestanol, and eliminated abnormal bile alcohols. Other therapies, such as UDCA, UCA, cholestyramine, and lovastatin, had no effect or increased toxic metabolites, indicating that they do not correct abnormal bile acid synthesis and therefore cannot be recommended for CTX.[18]

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[14] Mignarri, A., et al. 2016. Evaluation of cholesterol metabolism in cerebrotendinous xanthomatosis. J Inherit Metab Dis 39(1): 75–83.

[15] Verrips, A., et al. 2020. The safety and effectiveness of chenodeoxycholic acid treatment in patients with cerebrotendinous xanthomatosis: two retrospective cohort studies. Neurol Sci 41(4): 943–949.

[16] Mondelli, M., et al. 2001. Cerebrotendinous xanthomatosis: 11-year treatment with chenodeoxycholic acid in five patients. An electrophysiological study. J Neurol Sci 190(1–2): 29–33.

[17] Berginer, V. M., et al. 1994. Magnetic resonance imaging in cerebrotendinous xanthomatosis: a prospective clinical and neuroradiological study. J Neurol Sci 122(1): 102–108.

[18] Batta, A. K., et al. 2004. Hydrophilic 7β-hydroxy bile acids, lovastatin, and cholestyramine are ineffective in the treatment of cerebrotendinous xanthomatosis. Metabolism 53(5): 556–562.

### FDA Guidance Corner

*In this case study, substantial evidence of effectiveness was demonstrated using one adequate and well-controlled clinical investigation plus confirmatory evidence. To demonstrate efficacy, the Applicant assessed a disease-specific biomarker that FDA accepted as a validated surrogate endpoint and used pharmacodynamic data from other biomarkers, along with mechanistic and natural history data from the literature, as confirmatory evidence. The draft guidance document below, when final, will represent the Agency's current thinking, describes factors to consider when assessing whether a single adequate and well-controlled clinical investigation and confirmatory evidence are sufficient to demonstrate substantial evidence of effectiveness. It also provides examples of types of data that could be considered confirmatory evidence.*

Draft Guidance for Industry Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (September 2023)

When one adequate and well-controlled clinical investigation and confirmatory evidence are considered together to assess effectiveness, the quality and quantity of confirmatory evidence are important considerations. Confirmatory evidence should be evidence generated from quality data derived from an appropriate source. The quantity (e.g., number of sources) of confirmatory evidence necessary to support effectiveness may vary across development programs. Importantly, the quantity of confirmatory evidence needed in a development program will be impacted by the features of, and results from, the single adequate and well-controlled clinical investigation that the confirmatory evidence is intended to substantiate.

Under certain circumstances, strong mechanistic evidence of the drug's treatment effect in a particular disease may be appropriate to use as confirmatory evidence. In such cases, (1) the pathophysiology of the disease should be well understood and (2) the drug's mechanism of action should be both clearly understood and shown to directly target the major driver or drivers of the disease pathophysiology. The quality and strength of mechanistic data exist on a spectrum, ranging from exploratory in nature to results that demonstrate clear evidence for a particular pathophysiological mechanism of disease and the drug's effect on the established mechanism.

In certain circumstances, natural history data can provide confirmatory evidence to substantiate the results of a single adequate and well-controlled investigation. Such an approach can be useful when there is uncertainty about whether the outcomes observed in the control group accurately reflect those that would have been expected in the absence of the intervention. Natural history data being used as confirmatory evidence should be distinct from any data used as a control for the single adequate and well-controlled clinical investigation.

*For more examples of when natural history data may be appropriate for use as confirmatory evidence, please refer to the Draft Guidance for Industry which, when final, will represent the Agency's current thinking.*

## Conclusion

FDA approved chenodiol for CTX, repurposing a previously approved therapy for a rare indication, based on:

- **RESTORE Trial Findings**: In a single adequate and well-controlled trial, chenodiol produced significant reductions in plasma cholestanol and urine 23S-pentol, and withdrawal of treatment led to increases in both biomarkers.
- **Literature Evidence for Biomarkers**: The Applicant provided robust evidence from the literature showing that chenodiol treatment significantly reduces plasma cholestanol levels associated with improvement in CTX symptoms. These findings, along with the well-understood pathophysiology of CTX and mechanism of action of chenodiol, support the RESTORE trial's results, indicating that reduction in plasma cholestanol predicts clinical benefit in patients with CTX receiving chenodiol. Based on this evidence, FDA considered cholestanol reduction a validated surrogate endpoint predictive of clinical benefit for CTX patients receiving chenodiol.
- **Literature Evidence for Mechanistic and Natural History Data**: Strong mechanistic evidence demonstrates that chenodiol directly corrects the underlying metabolic defect in CTX. Natural history data further demonstrates that the biomarker changes observed in the RESTORE trial differ from the expected natural progression of CTX and are consistent with symptom improvement seen with chenodiol treatment.

## Key Takeaways

- The Applicant submitted a 505(b)(2) application to repurpose chenodiol for CTX, relying in part on published literature and FDA's previous findings of chenodiol's safety for the treatment of radiolucent gallstones, its already approved indication.
- Prior to the FDA approval for CTX, chenodiol had been used as the standard of care for CTX for decades, generating an extensive body of literature, including multiple large, long-term observational studies, that the Applicant could rely on as evidence supporting the predictive clinical benefit of biomarker reduction.
- Although the Applicant identified urine 23S-pentol as the primary efficacy endpoint, FDA focused its efficacy assessment primarily on plasma cholestanol based on published scientific literature linking cholestanol to the pathology and clinical features of CTX.
- Confirmatory evidence supporting the efficacy findings was drawn from the published literature and included both strong mechanistic data, which reflects the well-defined pathophysiology of CTX and chenodiol's established mechanism of action, and natural history data showing that cholestanol and other biomarkers (e.g., urine 23S-pentol) remain persistently elevated in untreated CTX and decrease with chenodiol therapy.
- While the RESTORE trial lacked clinical outcome data to directly demonstrate treatment benefit, robust and extensive evidence from the literature allowed FDA to determine that plasma cholestanol was acceptable as a surrogate endpoint predictive of clinical benefit.

## Critical Thinking Questions for the Repurposing of an Approved Drug for a Rare Disease

Rare disease drug developers should engage FDA early when preparing for and designing a clinical investigation to repurpose an approved drug for a new rare disease indication. In such cases, the following questions should be considered:

- To support SEE, will there be reliance upon existing safety and/or efficacy data from a previously approved drug, from published literature, or both?
- Can published literature (e.g., long-term observational studies or biomarker data) be leveraged to support that the surrogate endpoint predicts clinical benefit?
- Can disease-specific biomarkers be incorporated as efficacy endpoints in the clinical investigation?
- What is the evidence that shows changes in the surrogate endpoint predict a clinical benefit?
- Can the biomarkers be justified as validated surrogate endpoints suitable for traditional approval, or are they more appropriate as biomarkers that are reasonably likely to predict clinical benefit surrogate endpoints for accelerated approval?[19]
- To establish substantial evidence of effectiveness using a single adequate and well-controlled investigation plus confirmatory evidence trial design, consider the following questions early in the drug development process:
    - What data will be used in the confirmatory evidence package to support the one adequate and well controlled investigation?
    - Can mechanistic data (i.e., the disease pathophysiology and/or the drug's role in correcting the underlying defect) serve as confirmatory evidence?
- Can natural history data be leveraged as part of the confirmatory evidence package?

**We recommend meeting with the Agency early[20] in the drug development program to reach alignment regarding endpoint selection, trial design, and the approach to demonstrate substantial evidence of effectiveness.**

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[19] Surrogate Endpoint Resources for Drug and Biologic Development

[20] Please refer to the Additional Resources section for guidance on how to engage early with FDA, including information on Critical Path Innovation Meetings, INTERACT Meetings, and Pre-IND Meetings

## Additional Resources

1. Draft Guidance for Industry and FDA Staff: Biomarker Qualification: Evidentiary Framework https://www.fda.gov/media/122319/download
2. Guidance for Industry: Expedited Programs for Serious Conditions https://www.fda.gov/media/86377/download
3. Guidance for Industry: Critical Path Innovation Meetings. https://www.fda.gov/media/89497/download
4. Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products. https://www.fda.gov/media/172311/download
5. Draft Guidance for Industry: Early Drug Development and the Role of Pre-IND Meetings. https://www.fda.gov/media/117322/download

## Case Study References by Order of Appearance

**Page 1**

- See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download
- See the FDA webpage with a list of guidance documents for Rare Disease Drug Development available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2)), available at https://www.govinfo.gov/content/pkg/USCODE-2022-title21/html/USCODE-2022-title21-chap9-subchapV-partA-sec355.htm

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- See Surrogate Endpoint Resources for Drug and Biologic Development available at https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development
- See BEST (Biomarkers, EndpointS, and other Tools) Resource available at https://www.ncbi.nlm.nih.gov/books/NBK326791/
- See the FDA webpage with a list of guidance documents for Rare Disease Drug Development available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at https://www.fda.gov/media/72419/download. When final, this guidance will represent the Agency's current thinking on this topic

**Page 3**

- See Appadurai V. et al. (2015). Apparent underdiagnosis of Cerebrotendinous Xanthomatosis revealed by analysis of ~60,000 human exomes. Mol Genet Metab, 116(4), 298–304., available at https://pubmed.ncbi.nlm.nih.gov/26643207/
- See Verrips A. et al. (2000). Presence of diarrhea and absence of tendon xanthomas in patients with cerebrotendinous xanthomatosis. Arch Neurol, 57(4), 520–524., available at https://pubmed.ncbi.nlm.nih.gov/10768627/

**Page 4**

- See the LEADER 3D video on Challenges, Strategies, and Regulatory Considerations for Rare Disease Clinical Trial Design, available at https://youtu.be/KKm2hG7foQw

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- See the Integrated Review on page 76 for additional information on CTX biomarker results for Chenodiol (Ctexli), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2026/219488Orig1s000MultidisciplineR.pdf

**Page 6**

- See Höflinger, P., et al. 2021. Metabolic profiling in serum, cerebrospinal fluid, and brain of patients with cerebrotendinous xanthomatosis. J Lipid Res 62: 100078., available at https://pubmed.ncbi.nlm.nih.gov/33891937/
- See Inoue, K., et al. 1999. Cholestanol induces apoptosis of cerebellar neuronal cells. Biochem Biophys Res Commun 256(1): 198–203., available at https://pubmed.ncbi.nlm.nih.gov/10066446/
- See Duell P. B., et al., 2018. Diagnosis, treatment, and clinical outcomes in 43 cases with cerebrotendinous xanthomatosis. J Clin Lipidol 12(5):1169-1178, available at https://pubmed.ncbi.nlm.nih.gov/30017468/
- See Nakamura, T., et al., 1991. Combined treatment with chenodeoxycholic acid and pravastatin improves plasma cholestanol levels associated with marked regression of tendon xanthomas in cerebrotendinous xanthomatosis. Metabolism 40(7): 741–746., available at https://pubmed.ncbi.nlm.nih.gov/1908036/
- See Catarino, C. B., et al. 2018. Brain diffusion tensor imaging changes in cerebrotendinous xanthomatosis reversed with treatment. J Neurol 265(2): 388–393., available at https://pubmed.ncbi.nlm.nih.gov/29260356/

- See DeBarber, A. E., et al. 2024. Genetically and clinically confirmed atypical cerebrotendinous xanthomatosis with normal cholestanol and marked elevations of bile acid precursors and bile alcohols. J Clin Lipidol 18(3): e465–e476., available at https://pubmed.ncbi.nlm.nih.gov/38637260/

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- See Mignarri, A., et al. 2016. Evaluation of cholesterol metabolism in cerebrotendinous xanthomatosis. J Inherit Metab Dis 39(1): 75–83., available at https://pubmed.ncbi.nlm.nih.gov/26153518/
- See Verrips, A., et al. 2020. The safety and effectiveness of chenodeoxycholic acid treatment in patients with cerebrotendinous xanthomatosis: two retrospective cohort studies. Neurol Sci 41(4): 943–949., available at https://pubmed.ncbi.nlm.nih.gov/31863326/
- See Mondelli, M., et al. 2001. Cerebrotendinous xanthomatosis: 11-year treatment with chenodeoxycholic acid in five patients. An electrophysiological study. J Neurol Sci 190(1–2): 29–33., available at https://pubmed.ncbi.nlm.nih.gov/11574103/
- See Berginer, V. M., et al. 1994. Magnetic resonance imaging in cerebrotendinous xanthomatosis: a prospective clinical and neuroradiological study. J Neurol Sci 122(1): 102–108., available at https://pubmed.ncbi.nlm.nih.gov/8195796/
- See Batta, A. K., et al. 2004. Hydrophilic 7β-hydroxy bile acids, lovastatin, and cholestyramine are ineffective in the treatment of cerebrotendinous xanthomatosis. Metabolism 53(5): 556–562., available at https://pubmed.ncbi.nlm.nih.gov/15131757/

**Page 8**

- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023), available at https://www.fda.gov/media/172166/download. When final, this guidance will represent the Agency's current thinking on this topic.

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- See Surrogate Endpoint Resources for Drug and Biologic Development, available at https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development