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APPLICATION NUMBER:

205750Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205-750 (0)
Priority or Standard	Priority
Submit Date(s)	November 21, 2013
Received Date(s)	November 21, 2013
PDUFA Goal Date	March 5, 2015
Division / Office	Division of Gastroenterology and Inborn Errors Products / ODE3 / CDER
Reviewer Name(s)	Wen-Yi Gao, M.D., Ph.D.
Review Completion Date	February 12, 2015
Established Name	Cholic Acid
(Proposed) Trade Name	Cholbam
Therapeutic Class	Bile Acid
Applicant	Asklepiion Pharmaceuticals, LLC.
Formulation(s)	For oral administration
Dosing Regimen	10-15 mg/kg once daily in both pediatric and adult patients
Indication(s)	Treatment of bile acid synthesis disorders
Intended Population(s)	Pediatric and adult patients

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant Asklepiion Pharmaceuticals submitted an NDA for the treatment of bile acid synthesis disorders involving single enzyme defects (SED) and peroxisomal disorders (PD). The product cholic acid (Cholbam) is a new molecular entity for FDA review.

Cholic acid is an endogenous primary bile acid; [REDACTED] (b) (4)

[REDACTED] Impairment of bile acid synthesis is associated with insufficient bile fluid secretion by hepatocyte. The impairment of synthesis has been proposed to be responsible for the intrahepatic cholestasis in SED and PD patients. The sponsor is planning to use cholic acid replacement therapy to stimulate the conjugation of bile acids in hepatocytes, to increase the bile flow to small bile ducts, and to reduce the hepatic retention of bile acids.

SED and PD are rare diseases. This review assesses the effectiveness and safety primarily based on an open-label, single arm, and compassionate use study (CAC-91-10-10). The study continued for 18 years, and the data were collected from 54 SED patients and 31 PD patients (ITT population, 85 patients). The average age was 3 years at the initiation of treatment. The majority of patients were treated at the level of approximate 15 mg/kg PO daily for an average of 145 weeks (6 of the 85 patients, 4 SED and 2 PD patients, did not have a record of treatment). Blood and urine samples were examined at baseline, Month 1, and Month 6; then every 3 to 6 months. Liver biopsy was performed in some patients every 6 months.

The primary effectiveness analysis was based on the Post-Hoc analyses of the responders to cholic acid treatment that was defined by this reviewer. The sponsor used [REDACTED] (b) (4) in their submission which I did not agree.

Analyses are performed with the 79 patients (SED: 50, PD: 29) who received at least 1 dose of cholic acid during the study. The purpose of the analyses is to identify the number of patients who had intrahepatic cholestasis at baseline, and the number of patients who responded to the targeted treatment.

Baseline Cholestasis Criteria (Post-Hoc): Cholestasis was defined as patients who met ≥ 2 of abnormal biomarkers:

- ALT/AST values > 50 U/L;
- Total bilirubin values > 1 mg/dL or direct bilirubin > 0.3 mg/dL;
- Evidence of cholestasis on liver biopsy;
- Urinary FAB-MS score > 2 .

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Responder Criteria (Post-Hoc): Cholic acid responders were defined as patients who either a) met at least two of the laboratory criteria and were alive at the last follow-up; or met at least one laboratory criterion, had increased body weight and were alive at the last follow-up.

Laboratory Criteria:

- ALT/AST reduced to < 50 U/L, or baseline level reduced by 80%
- Total bilirubin reduced to \leq 1 mg/dL
- No evidence of cholestasis on liver biopsy

Clinical Criteria:

- Body weight increase by 10%, or stable at > 50 percentile
- Alive at the last follow-up.

The results show 68% of SED patients who had cholestasis at baseline; and 62% of SED patients who were cholic acid responders. Most of the responders met the body weight increase and survival criteria plus 1 to 3 laboratory criteria. Most of the responders were from the 3 β -HSD (3 β -hydroxy-5-C27-steroid dehydrogenase) deficiency.

On the other hand, the results show approximate 55% of PD patients who did not have commonly recognized cholestasis at baseline. None of the 29 PD patients was the cholic acid responder by the criteria. An alternative analysis of weight change plus survival shows two of the 29 PD patients who responded in both (the two patients had Refsum disease).

Safety assessments were based on Study CAC-91-10-10 (Safety Population) and compared with the historical control without treatment. In patients with SED, there were 6 deaths (12%, 6/50). The death rate on treatment was numerically lower than the historical untreated control (24%, 6/25). A historical sibling study shows that in a family with 3 β -HSD deficiency, 4 of the 5 siblings died at their early ages. The fifth child born to this family survived, because the patient started primary bile acid therapy at an early age. This sibling report is considered to be clinically relevant, because the majority of SED patients (70%, 35/50) in the study are 3 β -HSD deficiency.

In patients with SED, disease progression is the cause of deaths (6 cases). Disease progression was defined as increase of serum bile acids, transaminases, and bilirubin; or cholestasis on liver biopsy. Adverse events (AEs) were not recorded on a daily basis in the study. There were 4 patients who had non-fatal serious adverse events (SAEs). These were disease progression, jaundice, coagulopathy, and urinary tract infection. There were 7 patients who discontinued study medication due to an AE (14%, 7/50). These AEs were disease progression and cholestasis. The most common AEs in SED were pyrexia, diarrhea, jaundice, abdominal pain, respiratory tract infection, and epistaxis. Vital sign and clinical laboratory tests other than serum transaminases and bilirubin were not available for the review. There were 21 SED patients who continued from CAC-91-10-10 to CAC-002-01. The 120 day-safety update report was reviewed.

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There was no additional safety issue identified (see the safety review under Appendix 9.6).

In patients with PD, there were 14 deaths (48%, 14/29). The overall death rate on treatment was numerically lower than the historical untreated control (68%, 21/31). However, PD is a heterogeneous disease; and the majority live longer than 1 year old. In these patients, the death rate (60%, 12/20) of the treated is higher than the historical control (18%, 2/11); and the natural history study (29%, 9/31) reported by Poll-The et al. (Poll-The, 2004).

The most frequent causes of deaths in PD were disease progression (6 cases) and unknown causes (6 cases). There were 4 patients who had a non-fatal serious adverse event. These were diarrhea, gastroenteritis, and dehydration. There were 14 PD patients who discontinued study medication due an AE (48%, 14/29). The AE was disease progression. The most common AEs were convulsion, diarrhea, gastroenteritis, dehydration, respiratory tract infection, and pyrexia. Vital sign and clinical laboratory tests other than serum transaminases and bilirubin were not submitted. There was no sibling study with the PD patients. There were 10 PD patients continued from CAC-91-10-10 to CAC-002-01. The 120 day-safety update report was reviewed. There no additional safety issue identified (see the safety review under Appendix 9.6).

A PD mice model study by Keane shows that cholic acid and UDCA-fed mice worsened the pre-existing defects in mitochondria and hepatocytes; and that cholestasis precedes the deaths (Keane, 2007).

Taken together, the benefit-risk evaluation of SED shows that Cholbam treatment brought about clinically weight improvement and prolonged survival; the clinical improvements associated with the reduction of serum levels of transaminases and bilirubin (total and direct); and with the microscopic improvement of cholestasis. Responder analyses show that the majority of SED patients responded to cholic acid treatment, which is consistent with the numerically lower death rate than the historical untreated control. The major insufficiency of the study includes a) a single arm study; b) many missing data and protocol deviations which were identified by the clinical inspection team of DSI; and c) the responder analyses which contained 3 biomarker components (transaminases, bilirubin, and liver biopsy). The clinical benefits need to be demonstrated. In summary, the clinical reviewer recommends **Approval of Cholbam for the treatment of single enzyme defects** under the accelerated approval regulations, 21 CFR 314.510, requiring further adequate and controlled clinical trials to verify the clinical benefit.

The benefit-risk evaluation of PD shows an inconsistent pattern of the safety and effectiveness. None of the PD patients responded to cholic acid treatment based on the post hoc analyses defined by this reviewer. No long-term survival benefit is identified. The clinical reviewer cannot recommend approval based on the present application.

1.2 Risk Benefit Assessment

Unmet Medical Need and Benefit of SED Patients:

- Cholbam is the first product applied in the United States for the treatment of cholestasis of patients with single enzyme defects of bile acid synthesis.
- Most patients are responders to the treatment.
- 65% (20/31) of patients meet both of the clinical criteria of weight improvement and survival, plus 1 to 3 transaminases, bilirubin, and liver biopsy criteria.
- Numerically lower death rate on treatment (12%, 6/50) as compared with the historical untreated control (24%, 6/25);
- Historical Sibling Control supports the treatment benefit in patients with 3 β -HSD deficiency which is the major deficiency in the SED patients (70%, 35/50) of Study CVC-91-10-10.

Risks:

- In infants < 1 month of age, cholic acid treatment may cause cholestasis and hepatic damages;
- In patients with pre-existing biliary obstruction, cholic acid treatment may cause secondary cholestasis and hepatic damages.

In summary, in the reviewer's opinion, the above benefit-risk assessment is in favor of the approval of Cholbam for the treatment of patients with single enzyme defects. However, causation should be taken against bile acid toxicity.

Unmet Medical Need and Benefit in PD Patients:

- Cholbam is the first product applied in the United States for the treatment of cholestasis of patients with peroxisomal disorders.
- Numerically lower serum transaminase ALT/AST compared to the levels at baseline;
- Numerically lower overall death rate as compared with the historical untreated control (48% vs. 68%).

Risks:

- In PD patients age > 1 year old, the death rate on cholic acid treatment (60%, 12/20) is higher than the historical untreated control (18%, 2/11), and the natural history study (29%, 9/31) by Poll-The et al.
- Body weight percentile on treatment was decreased from median baseline percentile 4 to median post-treatment percentile 1;
- None of the PD patients was the responder to cholic acid treatment in the post hoc analysis performed by this reviewer.
- Pre-clinical study using PD mice model shows that cholic acid feeding worsened the pre-existing mitochondrial and cellular damages in the PD liver.

In summary, the benefit-risk assessment of PD data does not support the approval of Cholbam for the treatment of bile acid synthetic defects in patients with peroxisomal disorders.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendation of REMS.

1.4 Recommendations for Postmarket Registry Study

The sponsor should conduct a postmarketing efficacy and safety registry study to further assess clinical and laboratory outcomes in patients treated with Cholbam. The clinical data should be collected systematically on both patients with bile acid synthesis disorders involving single enzyme defects and patients with peroxisomal disorders. A draft protocol is proposed to facilitate the development of the registry study.

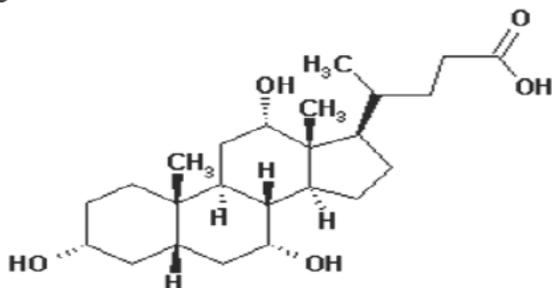
2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug product is Cholic Acid Capsules (Cholbam), and the strength is 50 mg and 250 mg. The product is (b) (4) which was manufactured by (b) (4).

Cholic acid belongs to the pharmacotherapeutic class of bile acid preparations (ATC Code A05AA03). The proposed indication is: "treatment of bile acid synthesis disorders (b) (4)".

Figure 1: Structural Formula of Cholic Acid



Cholic Acid (Cholbam)

2.2 Currently Available Treatments for Proposed Indications

To date, there is no approved therapy for the treatment of single enzyme defects or peroxisomal disorders in the United States.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is cholic acid which is not available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

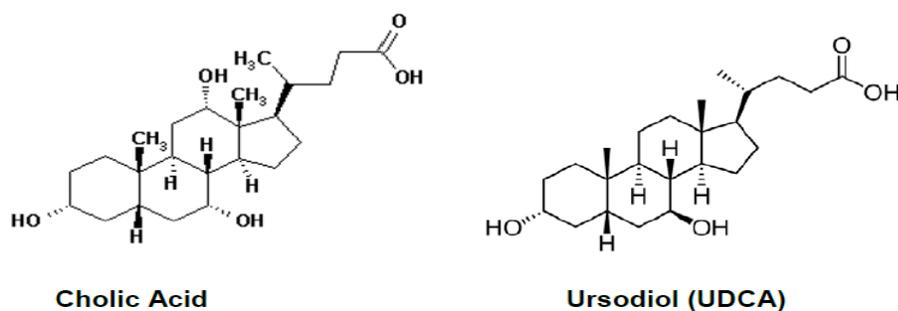
Cholic acid is a primary bile acid. In the same drug class, Ursodiol (URSO[®] & URSO Forte[®]), a secondary bile acid, was approved for the treatment of primary biliary cirrhosis (PBC) in December 1997 (NDA 20-675). FDA issued Warnings and Precautions of ursodiol in December 2012:

- Contraindications: contraindicate Urso in patients with complete biliary obstruction;
- Warnings and Precautions: warning regarding hepatotoxic effects, the need to maintain bile flow, and recommend liver function and bilirubin monitoring.

This regulatory action was based on the reports:

- In animal studies of bile duct obstruction, UDCA induced bile duct infarcts and bile leakage into the surrounding liver tissues.
- Safety database search by the sponsor (Aptalis Pharma US, Inc.) of ursodiol identified 215 case reports: There was a strong temporal relationship between UDCA administration and sharp increase of ALT and AST tests in patients with biliary obstruction. On the other hand, withdrawal of UDCA reduced the LFTs. Maintenance of the bile flow improved the clinical signs.

Figure 2: Structural formulation of Cholic Acid and Ursodiol



2.5 Summary of Pre-submission Regulatory Activities

Cholbam was studied under IND 45,470 submitted in June 1994. The IND was transferred to Asklepiion Pharmaceuticals, LLC in May 2007 for the purpose of commercializing the product. A brief summary of the regulatory history is listed as follows:

- The original research IND (IND 45,470) [REDACTED] (b) (4) [REDACTED] was submitted by the principal investigators James Heubi, MD, and Kenneth Setchell, PhD, in June 1994.
 - The first study protocol (CAC-91-10-10) was approved by IRB in January 1992, aimed at testing orally administered bile acid in patients with defects in enzymes responsible for catalyzing the initial reactions in the metabolism of cholesterol.
 - The study was extended to patients with defects in peroxisome functions (due to defects in peroxisomal single enzymes or structural proteins, peroxins, for normal peroxisome assembly). Peroxisome may involve the de novo synthesis and bile acid metabolism. These patients were enrolled under a sub-study protocol (CAC-92-8-19) that was conducted from September 1992 to August 2002. After the closure of CAC-92-8-19, patients continued the treatment under study CAC-91-10-10.
 - In May 2007, the investigators transferred IND 45,470 to Asklepiion Pharmaceuticals, LLC. Asklepiion had a Type C meeting with DGP to discuss the content of proposed NDA submission for Cholic Acid on September 25, 2007;
- On September 25, 2007, the Division addressed the concerns about the adequacy of the available clinical data to support an NDA at a Type C industry meeting with Asklepiion. On October 19, 2007, the Division issued meeting minutes to Asklepiion.
- On December 6, 2007, FDA opened the discussion with Asklepiion in three areas (i.e., study control groups, clinical efficacy endpoints, and bridging studies).
- Another meeting to discuss bridging study and clinical data for the planned NDA submission on September 17, 2009.
- In January 2010, Asklepiion defined that the cut-off date of data collection was December 31, 2009 for Study CAC-91-10-10 (January 3, 1992 to December 31, 2009). The patients were treated continuously, and the clinical data were collected under the clinical protocol CAC-002-01. The protocol of CAC-002-01 was approved by the IRB of Cincinnati Children's Hospital Medical Center (CCHMC) in December 2011. To avoid any gaps in data collection, the sponsor

retrospectively documented the data from January 1, 2010 to the protocol CAC-002-01.

- In January 2010, Asklepiion had a pre-NDA meeting with DGP to discuss the content of proposed NDA submission for Cholic Acid. During the meeting DGP stated the following:
 - The Agency may consider reviewing efficacy data retrospectively collected and analyzed if adequate justification for the use of this type of study is provided.
 - The data submitted suggest that efficacy may be limited to only 3 β -HSD and Δ^4 -3-oxosteroid 5- β -reductase deficiency patients.
 - Data may be retrospectively collected; however, these data must be compared to a carefully selected control population. Therefore identification of a historical control group based on the natural history data collected in the specific enzyme defect the investigators have studied is important to establish as an adequate comparator.
 - The investigators may choose to demonstrate efficacy based on normalization in atypical bile acid metabolites in serum and urine. If so, the investigators should consider using a method such as gas/liquid chromatography and mass spectrometry (G/LC-MS) to not only identify the peaks but also to provide quantification of atypical bile acids in urine and serum.
- In July 2012, Asklepiion had a meeting with the Division to discuss issues of historical control. During the meeting DGP stated the following:
 - To gain approval for Cholic Acid the sponsor will need to demonstrate in at least one adequate and well controlled trial with supportive evidence that Cholic Acid is safe and effective for a specific target population.
 - Carefully review the natural history of all available patients and kindred to identify a cohort of patients based on clinical criteria (e.g., bile acid profile at time of diagnosis, at age at diagnosis, degree of liver injury at the time of diagnosis) who are likely to rapidly progress to a serious clinical outcome (e.g., death, liver failure) over a defined period of time. Such a “natural history” cohort may be acceptable to serve as a nonconcurrent control group in a trial in which patients are prospectively enrolled based on criteria that are matched to the clinical features of the natural history cohort. However, the criteria must be defined *a priori* in order to avoid potential bias that may result for post-hoc identification of characteristics that may be associated with rapid progression of disease.

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- Retrospectively collected data to demonstrate efficacy is subject to significant systemic bias and is not considered to be “an adequate and well-controlled study” as defined under 21CFA314.126(b).
- Current Submission: The sponsor submitted NDA 205,750 on November 21, 2013. The proposed indication was [REDACTED] (b) (4)
- In late 2013, Asklepiion submitted a Marketing Authorization Application to EMA (European Medicines Agency) for Cholic Acid FGK for the treatment of inborn errors in primary bile acid synthesis, and the application was approved in January 2014 for the treatment of SED, but not PD.
- On March 21, 2014, Asklepiion submitted the Day 120-Safety Update Report. The safety data were summarized from Study CAC-002-01 which was the continuation study of CAC-91-10-10.
- On January 7, 2015, Asklepiion submitted the interim study report of CAC-002-01. The study was initiated on January 1, 2010, and the cut-off date for interim report was on September 30, 2012. A total of 41 patients (29 SED patients; 12 PD patients) were enrolled in the study. Among them, 31 patients were from the CAC-91-10-10 study, and 10 patients were treatment naïve.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of this submission is poor. The clinical data were generated by a research study for a compassionate use for more than 10 years. Rules of Good Clinical Practices were not followed. The sponsor stated that “any patient in the study may have protocol deviation at some point during the study period. In consequence, protocol violations were not used to exclude patients from the ITT data set.”

In summary, after a lot of information requests, the reviewer was able to complete the review. The final datasets allowed an independent review.

3.2 Compliance with Good Clinical Practices

According to the Applicant, Study CAC-91-10-10 (including sub-study CAC-92-8-19) was not conducted following Good Clinical Practice (GCP) guidelines (documented in the International Conference on Harmonization and the Food and Drug Administration).

DSI Clinical Inspection of Study CAC-91-10-10:

Overall Assessment of Findings and Recommendations

“For this application, inspections were conducted at Dr. Heubi’s site, the clinical study site where the study was conducted as a sponsor investigator study from 1994 to 2007 and an inspection was conducted at Asklepiion Pharmaceuticals, LLC, the sponsor / applicant site. The classification of Dr. Heubi’s site is Voluntary Action Indicated (VAI) because of violations concerning obtaining and documenting informed consent of study subjects, failure to follow the protocol and inadequate drug disposition records. None of these deficiencies are determined to have significantly impacted data integrity. Deficiencies concerning GCP are described in the clinical study report. The data is accurately reported in the clinical study report and datasets submitted in support of the application. The inspection did not uncover any new information or significant findings that would appear to contradict the study report. The study report and the data generated by the site may be used in evaluation for the efficacy of the product.” (Susan Leibenhaut, MD; Susan Thompson, MD; and Kassa Ayalew, MD; DARRTS, 9/3/2014)

OSI Inspection of Study CAC-003-01:

Study CAC-003-01 is entitled “Comparative Bioavailability of Three Formulations of Cholic acid in Healthy Male Subjects Using a Multiple Dose Repeated Measures Approach”. The inspection is part of FDA’s Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research and to ensure that the data are scientifically valid and accurate. The conclusion was the sponsor did not adhere to the applicable statutory requirement and FDA regulations (b) (4) for in vivo bioequivalence study. (Sean Kassim, PhD; DARRTS, 10/21/2014)

3.3 Financial Disclosures

The Applicant Asklepiion has submitted FDA Form 3455 to disclose that the Clinical Investigators (b) (6) had significant payments and equity interests with Asklepiion:

Summary of Form 3455 (b) (6)

1. Significant payments:

Reimbursed travel expenses

Asklepiion reimbursed a total of \$3,907.24 for attending meetings from (b) (6)

2. Significant equity interests:

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[Redacted] (b) (6)

Summary of Form 3455 [Redacted] (b) (6)

1. Significant payments:

Consulting services

Asklepiion paid a total of \$82,001.18 on [Redacted] (b) (6)

Reimbursed travel expenses

Asklepiion paid a total of \$22,952.66 from [Redacted] (b) (6)

2. Significant equity interests:

[Redacted] (b) (6)

Summary of Form 3454 for other clinical investigators:

The following six investigators had no financial interests to disclose: Beeno G. Roesch, MD; Alexander Miethke, MD; Wilfredo D. Garcia, MD; Nada Yazigi, MD; Gregory J. Thracey, MD; and John Bucuvalas, MD.

Clinical Investigator Financial Disclosure
 Review Template

Application Number: NDA 205750
 Submission Date(s): November 21, 2013
 Applicant: Asklepiion Pharmaceuticals, LLC
 Product: Cholbam (cholic acid)
 Reviewer: Wen-Yi Gao
 Date of Review: June 16, 2014
 Covered Clinical Study (Name and/or Number): Study CAC-91-10-10

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 92		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

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Note: Based on the report of FDA inspection team, DGIEP requested the financial disclosure forms of five additional clinical investigators whose names were not on the Form 3454 on May 8, 2014. The physicians' names were Samuel Kocoshis, MD; Hisham Nazer, MD; Mohammed Othman Banemai, MBBS; Erick Hernandez, MD; and Milton Scharff, MD.

Asklepion responded on June 16, 2014. The letter stated that "There were total 92 patients at over 70 different locations around the world enrolled the 91-10-10 study. There is no evidence that any financial or other material payment was ever provided to any of the 92 referring physicians."

Medical Officer Comments:

The Applicant has reasonably disclosed financial arrangements with clinical investigators in this application. The submitted financial disclosures do not bring up concerns which would possibly jeopardize the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Chemistry Manufacturing and Controls (CMC) were reviewed by the chemistry reviewers Drs. Gene Holbert and Moo Jhong Rhee. They recommend that "This NDA has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facility involved are not in compliance with cGMP and labels do not have adequate information as required. Therefore, from a CMC perspective, this NDA is not ready for "Approval" in its present form per 21 CFR 314.125 (b)(1),(6), and (13)." (DARRTS, August 4, 2014).

4.2 Clinical Microbiology

There is no clinical microbiological issue raised by the current submission. The Quality Microbiology was reviewed by Drs. Bryan Riley and Stephen Langille. The summary recommendation was as follows: "The Microbial Limits specification for Cholic Acid Capsules (50 mg and 250 mg) is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology." (DARRTS, December 4, 2013).

4.3 Preclinical Pharmacology/Toxicology

Preclinical Pharmacology and Toxicology were reviewed by Drs. Ke Zhang and David Joseph. They did not identify an issue that would preclude approval (DARRTS on July 21, 2014).

Dr. Zhang commented that “No nonclinical studies of cholic acid were conducted to support approval of this application. Since cholic acid is the most abundant bile acid in humans, there is minimal concern about its safety from a nonclinical viewpoint. In response to a request from the Agency, the sponsor provided data which indicate that the total body content of cholic acid at the proposed dose level in pediatric patients with defects in bile acid synthesis (the target patient population) will not exceed that of the normal pediatric population. Thus, the drug product (Cholbam) can be accurately described as a bile acid replacement therapy in the context of the proposed indication.” “From a nonclinical standpoint, the NDA application should be approved for the proposed indication”. The Associated Director of Pharmacology/Toxicology, OND, Dr. Abby Jacobs commented “No nonclinical studies were conducted to support approval, but this is OK, since cholic acid is an abundant bile acid in humans. I concur that there are no outstanding pharm/tox approval issues”; and “I concur with the recommendations for the division regarding labeling of pharm-tox sections”. (DARRTS, July 30, 2014)

4.4 Clinical Pharmacology

The Clinical Pharmacology review was performed by Drs. Insook Kim and Sue Chih Lee. Drs. Kim and Lee did not identify an issue that would preclude approval of the NDA (DARRTS, July 23, 2014).

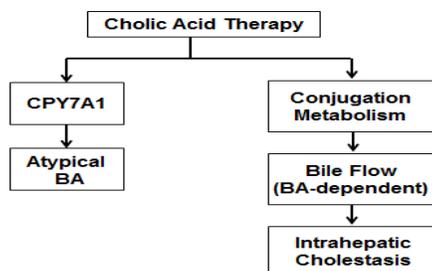
The Biopharmaceutics was reviewed by Drs. Kareen Riviere and Tapash Ghosh. They recommended approval for NDA 205750/Cholbam (DARRTS, July 24, 2014 and December 5, 2014).

DGIEP invited the Maternal Health team, Drs. Tamara Johnson Carrie Ceresa and Lynne P. Yao to attend meetings and to assist in the labeling review. The Maternal Health team did not identify an issue that would preclude approval of the NDA (DARRTS, June 30 and December 15, 2014).

4.4.1 Mechanisms of Action

Bile acids binding to their nuclear receptors (such as FXR, also known as farnesoid X receptor) in hepatic cells down-regulates the transcription of *CYP7A1* gene and up-regulates the transcription of genes that code for metabolic conjugation enzymes. The clinical significance of the up-regulation of metabolic conjugation of bile acids, leading to increase of bile-acid dependent bile flow are well established, whereas the clinical significance of down-regulating the transcription of *CYP7A1* is not entirely clear.

Figure 3: Mechanisms of Cholic Acid Actions



(1) Up regulation of hepatic conjugation enzymes.

Binding of bile acids (such as cholic acid) to FXR induces microsomal UDP-glucuronosyltransferase and cytosolic sulfotransferase transcription. As a result, metabolic conjugation of bile acids at microsome and cytoplasm increases, and bile acid-dependent bile flow increases. Hepatocytes secrete bile acid-dependent bile; while cholangiocytes contribute to bile acid-independent bile flow. Effect of cholic acid on bile acid independent (glutathione) bile flow is not clear. In summary, it is the metabolic conjugations that reduce bile acids retention (Barbier, 2003; Trottier, 2006; Li, 2000). “Cholestasis” denotes retention of bile in the liver; and the term “cholestatic jaundice” is commonly used when conjugated hyperbilirubinemia results from impaired bile flow. This is because bilirubin uses the same set of transporters and conjugation enzymes for the metabolism (Li, 2000; Trottier, 2011). Because the impairment of hepatic conjugation in SED and PD liver, total bilirubin and direct bilirubin are used as a biomarker for cholic acid actions in this study.

Other ligand-activated nuclear receptors of bile acid metabolism include peroxisome proliferator-activated receptor α (PPAR α) and pregnane X receptor (PXR).

(2) Down regulation of bile acid synthesis: Suppression of the transcription of cholesterol 7 α -hydroxylase (*CYP7A1*) is another function of activated FXR. Cholesterol 7 α -hydroxylase is the rate-limiting enzyme in bile acid synthesis from cholesterol. Suppression of the transcription may reduce the de novo synthesis of primary bile acids. Many bile acids including ursodiol are able to trigger the down-regulation of *CYP7A1* gene expression. Chenodeoxycholic acid (CDCA) is the most potent endogenous activator of FXR among bile acid metabolites.

(3) Cholestasis and control of bile acid toxicity

At physiological condition, glycine and taurine conjugations are the main metabolic pathway; when retention of bile acids occurs, UDP and sulfa conjugations take over (Barbier, 2003; Trottier, 2006; Russell, 2003; Barbier, 2003). Tauroithochoic acid is the most potent inhibitor of UDP-glucuronosyltransferase (Fang, 2013).

4.4.2 Pharmacodynamics

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Cholic acid is a primary bile acid and a physiological end product of cholesterol metabolism in human. At therapeutic doses, cholic acid stimulates bile flow by up-regulating UDP-glucuronosyltransferase expression, and inhibits endogenous over production of cholestatic bile acid by down-regulating cholesterol 7- α -hydroxylase expression.

Functional properties of bile acid

Newly synthesized bile acids are secreted by hepatocytes along with bile into small bile ducts and delivered to the lumen of small intestine where they emulsify dietary fat, cholesterol, and fat-soluble vitamins into small fat globules (micelles). Bile salts are on the outside of the micelle. The micelles move along the intestinal microvilli surface allowing their lipids to diffuse across the microvilli membrane (passive diffusion) and into the enterocyte. Then the bile salts, freed of associated lipids, are absorbed in the terminal ileum by a Na⁺-dependent active transport process.

Role of nuclear receptors in reduction of bile acid toxicity

Bile acid synthesis in the liver is regulated precisely. When bile acids accumulate, synthesis is reduced by a negative feedback mechanism that decreases the expression of two enzymes in the biosynthetic pathway, cholesterol 7 α -hydroxylase and 12 α -hydroxylase. Conversely, cholesterol accumulation induces bile acid synthesis by activating cholesterol 7 α -hydroxylase in human (Russell, 2003). The regulation of cholesterol 7 α -hydroxylase takes place at the transcriptional level (Russell, 1992).

Farnesoid X Receptor

Suppression of bile acid synthesis is mediated by FXR, which binds bile acids and activates the transcription of genes. The bile acid pool contains more than twenty different bile acids that vary in their abilities to activate FXR. In vitro studies show that chenodeoxycholic acid is the most potent FXR ligands, whereas cholic acid and ursodexoycholic acid are less active.

4.4.3 Pharmacokinetics

Absorption

Orally administered cholic acid is absorbed by passive diffusion through plasma membranes along the length of the gastrointestinal tract, because of its hydrophobicity. Glycol- and taurine-conjugated bile acids are absorbed at ileum through receptor-mediated transportation (apical sodium-dependent bile-acid transporter, ASBT). In the presence of enteral bacteria, a portion of cholic acid may be dehydroxylated to form secondary bile acid. Absorbed cholic acid enters blood stream of portal vein, and is taken up by hepatocyte via Na⁺-dependent and Na⁺-independent transporters.

Distribution

Internalized cholic acid distributes to cytoplasm and smooth endoplasmic reticulum where ring-structure modification and side chain oxidation take place. Modified cholic

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acids then bind to ligand-activated nuclear receptors, such as FXR, stimulate the expression of UGT, and down-regulate the expression of cholesterol 7 α -hydroxylase.

Biotransformation

In physiologic condition, bile acids conjugate with amino acids, glycine or taurine, to form bile salts. Conjugated bile acids have lower pKa (1 to 4), which makes them much water soluble and easy to emulsify fats at small intestine. In pathologic condition, bile acids conjugate UDP through stimulation of UGT expression. Conjugated bile acids become removable from hepatocytes.

Excretion

Removal of conjugated bile acids from hepatic cells to biliary canaliculi through receptor-mediated transportation, and bile is stored at gallbladder. Dietary fat stimulates secretion of bile salts. In total about 20 to 30 grams of bile acid are secreted into the intestine daily. About 90% of excreted bile acids are reabsorbed by active transport in the ileum and recycled that is called “enterohepatic circulation”. About 95% of bile acids in the portal circulation are actively up-taken by hepatocyte. The rest 5% enters systemic circulation. In the kidney, bile acids pass glomerular filtration, and are reabsorbed by proximal renal tubular cells. The un-absorbed bile acids are excreted from urine.

As a result, about 600 mg of bile salts are synthesized daily to replace bile acids lost in the feces and urine. The rationale of cholic acid dosing regimen in this study is to replace the lost bile acids.

PK Parameters

The pharmacokinetic profile (C_{min} , C_{max} , T_{max} , $T_{1/2 Elim}$ and AUC_{tau}) of the to-be marketed capsules was compared with the clinical research capsules in 18 healthy male volunteers (CAC-003-01). (b) (4)

The sponsor concluded that these two capsule formulations are equally bioavailable. The elimination-half-live of cholic acid was $T_{1/2} \approx 3$ hours in healthy adult males.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Key Studies Submitted

- Primary Study: Study CAC-91-10-10 including sub-study CAC-92-8-19:
 - Open-label, single arm, and compassionate use study in patients with single enzyme defects of bile acid synthesis, or with peroxisomal disorders.

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- ITT population 85 patients (SED: 54; PD: 31): defined as subjects who have an inborn error in bile acid synthesis identified at baseline.
- ITT population for responder analyses 79 patients (SED: 50; PD: 29): defined as subjects who had an identified inborn error, and received at least one dose of cholic acid.
- Other supportive studies:
 - Study CAC-001-01 (therapeutic equivalency TBM vs. CU: 16 SED patients)
 - Study CAC-003-1 (PK study): 18 healthy adults.

Historical Control Submitted

Literature search for SED patients who had ≥ 2 years of untreated history was performed by Asklepiion. Also 10 cases of SED sibling data were submitted. Literature search for PD patients did not have the requirement of ≥ 2 years of untreated history.

- SED history control
A total of 18 papers were identified, which provided 25 cases of historical control across 4 disorders (β -HSD, AKR1D1, CTX, and Smith-Lemli-Opitz disease).

Table 1: Historical Control Cases of SED

HSPID#	Defect	Age at Dx (yr)	Age at Death (yr)	Source
1	β -HSD	3.5	NA	Akobeng 1999
2	β -HSD	3	NA	Akobeng 1999
3	β -HSD	2.75 (2 yr 9 mo)	NA	Buchmann 1990
4	β -HSD	26	NA	Fischler 2007
5	β -HSD	23	NA	Kobayashi 2000
6	β -HSD	24	NA	Molho-Pessach 2012
7	β -HSD	3	NA	Riello 2010
8	β -HSD	5.5	NA	Riello 2010
9	AKR1D1	0.75 (9 mo)	0.75 (9 mo)	Kimura 1998
10	AKR1D1	9	NA	Narchi 1999
11	AKR1D1	0.08 (1 mon)	0.12 (44 d)	Ueki 2009
12	AKR1D1	0.03 (12 d)	0.21 (77 d)	Ueki 2009
13	AKR1D1	0.03 (10 d)	0.09 (32 d)	Ueki 2009
14	AKR1D1	0.04 (14 d)	0.24 (87 d)	Ueki 2009
15	CTX	55	NA	Bel 2001
16	CTX	40	NA	Bencze 1990
17	CTX	21	NA	Bonnot 2010
18	CTX	32	NA	Soffer 1995
19	CTX	34	NA	Bumett 2001
20	CTX	43	NA	Fiorelli 1990
21	CTX	33	37	Donaghy 1990
22	Smith-LO	10	NA	Irons 1994
23	Smith-LO	3.5	NA	Irons 1994
24	Smith-LO	13	NA	Irons 1994
25	Smith-LO	8.5	NA	Starck 1999

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Mean (yr)	15.74 ±16.16	6.40 ±14.99	
Historical Patients	n = 25	n = 6	

From the Historical Control Summary, NDA 205,750. Smith-LO: Smith-Lemli-Opitz disease; HSPID#: Historical SED patient identification number; Dx: diagnosis; Yr: years; Mo: months; d: days; NA: data not available.

- SED sibling control
A total of 10 sibling cases: 3β-HSD: 7 cases; AKR1D1: 2 cases; and AMACR: 1 case.
- PD historical control
A total of 9 papers were identified, which provided 29 cases of historical PD control. The subtype disorders are not available. However, according to the phenotypic category of PD by Poll-The and his colleagues (Poll-The, 2004), there are 18 patients who died before 1 year of age belonging to the classical Zellweger syndrome; and there are 11 patients who survived more than 1 year of age belonging to the milder PD.

Table 2: Historical Control Cases of Peroxisomal Disorders

HPPID#	Age at Dx (yr), n=31	Age at Death (yr), n=21	Source
1	0.25 (3 mo)	0.67 (8 mo)	Aubourg 1985
2	0.17 (2 mo)	0.33 (4 mo)	Aubourg 1985
3	2	3.08 (37 mo)	Barth 1990
4	0.75 (9 mo)	NA	Barth 1987
5	0.08 (neo)	NA	Barth 1987
6 (NA)	0.42 (5 mo)	0.42 (5 mo)	Clayton 1988
7 (NB)	0.71 (8.5 mo)	0.71 (8.5 mo)	Clayton 1988
8 (IB)	0.75 (9 mo)	0.75 (9 mo)	Clayton 1988
9	0.92 (11 mo)	0.92 (11 mo)	Goldfischer 1986
10 (EN)	0.46 (5.5 mo)	0.46 (5.5 mo)	Govaerts 1982
11 (DB)	0.42 (5 mo)	0.42 (5 mo)	Govaerts 1982
12 (TB)	0.58 (7 mo)	0.58 (7 mo)	Govaerts 1982
13 (JF)	0.02 (1wk)	0.02 (1 wk)	Govaerts 1982
14 (RF)	0.10 (5 wk)	0.10 (5 wk)	Govaerts 1982
15 (BM)	0.50 (6 mo)	0.50 (6 mo)	Govaerts 1982
16 (JS)	>5	NA	Govaerts 1982
17 (CD)	>5	NA	Govaerts 1982
18 (MR)	2.75	2.75	Govaerts 1982
19 (TB)	0.1 (5 wk)	0.10 (5 wk)	Govaerts 1982
20 (BR)	>3.5	NA	Govaerts 1982
21 TvM	>2.5	NA	Govaerts 1982
22 (RL)	0.08 (1 mo)	0.08 (1 mo)	Govaerts 1982
23 (KM)	0.25 (3 mo)	0.25 (3 mo)	Govaerts 1982
24 (SL)	0.17 (2 mo)	0.17 (2 mo)	Govaerts 1982
25 (MG)	>4	NA	Govaerts 1982
26	0.67 (8 mo)	0.67 (8 mo)	Hanson 1975

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27	0.33 (4 mo)	1.91 (23 mo)	Hanson 1975
28	9	NA	Mandel 1994
29	5	NA	Mandel 1994
30	15	NA	Santer 1993
31	0.08 (1 mo)	0.33 (4 mo)	Van Maldergem 1992
Mean	1.98 ±3.21, n=31	0.72 ±0.84, n=21	

From the Historical Control Summary, NDA 205,750. HPPID#: Historical PD patient identification number; Dx: diagnosis; yr: years; mo: months; wk: weeks; d: days; NA: data not available.

Natural History Control Reported by Poll-The

The natural history control consists of 31 PD patients (age 1.2-24 years). By definition, they are in the category of milder PD. In general, most PD patients (60-70%) belong to this category (Poll-The, 2004).

Table 3: Biochemical Characteristics of 31 PD Patients (Poll-The, et al.)

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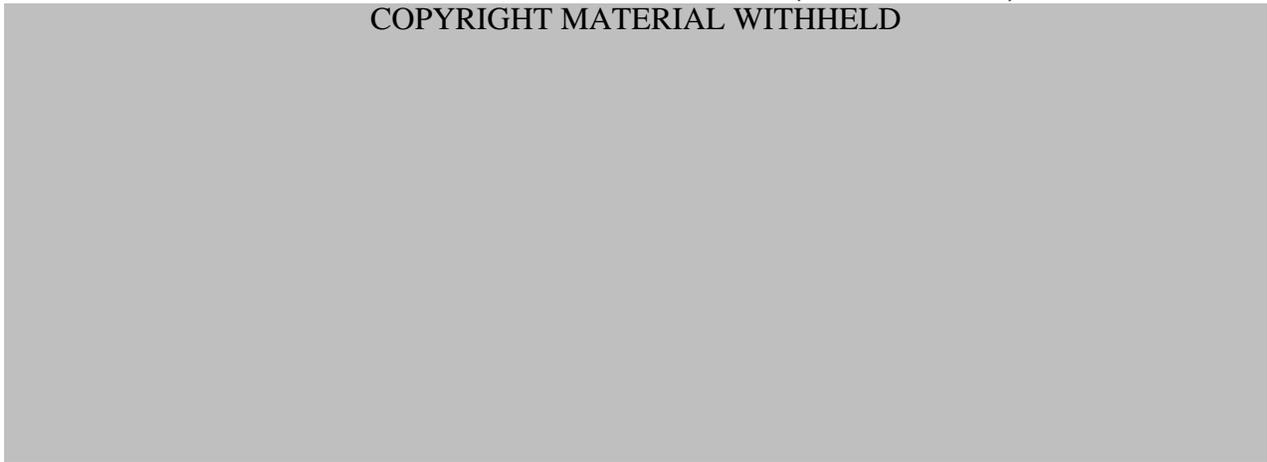
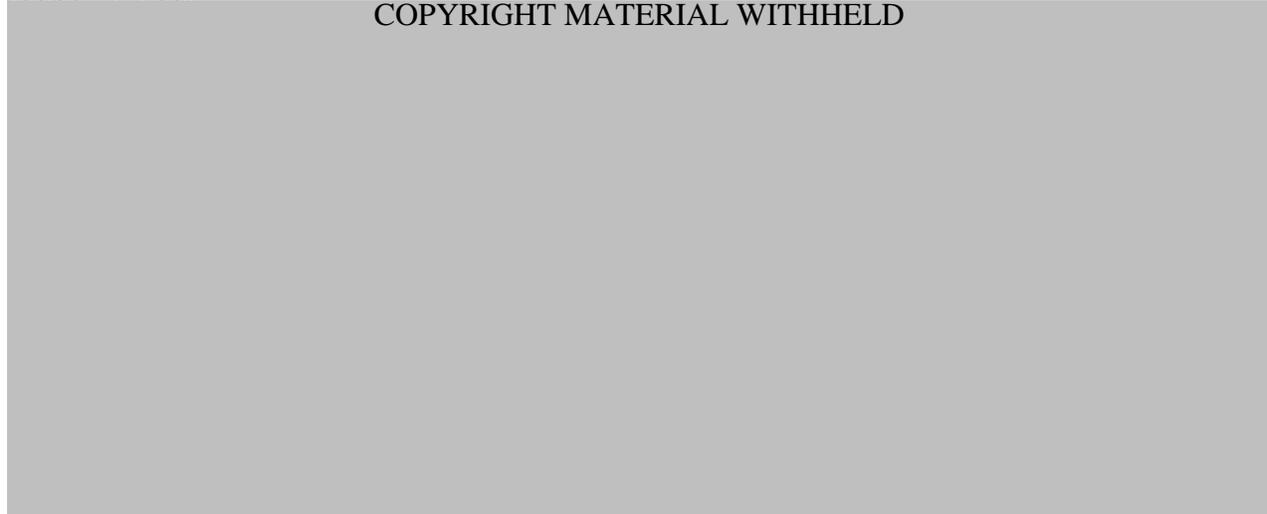


Table 4: Initial Clinical Symptom and Age at Diagnosis in 31 PDs with Survival of at least >1 Year

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From Poll-The, et al. Peroxisome biogenesis disorders with prolonged survival: Phenotypic expression in a cohort of 31 patients. Am J Med Gene 2004;126A:333-338.

Safety and Effectiveness with SED Patients (Gonzales)

- 15 SED patients treated with cholic acid for a median of 12.4 years
- Resolution of jaundice, steatorrhea, weight and height in all
- Hepatosplenomegaly in 14 patients
- Liver biopsy (after ≥ 5 years on cholic acid) showed no cholestasis in 14 patients
- Normal sexual maturation in all; 4 normal pregnancies.

Toxicity Study with PD Mice by Keane et al.

- Feeding with cholic acid worsened the pre-existing mitochondrial and cellular damage in peroxisome-deficient liver.
- Cholestasis preceding death.

5.2 Review Strategy

A. Assessment of effectiveness was based on one open-label, single arm clinical study (CAC-91-10-10).

Background knowledge

- Mechanisms of cholic acid action include a) stimulation of hepatic metabolic conjugation, b) increase of bile acid-dependent bile flow, and c) reduce of intrahepatic cholestasis.
- The primary pathology of SED is intrahepatic cholestasis;
- The primary pathologies of PD are mitochondrial and peroxisomal defects; and intrahepatic pathology is complicated by pre-existing conjugation and transporter defects.

Review strategy

- To evaluate the proportion of patients who have cholestasis at baseline by generating baseline cholestasis criteria using multiple biomarkers
- To assess the proportion of patients who are cholic acid treatment responders by generating responder criteria using both clinical criteria (body weight improvement and survival) and biomarker criteria (transaminases, bilirubin, and liver biopsy)

B. Safety assessment was also based on the study, but referenced to a history control cohort submitted by Asklepiion, and a natural history control of PD patients by Poll-The et al. The natural history data included (1) review of case reports from the literature; (2) review of the pre-treatment data; and (3) review of sibling data from the same disease.

The studies conducted by the sponsor, and literature search by the sponsor and the clinical reviewers supported a substantive clinical review.

5.3 Discussion of Study CAC-91-10-10

To avoid duplication, this section is focused on discussion of the trial design of Study CAC-91-10-10.

5.3.1 Indication

The proposed indication is treatment of bile acid synthetic disorders.

5.3.1.1 Methods

Responder Analyses

Determination of effectiveness is primarily based on the responder analyses (post-Hoc). Responder must meet ≥ 2 biomarker criteria plus survival, or meet 2 clinical criteria plus ≥ 1 biomarker criterion.

- Biomarker Criteria:
 - ALT/AST reduced to < 50 U/L, or baseline level reduced by 80%;
 - Total bilirubin reduced to ≤ 1 mg/dL;
 - No evidence of cholestasis on liver biopsy.
- Clinical Criteria:
 - Body weight increase by 10%, or stable at > 50 percentile;
 - Alive at the last follow-up.

Baseline cholestasis criteria: Cholestasis at baseline must meet ≥ 2 of abnormal biomarkers:

- ALT/AST > 50 U/L;
- Total bilirubin > 1 mg/dL, or direct bilirubin > 0.3 mg/dL;
- Evidence of cholestasis on liver biopsy;
- Urinary FAB-MS score > 2 .

Long-Term Survival Assessment of PD Patients

The long-term survival data of PD patients in Study CAC-91-10-10 was submitted on 10/21/2014 (SN036, NDA 205,750). The natural history study by Poll-The, et al. is used as one of the untreated controls (Poll-The, 2004). The overall survival rate of PD patients age > 1 year old from Study CAC-91-10-10 is compared with the Poll-The's study and the historical control. Also, the 4-year survival rate of Study CAC-91-10-10 is compared with the Poll-The's study.

Sensitivity Analyses

The primary endpoints of effectiveness (changes in ALT/AST levels, bilirubin levels, height/weight percentiles from the pre- to the post-treatment) were analyzed. The sponsor submitted the ^{(b) (4)} analysis. The reviewers did not agree the type of analysis. DGIEP requested the median to median analysis to determine efficacy, because it is a sensible approach.

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Although the sponsor used the changes of atypical urinary bile acids to support their efficacy claim, this reviewer did not think the method was acceptable. (b) (4)

(b) (4)

Safety Evaluations

Safety variables included death rates, treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious adverse events (SAEs), TEAEs resulting in study drug discontinuations, physical examination, vital signs, and clinical laboratory findings.

5.3.1.2 General Discussion of Endpoints

(b) (4)

(b) (4)

(b) (4) (b) (4)

(b) (4)

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(b) (4)



(b) (4)



(b) (4)



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(b) (4)

Medical Officer Comments:

The use (b) (4) is not validated. Specific concerns are as follows:

(b) (4)

5.3.1.3 Design of Study CAC91-10-10

Study CAC91-10-10 was an open-label, single arm, compassionate use study of cholic acid in subjects with single enzyme defects of bile acid synthesis and peroxisomal disorders. The study had 57 patients at CCHMC (Cincinnati Children's Hospital Medical Center), and 28 international out-patients. Forty patients had 15 mg/kg cholic acid PO daily, and 39 patients had both Cholic Acid in combination with ursodiol or alternatively with ursodiol. The patients at CCHMC had blood and urine bile acids examined at baseline, Month 1, and Month 6; then every 3 to 6 months; liver biopsy was performed in some patients every 6 months. The out-patients were examined monthly for the first 3 months; then every 6 months.

Table 6: Patients Treated at CCHMC

Assessment or Procedure	Base-line	Treatment start	On-treatment		
			CAC-91-10-10 (Until 7 Jun 2004) CAC-92-8-19		CAC-91-10-10 (From 8 Jun 2004)
			Month 1	Month 6	Month 3-6
Confirm eligibility (patient meets study criteria)	x				
Obtain written informed consent from patient and/or parents/legal guardian	x				
Demographic data and disease and medication history	x				
Initiate study drug therapy		x			
Total bile acid pool	x		x		x
Blood and urine samples for FAB-MS/GC-MS analysis	x ^a		x ^b		x ^b
Blood samples for LFT analysis	x		x ^b	x	x
Blood samples for other lab analyses	x		x		
Body measurements	x		x	x ^c	x
Liver biopsy	x ^d		x	x ^e	x
Nutritional evaluation	x		x	x	x
Neurologic examination and history	x ^f				
Adverse events	x		x	x	x
Monitor study drug therapy and adjust dose as needed			x	x	x

^a May have been obtained through diagnostic screening.

^b To be performed on a monthly outpatient basis if no clinic visit was scheduled.

^c Patients in study 91-10-10 only.

^d Unless historical data were available. In peroxisomal patients only if no other disease-related conditions increased the risk of the procedure.

^e Only if the 1-month biopsy was abnormal. In peroxisomal patients only if no other disease-related conditions increased the risk of the procedure.

^f Patients in study CAC-92-8-19 only.

From the Study Report of CAC-91-10-10, Section 9.1, Page 29.

Safety assessments included treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious adverse events (SAEs), TEAEs resulting in study drug discontinuations, physical examination, vital signs, weight and height percentiles, and clinical laboratory findings (transaminases and bilirubin).

5.3.1.4 Eligibility/Inclusion and Exclusion Criteria

Inclusion Criteria

All patients

- Patients of any age with cholestatic liver disease if urine screens suggested that they had inborn errors of bile acid metabolism.
- The patient and/or parent/legal guardian must have signed the written informed consent document before study start.
- The patient and/or parent/legal guardian must have been willing and able to comply with all study assessments and procedure.

Key entry criteria for single enzyme defects include:

- Cholestasis defined as serum conjugated bilirubin >2 mg/dL, or increased serum bile acids;
- Urinary FAB-MS analysis of atypical bile acids positive.

Key entry criteria for peroxisomal disorders

- Neurologic evaluation (criteria not submitted);

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- Serum long-chain fatty acids positive;
- Urinary FAB-MS analysis positive for atypical bile acids

Exclusion Criteria

No exclusion criteria were designed for the study. Patients with other organ dysfunction were not excluded, if the inclusion criteria were met.

5.3.1.5 Prior and Concomitant Medications

Prior and concomitant therapy was not documented in this study. No concomitant medications were prohibited during the study. At the early stage of Study CAC-91-10-10, cholic acid was used in combination with ursodiol, i.e., either in combination or as single treatments following each other. Ursodiol was removed in June 2001. In addition, 6 patients had CDA (chenodeoxycholic acid) for 22 weeks. Five patients had DHA (decosahexaenic acid) for 217 weeks.

6 Review of Effectiveness

Summary of Effectiveness

- The responder analyses (post-Hoc) is based on the open-label, single arm, compassionate use study (CAC-91-10-10) in 79 patients (50 SED and 29 PD, ITT population) who received at least one dose of cholic acid, and had a narrative. Response was assessed by the following criteria:

Laboratory criteria:

- ALT or AST values reduced to <50 U/L, or baseline levels reduced by 80%;
- Total bilirubin values reduced to ≤ 1 mg/dL;
- No evidence of cholestasis on liver biopsy; plus the following clinical criteria

Clinical criteria:

- Body weight increased by 10% or stable at $>50^{\text{th}}$ percentile;
- Alive at the last follow-up.

Responders were defined as patients who either (1) met at least two of the laboratory criteria and were alive at the last follow-up; or (2) met at least one laboratory criterion, had increased body weight and were alive at the last follow-up.

Results show that 62% (31/50) of the SED patients are the cholic acid treatment responders. However, none of the PD patients are the responder (0/29).

- Long-term survival analysis is based on the 29 PD patients with peroxisomal disorders from Study CAC-91-10-10, the 31 PD cases from the historical control

submitted by Asklepion, and the 31 PD patients from the natural history study by Poll-The, et al.

Results show that cholic acid treatment did not bring about the benefit of long-term survival to the 29 PD patients. The survival rate of the 29 patients age >1 year old is 40% (8/20), comparing to that of the historical control (82%, 9/11) and the natural history study of untreated PD patients (71%, 22/31).

6.1 Indication

The proposed indication is:

“...for the treatment of bile acid synthesis disorders.”

6.1.1 Methods

Determination of efficacy is based on the review of the data from Study CAC-91-10-10 submitted to the NDA. Response to cholic acid treatment was assessed by the following criteria:

Laboratory criteria:

- ALT or AST values reduced to <50 U/L, or baseline levels reduced by 80%;
- Total bilirubin values reduced to ≤ 1 mg/dL;
- No evidence of cholestasis on liver biopsy; plus the following clinical criteria

Clinical criteria:

- Body weight increased by 10% or stable at >50th percentile;
- Alive at the last follow-up.

Responders were defined as patients who either (1) met at least two of the laboratory criteria and were alive at the last follow-up; or (2) met at least one laboratory criterion, had increased body weight and were alive at the last follow-up.

6.1.2 Demographics

Table 7 summarized the demographic characteristics of Study CAC-91-10-10. The mean age at diagnosis was 2 years, and started treatment at 3 years of age (Safety population). The range of age at diagnosis varied from 0 to 13 years of age, and treatment start from 0 to 16 years old (SED age: 3 weeks old to 16 years old; PD age: 2 months old to 10 years old). About 54% of the patients were below 6 months of age at diagnosis. Overall, 37% were female, 61% were male, and 3% were unknown (Table 2, safety population).

Table 7: Summary of Demographic and Baseline Characteristics

Characteristic		ITT (N = 85)	Safety (N = 79)	mITT (N = 70)
Gender [N (%)]	Female	31 (36)	29 (37)	25 (36)
	Male	50 (59)	48 (61)	45 (64)
	Unknown	4 (5)	2 (3)	0 (0)
Race [N (%)]	Arabic	1 (1)	1 (1)	1 (1)
	Asian Indian	2 (2)	2 (3)	2 (3)
	Black/African American	1 (1)	1 (1)	1 (1)
	Egyptian	1 (1)	1 (1)	1 (1)
	Haitian	1 (1)	1 (1)	1 (1)
	Hispanic	10 (12)	10 (13)	10 (14)
	Middle Eastern	7 (8)	7 (9)	6 (9)
	Persian/Iranian	1 (1)	1 (1)	1 (1)
	Portuguese	2 (2)	2 (3)	2 (3)
	UNK	29 (34)	23 (29)	16 (23)
	White	30 (35)	30 (38)	29 (41)
Age at diagnosis [years]	Mean ± SD	2 ± 4 (n = 74)	2 ± 4 (n = 71)	2 ± 4 (n = 62)
	Min, Max	0, 13 (n = 74)	0, 13 (n = 71)	0, 13 (n = 62)
Age group at diagnosis [N (%)]	<3 months		23 (27)	
	3-6 months		19 (22)	
	7-12 months	NA	13 (15)	NA
	13-36 months		12 (14)	
	>36 months		18 (21)	
Age at treatment start [years]	Mean ± SD	3 ± 4 (n = 77)	3 ± 4 (n = 77)	3 ± 4 (n = 68)
	Min, Max	0, 16 (n = 77)	0, 16 (n = 77)	0, 16 (n = 68)
Baseline height percentile	Mean ± SD	33 ± 31 (n = 16)	33 ± 31 (n = 16)	34 ± 31 (n = 15)
	Min, Max	0, 92 (n = 16)	0, 92	0, 92 (n = 15)
Baseline weight percentile	Mean ± SD	39 ± 36 (n = 16)	39 ± 36 (n = 16)	35 ± 35 (n = 15)
	Min, Max	0, 98 (n = 16)	0, 98 (n = 16)	0, 98 (n = 15)

N = number of patients, n = number of patients with data available, NA = not assessed, SD = standard deviation.
Source: Tables 14.1.2.1 to 14.1.2.7

From the Study Report of CAC-91-10-10, Section 11.2, Page 55.

6.1.3 Subject Disposition

In total, 85 subjects with a defect in bile acid synthesis diagnosed by FAB-MS (b) (4) were enrolled in Study CAC-91-10-10 (or substudy CAC-92-8-19). Of these, 79 subjects have received study medication (50 SED patients, 29 PD patients). Four of them discontinued the study because of liver transplantation and one due to worsening cholestasis. A total of 20 patients died during the study period (6 SED patients, 14 PD patients).

Table 8: Summary of Subject Disposition (All Subjects)

Disposition	Total	91-10-10	92-8-19
Screened	N = 85	N = 54	N = 31
Treated	79	50	29
Untreated	6	4	2
Patient expired	20	6	14
Discontinued	21	7	14
Had pre- & post-assessment	70	43	27

From the Study Report of CAC-91-10-10, Section 10.1, Page 50.

Datasets Analyzed

Three populations were used for study analyses:

- ITT population:
All subjects identified as having an inborn error in bile acid synthesis at baseline were included in the ITT population. A total of 85 subjects were included in the ITT population.
- MITT population:
Subject had both a pre-and a post-treatment assessment for any of the main endpoints (LFT, FAB-MS, or height/weight), that subject was included in the mITT population. A total of 70 subjects were included in the mITT population.
- Safety population:
Subjects received at least one dose of cholic acid were included in the safety population. A total of 79 subjects were included in the safety population.

Protocol Deviations

The sponsor explained that because the cholic acid program was an academic research project with the compassionate use, many GCP deviations occurred. Protocol violations were not used to exclude patients from the study. Table x shows a summary of the protocol deviations. A total of 52 patients had not received both CA and URSO treatment up to June 1, 2001, although both were mentioned as study medication in the original protocols. The sponsor stated that the 79 patients (50 in SED and 29 in PD) in the safety set had received CA. After URSO treatment was removed from the study procedures in June 2011, only 10 patients received treatment other than CA. Most frequently, patients had no post-treatment nutritional assessment and no pre-treatment liver biopsy.

Table 9: Summary of Protocol Deviations

Protocol Violation	Number of Patients
Did not receive both CA+URSO (at least once) up to 11JUN2001	52
Received URSO, CHENO, or DHA from 12Jun2001 onwards	10
Patient has interruption of Study Medication Documentation ^a	16
Received CA doses >15 mg/day at any time during study	35
Documented Direct Bilirubin ≤ 2 mg/dL at baseline	26
No pre-treatment FAB-MS Assessments	3
No pre-treatment LFT Assessments	9
No pre-treatment Bilirubin Assessments	21
No pre-treatment Body Measurements	14
No pre-treatment Liver Biopsy	34
Less than 2 post-treatment FAB-MS Assessment	9
No post-treatment FAB-MS Assessments	10
Less than 2 post-treatment LFT Assessment	13
No post-treatment LFT Assessments	10
Less than 2 post-treatment Bilirubin Assessment	8
No post-treatment Bilirubin Assessments	11
Less than 2 post-treatment Body Measurements	16
No post-treatment Body Measurements	12
No post-treatment Liver Biopsy	10
No Post-Treatment Bile Acid Pool Assessments	26
No Post-Treatment Nutritional Assessment	70

^aBased on shipping log documentation for CA.
Source: Listing 16.2.2

Detailed protocol deviations are listed by Asklepiion in Section 16.2.2 of NDA 205,750.

6.1.4 Analysis of Primary Variables

The main efficacy variables of Study CAC-91-10-10 were clinical relevant biomarkers and clinical responses as follows:

- (1) Changes in urinary bile acids from pre- to post-treatment
- (2) Changes in liver function tests (AST/ALT) from pre- to post-treatment
- (3) Changes in height/weight from pre- to post-treatment

Additional efficacy variables were:

- Changes in bilirubin from pre- to post-treatment
- Changes in liver histology from pre- to post-treatment (for patients with liver biopsies)

The analytical methods:

- LFTs (transaminases) were evaluated as continuous measurement
- Bilirubin was also evaluated as continuous measurement.
- Liver histopathology was evaluated by identifying pathologist-noted-improvement or worsening in the categories of inflammation (lobular and periportal), fibrosis, necrosis, and cholestasis. The comparative evaluation was performed in patients who had both pre- and post-treatment liver biopsies.
- Height and weight percentiles were also evaluated as continuous measurement.
- Survival was evaluated as alive at the last visit of the study.
- Urinary bile excretion was scored using the scale of 0, normal; 1, slight; 2, significant; or 3, marked.

A. Responder Analyses

Asklepiion submitted the narratives of 79 patients (50 with SED, 29 with PD) on September 10 and 12, 2014 (SN034 and SN035), and the revised narratives on October 22, 2014 (SN037). All of the patients received at least one dose of cholic acid during the study. The purpose of the analyses is to identify the number of patients who had intrahepatic cholestasis at baseline, and who responded to cholic acid treatment.

Baseline Cholestasis Criteria (Post-Hoc):

Cholestasis at baseline must meet ≥ 2 of abnormal biomarkers. Abnormal biomarker criteria:

- ALT/AST > 50 U/L;
- Total bilirubin > 1 mg/dL, or direct bilirubin > 0.3 mg/dL
- Evidence of cholestasis on liver biopsy
- Urinary FAB-MS score > 2

Responder Criteria (Post-Hoc):

Responder must meet:

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- ≥ 2 biomarker criteria plus survival, or
- 2 clinical criteria plus ≥ 1 biomarker

Biomarker Criteria:

- ALT/AST reduced to <50 U/L, or baseline level reduced by 80%
- Total bilirubin reduced to ≤ 1 mg/dL
- No evidence of cholestasis on liver biopsy

Clinical Criteria:

- Body weight increase by 10%, or stable at >50 percentile
- Alive at the last follow-up

Results:

According to the above criteria, 68% of the SED patients had cholestasis at baseline; and that 62% of the patients were the responders to cholic acid treatment. Most responders met the 2 clinical criteria plus 1 to 3 biomarker criteria. Most responders are from 3β -HSD deficiency group (Tables 10, 11, and 12).

In contrast, only 28% of the PD patients had cholestasis at baseline; and their cholestasis did not appear to be responsible to cholic acid treatment (Tables 13 and 14). As a result, none of the PD patients met the responder criteria.

Table 10: Summary of SED Responder in Study CAC 91-10-10 (ITT Population)

SED/ Subtype: N	Baseline			CA Treatment		
	Cholestasis	No Cholestasis	Data N/A	Responder	Non- Responder	Data N/A
SED: 50	34/50=68%	6/50=12%	10/50=20%	31/50=62%	11/50=22%	8/50=16%
3β -HSD: 35	26	6	3	24	8	3
AKR1D1: 9	4	0	5	3	2	4
CTX: 3	2	0	1	3	0	0
AMACR: 1	1	0	0	1	0	0
SmithLO: 1	1	0	0	0	1	0
CYP7A1: 1	0	0	1	0	0	1

From the clinical reviewer's notes based on SN 34, 35, and 37, NDA 205,750

Note: SmithLO denotes Smith-Lemli-Opitz disease

Table 11: Summary of Responder Distribution: SED ITT population

Single Enzyme Defect	Clinical & Biomarkers	31	Patient ID
2 clinical + 3 biomarkers	SWEBB _x	2	34, 76
2 clinical + 2 biomarkers	SWEB	9	01, 57, 65, 86, 93, 95, 100, 149, 175
	SWEB _x	1	33
	SWBB _x	1	79

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2 clinical + 1 biomarker	SWE	5	18, 27, 40, 55, 73
	SWB	2	31, 90
1 clinical + 2 biomarkers	SEB	11	68, 78, 102, 105, 107, 134, 138, 142, 145, 153, 157

Note: S: survival; W: weight increase; E: ALT/AST improvement; B: total bilirubin improvement; and B_x: liver biopsy improvement.

3βHSD: 1 patient who meets 2 clinical + 3 biomarkers; 8 patients who meet 2 clinical + 2 biomarkers; and 15 patients who meet 2 clinical + 1 biomarker, or survival + 2 biomarkers.

AKR1D1: 3 patients who meet survival + 2 biomarkers.

CTX: 3 patients who meet 2 clinical + 1 or 2 biomarkers.

AMACR: 1 patient who meet 2 clinical + 3 biomarkers.

Table 12: Individual Responder Analysis: SED ITT Study CAC-91-10-10

SED/PID#	Baseline			CA Treatment		
	Cholestasis	No Cholestasis	Data N/A	Responder	Non-Responder	Data N/A
SED: 50	34/50=68%	6/50=12%	10/50=20%	31/50=62%	11/50=22%	8/50=16%
3β-HSD: 35	26	6	3	24	8	3
#001 ^v	+(E, B)		+Fab	+(E, B, W)		+B
#009	+(B, B _x , Fab)	+EN		+W	+(E, B); LOC	
#018 ^v	+Fab		+(E, B)	+(EN, W _H)	+B	
#024	+Fab	+EBN		+W	+EBN	
#031 ^v	+(B, Fab)	+EN		+(B, W)	+EN	
#033 ^v	+(E, B, B _x , Fab)			+(E, B _x , W)	+B; LOC	
#034 ^v	+(E, B, B _x , Fab)			+(E, B, W, B _x)	LOC	
#040 ^v	+(B, Fab)	+EN		+(W, E)		+B
#047	+(E, B, Fab)			+E	+(B, W)	
#055 ^v	+(E, B, Fab)			+(E, W)		+B
#056	+(B, Fab)	+EN			+EN; LOC	+B [#]
#057 ^v	+(E, B, Fab)			+(E, B, W)		
#073 ^v	+(E, B, Fab)			+(E, W)	+B; LOC	
#074	+(B, Fab)	+EN		+BN	+(W, E); LOC	
#078 ^v	+(E, B, Fab)			+(E, B)		+W
#079 ^v	+Fab	+EBN		+(B, B _x , W)	+E	
#083	+(B, Fab)		+E		+B; EN	+W
#090 ^v	+(B, B _x , Fab)	+EN		+(B, W _H)	+EN	

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	Fab)					
#093 ^v	+(E, B, Bx, Fab)			+(E, B, W)		
#095 ^v	+(E, B, Fab)			+(E, B, W)		
#100 ^v	+(E, B, Fab)			+(E, B, W)		
#106	+(Fab, B)	+EN		+W	+(E, B); LOC	
#107 ^v	+(E, B, Fab)			+(E, B)		+W
#134 ^v	+Fab	+(EBN, Bx)		+EBN	LOC	+W
#138 ^v	+Fab	+EN	+B [#]	+EBN	LOC	+W
#142 ^v	+(E, Fab, Bx)		+B	+EBN	LOC	+W
#143*	+(E, B, Fab)			+E	+B	+W
#145 ^v	+(E, B, Fab)			+(E, B)	+W	
#149 ^v	+Fab	+EBN		+EBN; W _H		
#153 ^v	+Fab	+EBN		+EBN		+W
#156	+Fab		+(E, B)		+W	+(E, B)
#157 ^v	+(E, B, Fab)			+(E, B)		+W
#159	+Fab	+EN	+B [#]	+EN	+(W, B); LOC	
#175 ^v	+Fab	+EBN		+(E, B, W _H)		
#177	+(B, Fab)	+EN				+(E, B, W)
	Cholestasis	No Cholestasis	Data N/A	Responder	Non-Responder	Data N/A
AKR1D1: 9	4	0	5	3	2	4
#000*	+Fab		+(E, B)			+(E, B, W)
#068 ^v	+(E, B, Fab)			+(E, B)	+W	
#075	+Fab		+(E, B)			+(E, B, W)
#102 ^v	+(E, B, Fab)			+(E, B)	+W	
#103*	+(E, B, Fab)			+E	+B	+W
#105 ^v	+Fab		+(E, B)	+EBN		+W
#133	+(E, Fab)	+B		+BN	+(W, E)	
#152*	+Fab		+(E, B)			+(E, B, W)
#193	+Fab		+(E, B)			+(E, B, W)
CTX: 3	2	0	1	3	0	0

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#027 ^v	+Fab		+(E, B)	+(E, W)		+B
#065 ^v	+(E, B, Bx, Fab)			+(E, B, W)	+Bx	
#086 ^v	+(E, B)	+Fab		+(E, B, W)		
AMACR: 1	1	0	0	1	0	0
#076 ^v	+(E, B, Bx, Fab)			+(E, B, W, Bx)		
SmithLO: 1	1	0	0	0	1	0
#127*	+(E, B, Fab)				+(E, B)	+W
CYP7A1: 1	0	0	1	0	0	1
#016*	+Fab		+(E, B)			+(E, B, W)

The purpose of the analysis is to identify the number of patients who had intrahepatic cholestasis at baseline, and the number of patients who responded to cholic acid treatment. Five criteria are chosen for the determination of Cholic acid responder, because the treatment targets at intrahepatic cholestasis, and should improve survival and growing. The 5 criteria are: 1) ALT/AST values reduced to <50 U/L, or baseline levels reduced by 80%; 2) total bilirubin values reduced to ≤1 mg/dL; 3) no evidence of cholestasis on liver biopsy; 4) body weight increase by 10%, or stable at >50 weight percentile; and 5) patient alive at the end of the trial. The responder must meet at least two criteria of the biomarkers plus the clinical survival; or at least one criterion of the biomarker plus two clinical criteria: i.e., weight percentile increase and survival. FAB-MS urinary score is not used for the responder analysis (b) (4)

Because the treatment targets at intrahepatic cholestasis, baseline cholestasis is determined by 1) Abnormal ALT/AST values, 2) Abnormal bilirubin (total and direct), 3) Urinary bile acid score ≥2, and 4) evidence of cholestasis on liver biopsy. The patient who had cholestasis at baseline must meet at least two criteria of the abnormal biomarkers.

Note: PID^v: Responder to cholic acid treatment; PID*: Patient died during treatment; LOC: Lack of compliance; N: Normal value; E: ALT/AST; B: Total bilirubin or Direct bilirubin; EBN: Both ALT/AST and bilirubin being normal; Fab: FAB-MS score; W_H: body weight kept at >80 percentile; Bx: liver biopsy; B[#]: Confirmatory bilirubin data not available; SmithLO: Smith-Lemli-Opitz defect; CYP7A1: CYP7A1 defect.

Table 13: Summary of Baseline Cholestasis and CA Treatment Responder: PD ITT

PD/Subtype: N	Baseline			CA Treatment		
	Cholestasis	No Cholestasis	Data N/A	Responder	Non-Responder	Data N/A
PD: 29	8/29=28%	16/29=55%	5/29=17%	0	22/29=76%	7/29=24%
Zellweger's: 11	4	5	3	0	5	6
NALD: 8	2	5	1	0	7	1
Unknown: 5	1	3	1	0	5	0
Refsum's: 4	2	2	0	0	4	0
Generalized: 1	0	1	0	0	1	0

From Table 2 of clinical reviewer's notes

Table 14: Responder Analysis & Baseline Cholestasis: PD ITT population

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PD/PID#	Baseline			CA Treatment		
	Cholestasis	No Cholestasis	Data N/A	Responder	Non-Responder	Data N/A
PD: 29	8/29=28%	16/29=55%	5/29=17%	0	22/29=76%	7/29=24%
Zellweger's: 11	3	5	3	0	5	6
#011	+Fab	+(BN, Bx)			+(E, W)	
#017*			+(E, B, Fab)		+Bx	+(E, B, W)
#019*	+E	+BN, FabN			+E	+(B, W)
#032	+Fab	+(EBN, Bx)			+(EBN, Bx, W)	
#036*	+Fab	+EBN		+W	+(E, B)	+Bx
#046		+EBN, Bx, FabN			+(EBN, Bx, W)	
#059*	+(E, Bx, Fab)	+BN				+(E, B, W, Bx)
#080*	+(E, B, Bx, Fab)				+(E, B, W)	+Bx
#123*	+Fab		+(E, B)			+(E, B, W)
#132	+E	+Fab	+B [#]	+E		+(B, W)
#173	+(E, B, Fab)			+E	+W	+B [#]
NALD: 8	2	5	1	0	7	1
#007		+(EBN, FabN, Bx)			+(EBN, W)	
#012	+E	+(BN, Bx)	+Fab(Urs)	+E	+(BN, W)	+Bx
#029*		+(EBN, FabN)			+W	+EB
#030	+E	+(BN, Bx, FabN)		+E	+(BN, W, Bx)	
#035	+(E, B, Fab)	+Bx			+(E, W); LOC ^Δ	+Bx
#037*	+(E, Fab)	+ (Bx, B)			+(E, B, Bx, W) ^Σ	
#064		+(EBN, FabN)			+(E, Bx, BN, W)	
#069*	+Fab	+EN	+B [#]	+W	+(E, B)	
	Cholestasis	No Cholestasis	Data N/A	Responder	Non-Responder	Data N/A
Unknown: 5	1	3	1	0	5	0
#013*	+(E, Bx, Fab)	+BN			+(E, W, BN)	
#051		+(EBN, Bx, FabN)			+(EBN, W, Bx)	
#087*		+(EBN, FabN, Bx)			+(EBN, W)	+Bx

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#091*	+Bx	+(EN, FabN)	+B		+(EBN)	+(Bx, W)
#130*	+Fab	+EN	+B [#]		+(EBN)	+W
Refsum's: 4	2	2	0	0	4	0
#020	+Fab	+(EBN, Bx)		+W	+(EBN, Bx)	
#021	+Fab	+(EBN, Bx)			+EBN	+W
#072*	+(E, Fab)	+(BN, Bx)			+(E, W)	+(B, Bx)
#128	+(E, Fab)	+BN		+W	+(E, BN)	
Generalized: 1	0	1	0	0	1	0
#092	+E	+(BN, Bx, FabN)			+(E, BN, Bx, W)	

The purpose of the analysis is to identify the number of patients who had intrahepatic cholestasis at baseline, and the number of patients who responded to cholic acid treatment. Five criteria are chosen for the determination of Cholic acid responder, because the treatment targets at intrahepatic cholestasis, and should improve survival and growing. The 5 criteria are: 1) ALT/AST values reduced to <50 U/L, or baseline levels reduced by 80%; 2) total bilirubin values reduced to ≤1 mg/dL; 3) no evidence of cholestasis on liver biopsy; 4) body weight increase by 10%, or stable at >50 weight percentile; and 5) patient alive at the end of the trial. The responder must meet at least two criteria of the biomarkers plus the clinical survival; or at least one criterion of the biomarker plus two clinical criteria: i.e., weight percentile increase and survival. FAB-MS urinary score is not used for the responder analysis (b) (4)

Because the treatment targets at intrahepatic cholestasis, baseline cholestasis is determined by 1) Abnormal ALT/AST values, 2) Abnormal bilirubin (total and direct), 3) Urinary bile acid score ≥2, and 4) evidence of cholestasis on liver biopsy. The patient who had cholestasis at baseline must meet at least two criteria of the abnormal biomarkers.

Note: LOC: Lack of compliance; PID*: Patient died during treatment; N: Normal value; E: ALT/AST; B: Bilirubin (total and/or direct); EBN: ALT/AST and bilirubin both normal; Fab: FAB-MS score; FabN: Normal FAB-MS score; Bx: liver biopsy; B[#]: Confirmatory bilirubin data not available; W_H: body weight maintained at >80 percentile; (EB, Bx, W)₂: the patient who had pre-treatment biopsy of no cholestasis developed cholestasis (60 mg CA/day for 4 months). CA dosing was increased to 90 mg/day. The patient died on 90 mg CA/day.

B. Long-Term Survival Data of PD Patients

Asklepiion submitted a claim that cholic acid treatment prolonged the survival of PD patients on October 21, 2014 (SN036, NDA 205,750). SN036 contains the revised narratives of 8 PD patients (IDs 012, 020, 021, 030, 046, 051, 064, and 092) who are currently alive, and the revised narratives of 14 PD patients who survived ≥ 3 years (IDs 7, 11, 12, 20, 21, 30, 35, 46, 51, 64, 91, 92, 128, and 132). The survival data are reviewed.

Peroxisomal disorders are a heterogeneous disease which has at least 11 different genetic groups (Moser et al., 1995; Gould and Valle, 2000). In general, PD can be classified into 2 phenotypical categories: a) the classical Zellweger syndrome is defined as a patient who has 1 year to live; and b) the milder PD is defined as a patient who survives for > 1 year of age (Poll-The, 2004).

Studies by Poll-The show that a) it is not new that milder PD patients can have prolonged survivals (Figure 5); b) there was 71% (22/31) of PD patients who lived > 1 year of age in Poll-The's study, comparing to 40% (8/20) of PD patients who were > 1

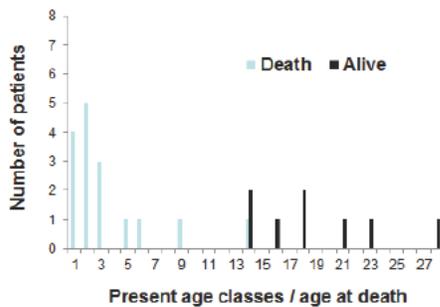
year of age in Study CAC-91-10-10; and c) the 4-year survival rate of untreated milder PD in Poll-The study is higher than the Study CAC-91-10-10 (77% vs. 60%, Table 15).

These data do not support the statement that cholic acid treatment brings about long-term survival benefit to the PD patients.

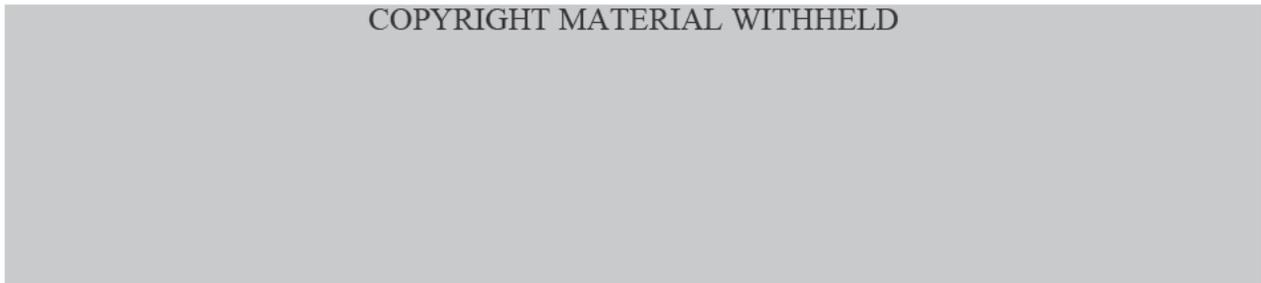
The reviewer also reviewed the medical histories of the 8 long-term survivors who are currently alive. The results show that none of them had cholestasis at baseline; and none of them were responders to cholic acid treatment (CAC 91-10-10) (Tables 14 and 16).

Figure 5: Comparison of Long-Term Survival with Natural History Control

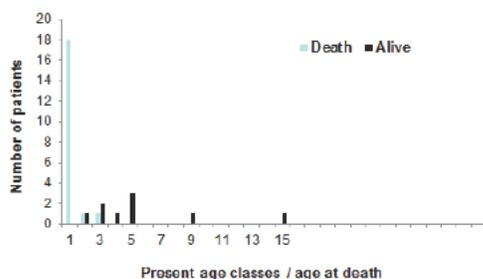
Long-Term Survival Data of NDA 205-750



Natural History Control by Poll-The et al.



Historical Control by Asklepion



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Note: Data of upper panel are from SN036, NDA 205,750; data of lower panel from Historical Control Summary, NDA 205,750; Middle panel is cited from Poll-The, et al. Am. J. Med. Genet. 126A:333-338, 2004.

Table 15: Comparison of Survival Rates of PD Patients Age > 1 Year Old (CAC-91-10-10, Historical Control, and Natural History Control)

Study Name	Total PD Patients, n	Classic ZS (age ≤1 yr), n	Milder PD (age >1 yr), n	Survival of Milder PD, %	4-year Survival of MPD, %	Data N/A, n
CAC-91-10-10	29	4	20	40 (8/20)	60 (12/20)	5
Natural History by Poll-The	31	0	31	71 (22/31)	77 (24/31)	0
Historical Control by Asklepiion	31	18	11	82 (9/11)	N/A	2

From the Study Report of CAC-91-10-10, SN036, and Historical Control Summary, NDA 205,750; Natural history data from the study by Poll-The et al. (Poll-The, 2004). Note: the 4-year survival data of the historical PD control is not submitted. MPD denotes milder PD (age >1 year); N/A: data not available; ZS: Zewellger syndrome.

Table 16: Long-Term Survivors of Peroxisomal Disorders (CAC-91-10-10, ITT)

PID	Primary diagnosis	Status	Date of Birth	Date of Death	Classic ZS (Age ≤1 yr), yr	Milder PD (Age >1 yr), yr
#007	NALD	Expired	07/06/90	10/09/04		14
#11	ZS	Unknown	07/16/99	N/A		
#12*	NALD	Alive				18
#13	Type unk	Expired	08/04/92	03/07/94		1.6 (1 yr 7 mo)
#17	ZS	Expired	05/28/99	11/11/00		1.4 (1 yr 5 mo)
#19	ZS	Expired	02/14/92	10/1992	0.7 (8 mo)	
#20*	Refsums	Alive	03/30/00			14
#21*	Refsums	Alive	03/30/00			14
#29	NALD	Expired	04/17/93	05/28/94		1.1 (1 yr 1 mo)
#30*	NALD	Alive	12/11/90			23
#32	ZS	Unknown	07/29/95	N/A		
#35	NALD	Unknown	02/08/95	N/A		
#36	ZS	Expired	03/08/96	04/07/98		2.1 (2 yr 1 mo)
#37	NALD	Expired	01/02/95	01/12/96	1	
#46*	ZS	Alive	01/10/96			18
#51*	Type unk	Alive	02/28/96			28
#59	ZS	Expired	03/12/00	2001	1	
#64*	NALD	Alive	05/23/93			21
#69	NALD	Expired	12/06/91	06/19/93		1.5 (1 yr 6 mo)
#72	Refsums	Expired	05/23/98	10/31/00		2.4 (2 yr 5 mo)
#80	ZS	Expired	04/01/92	11/12/92	0.6 (7 mo)	
#87	Type unk	Expired	09/14/93	12/22/94		1.3 (1 yr 3 mo)
#91	Type unk	Expired	12/28/97	12/18/04		6

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#92*	GPD	Alive	12/03/97			16
#123	ZS	Expired	01/30/06	N/A		
#128	Refsums	Expired	10/29/03	12/29/12		9
#130	Type unk	Expired	11/05/06	10/24/10		3
#132	ZS	Expired	03/03/07	12/07/12		5
#173	ZS	Unknown	03/10/09	N/A		
Total 29 PD patients grouped into 3 categories				N/A: 5 patients	Classic ZS: 4 patients	MPD: 20 patients

From Study Report CAC-91-10-10, NDA 205,750. Note: PID: patient identification number; PID*: long-term survivor currently alive; Classic ZS: classic Zellweger's syndrome denotes PD patient who survived at age ≤ 1 year old; MPD: Milder PD defined as PD patient who survived over 1 year of age; ZS: primary diagnosis is Zellweger's syndrome; NALD: neonatal adrenoleukodystrophy; Type unk: PD type unknown; Refsum's disease; GPD: Generalized peroxisomal disorder; N/A: data not available; yr: year; mo: month.

C. Review of Kaplan-Meier Survival Data

Asklepion submitted the PD survival data of Study CAC-91-10-10 and the Kaplan-Meier analysis compared with the historical control on June 20, 2014 (SN026, NDA 205,750).

(b) (4)

Review findings: (1) there were a total of 10 papers for the PD control with 29 untreated cases; (2) there was no follow-up of the historical control arm, while there was a 129 months follow-up of the treated arm in Study CAC-91-10-10; and (3) Asklepion compared the median of survival on treatment of PD patients who is alive (Milder PD) from Study CAC-91-10-10 with the historical control who was died at 9 months of age (Classical Zellweger syndrome) (Tables on page 7, 9, 19, and 21 of SN026). The clinical relevance of the comparison is not clear (Poll-The, 2004).

Review comments on Kaplan-Meier method: Asklepion used the Kaplan-Meier method for the survival analysis. The reviewer has 3 concerns:

- 1) Kaplan-Meier method requires the two arms have comparable follow-up durations:

However, Study 91-10-10 followed the survival for more than 10 years, while the historical control did not;

- 2) Kaplan-Meier method requires the two arms have comparable methods for the follow-up.

However, Study 91-10-10 had physician visits every 3 to 6 months, while the historical control did not report;

- 3) Kaplan-Meier method requires the two arms have comparable confounding factors on the survival (i.e., hospital care and living conditions).

Study 91-10-10 provided the standard hospital care for the treated neonates and infants, while a large proportion of the untreated historical neonates and infants lived in the developing countries without hospital care. The effects of these confounding factors on the survival of historical control are not evaluated.

In summary, the three criteria of Kaplan-Meier analysis are not met. The clinical relevance of the analysis is not clear.

6.1.5 Subpopulations

LFTs, bilirubin, and height/weight percentile were analyzed with gender and race subgroups. The analyses did not reveal any clinically meaningful difference due to small sizes of data.

6.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed dosing regimen is 10 to 15 mg/kg PO once daily. The rationale is to replace the daily excreted bile acids in feces and urine. According to the investigators' statement, this is a safe and effective range.

6.1.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

Cholic Acid is one of the endogenous primary bile acids. The persistence of efficacy and the tolerance of cholic acid are not studied.

6.1.8 Additional Effectiveness Analyses

Additional effectiveness analyses of Study CAC-91-10-10 include categorical evaluations of the 5 efficacy variables in SED and PD patients:

Main efficacy variables:

- Changes in urinary bile acids from pre- to post-treatment
- Changes in liver function tests (AST/ALT) from pre- to post-treatment
- Changes in height/weight from pre- to post-treatment

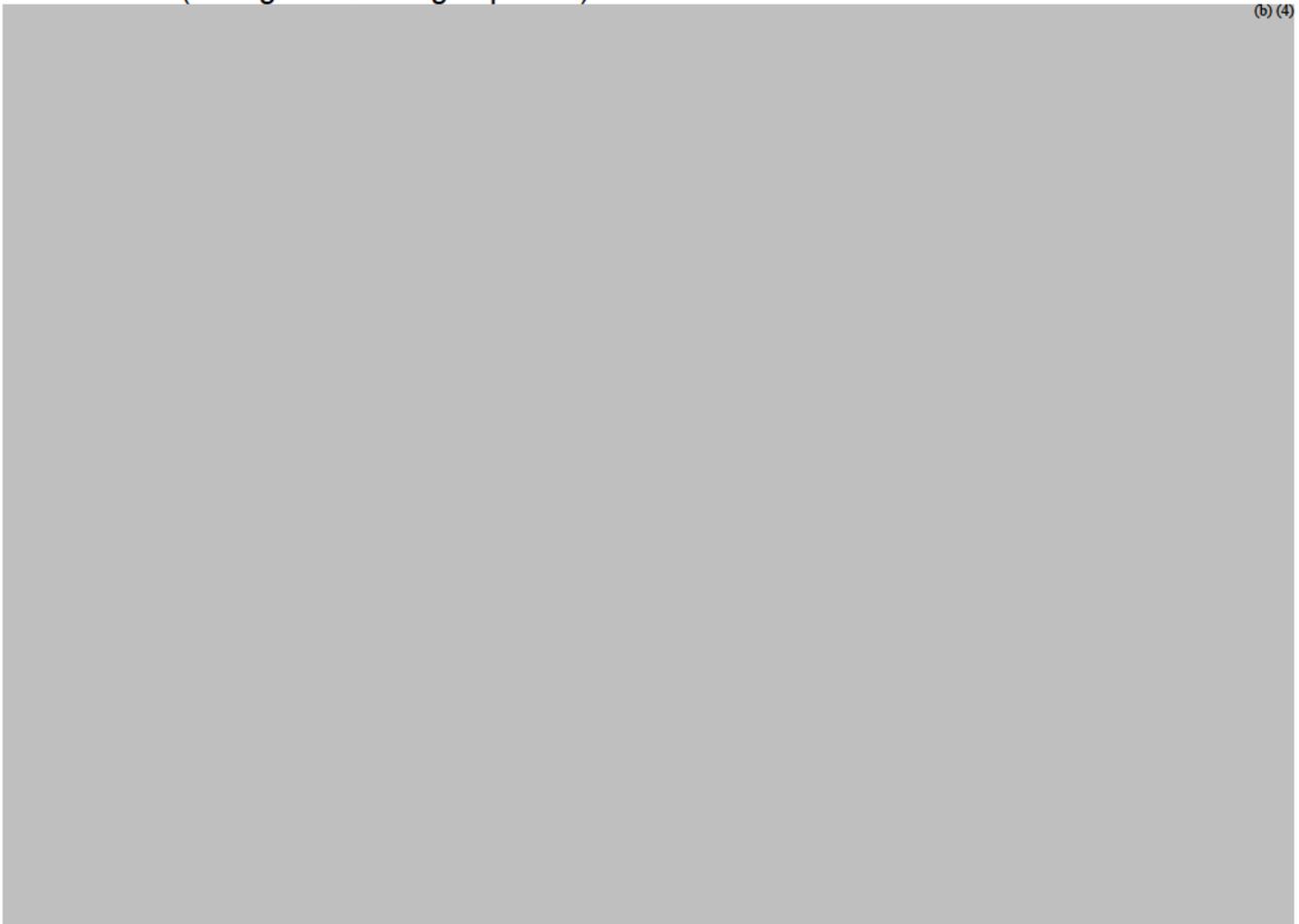
Additional efficacy variables:

- Changes in bilirubin from pre- to post-treatment
- Changes in liver histology from pre- to post-treatment (for patients with liver biopsies)

(b) (4)

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(b) (4)



Medical Officer Comments:

(b) (4)
Taken
together, the clinical relevance of the above (b) (4) data is unclear.

Serum Transaminases

The LFTs (transaminases) were evaluated using a method of “median pre-treatment to median post-treatment”. Cholic acid treatment consistently reduced the ALT and AST levels of SED patients. However, there was an inconsistency in PD patients: the median pre-treatment to median post-treatment of AST was increased from 164 to 186.

Table 18: Effects of Cholic Acid Treatment on Liver Function Tests in SED Patients, ITT (CAC91-10-10)

Comparison	LFT	Visit	n	Mean	SD	Median
Median Baseline to		Baseline	45	116	±146	61

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Median Post-TMT	ALT	Post-TMT	45	54	±60	36
		Baseline	45	152	±220	64
Last Baseline to Last Post-TMT	AST	Post-TMT	45	72	±122	50
		Baseline	45	130	±163	58
	ALT	Post-TMT	45	50	±63	28
		Baseline	45	174	±255	54
AST	Post-TMT	45	64	±92	35	

From the Liver Function Tests Supplemental Analysis submitted on April 4, 2014 (Study CAC-91-10-10).
Post-TMT: post-treatment

Table 19: Effects of Cholic Acid Treatment on Liver Function Tests in Peroxisomal Disorder, ITT (CAC91-10-10)

Comparison	LFT	Visit	n	Mean	SD	Median
Median Baseline to Median Post-TMT	ALT	Baseline	29	155	±129	102
		Post-TMT	29	99	±79	69
	AST	Baseline	29	327	±292	164
		Post-TMT	29	244	±242	186
Last Baseline to Last Post-TMT	ALT	Baseline	29	122	±90	90
		Post-TMT	29	75	±62	55
	AST	Baseline	29	240	±208	143
		Post-TMT	29	196	±199	108

From the Liver Function Tests Supplemental Analysis submitted on April 4, 2014 (Study CAC-91-10-10).
Post-TMT: post-treatment.

Serum Bilirubin

Serum bilirubin was an additional efficacy endpoint. On September 5, 2014, the Division requested additional bilirubin data based on the inspection by DSI. The sponsor submitted the additional bilirubin data collected from CCHMC (Cincinnati Children's Hospital Medical Center), along with comparative bilirubin analyses in ITT population with no imputation. The results show that cholic acid treatment reduced the mean of median baseline to median post-treatment values of total, direct and indirect bilirubin of SED patients. However, the treatment did not reduce the mean of median baseline to median post-treatment of total and direct bilirubin values of PD patients (see the following tables).

Table 20: Summary of Bilirubin Data of SED Patients (ITT) CAC-91-10-10

Comparison	Bilirubin	Visit	n	Mean	SD	Median
Median Baseline to Median Post-TMT	Direct	Baseline	36	2.9	±6.0	0.7
		Post-TMT	36	1.8	±5.2	0.1
	Indirect	Baseline	12	1.6	±2.0	0.6
		Post-TMT	12	0.9	±1.7	0.4
	Total	Baseline	39	5.1	±8.3	1.2
Post-TMT		39	3.3	±7.7	0.5	
Last Baseline to Last Post-TMT	Direct	Baseline	36	3.5	±8.5	0.5
		Post-TMT	36	2.4	±8.1	0.1
	Indirect	Baseline	12	1.5	±2.0	0.5

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	Total	Post-TMT	12	1.0	±1.8	0.4
		Baseline	39	6.3	±15.6	1.2
		Post-TMT	39	4.9	±15.4	0.4

From the Bilirubin-ITT Population submitted on October 24, 2014 (SN038, Study CAC-91-10-10). Post-TMT: post-treatment. Normal upper limit is defined as 0.3 mg/dL for Direct Bilirubin; 0.7 mg/dL for Indirect Bilirubin; and 1.0 mg/dL for Total Bilirubin.

Table 21: Summary of Bilirubin Data of PD patients (ITT) CAC91-10-10

Comparison	Bilirubin	Visit	n	Mean	SD	Median
Median Baseline to Median Post-TMT	Direct	Baseline	24	0.8	±1.8	0.2
		Post-TMT	24	0.9	±1.8	0.1
	Indirect	Baseline	6	0.1	±0.1	0.1
		Post-TMT	6	0.2	±0.1	0.2
	Total	Baseline	24	1.5	±2.7	0.5
		Post-TMT	24	1.6	±4.1	0.5
Last Baseline to Last Post-TMT	Direct	Baseline	24	0.8	±1.8	0.1
		Post-TMT	24	0.9	±1.8	0.1
	Indirect	Baseline	6	0.1	±0.2	0.1
		Post-TMT	6	0.2	±0.2	0.2
	Total	Baseline	24	1.5	±2.7	0.5
		Post-TMT	24	1.6	±4.1	0.5

From the Bilirubin-ITT Population submitted on October 24, 2014 (SN038, Study CAC-91-10-10). Post-TMT: post-treatment. Normal upper limit is defined as 0.3 mg/dL for Direct Bilirubin; 0.7 mg/dL for Indirect Bilirubin; and 1.0 mg/dL for Total Bilirubin.

Height and Weight Percentiles

The “median pre-treatment to median post-treatment” method is used to evaluate the height and weight percentiles of patients with SED or PD. Cholic Acid treatment numerically improved the “mean of medians” in patients with SED and PD. However, it did not improve the “median of medians” of weight percentile of the PD patients, and it decreased from 4 percentile to 1 percentile (see the following tables).

Table 22: Summary of Height and Weight Percentile, Single Enzyme Defect ITT, (CAC91-10-10)

Comparison	Percentile	visit	n	Mean	SD	Median
Median Baseline to Median Post-TMT	Height	Baseline	25	41	±35	28
		Post-TMT	25	42	±36	28
	Weight	Baseline	38	41	±35	38
		Post-TMT	38	45	±36	40
Last Baseline to Last Post-TMT	Height	Baseline	25	42	±35	34
		Post-TMT	25	43	±36	34
	Weight	Baseline	38	42	±35	41
		Post-TMT	38	47	±37	39

From the Height and Weight Percentiles Supplemental Analyses (Study CAC91-10-10) submitted on April 4, 2014. Post-TMT: post-treatment.

Table 23: Summary of Height and Weight Percentile, Peroxisomal Disorder ITT, (CAC91-10-10)

Comparison	Percentile	visit	N	Mean	SD	Median
Median Baseline to Median Post-TMT	Height	Baseline	9	18	±15	13
		Post-TMT	9	16	±15	13
	Weight	Baseline	29	12	±18	4
		Post-TMT	29	14	±24	1
Last Baseline to Last Post-TMT	Height	Baseline	9	22	±22	11
		Post-TMT	9	18	±22	11
	Weight	Baseline	29	11	±20	2
		Post-TMT	29	17	±28	1

From the Height and Weight Percentiles Supplemental Analyses (Study CAC91-10-10) submitted on April 4, 2014. Post-TMT: post-treatment.

Liver Histopathology

Changes in liver histopathology are an additional endpoint. There were 16 patients (SED and PD) who had only one liver biopsy at baseline, and there were 21 patients (SED: 9 and PD: 12) who had both pre- and post-treatment liver biopsies. Comparative analysis is performed in the 21 patients who had both pre- and post-treatment biopsies. The biopsies were examined by independent central pathologists at the CCHMC. Pre- and Post-treatment liver biopsies were evaluated for the presence of inflammation, fibrosis, necrosis, and cholestasis.

As shown in the Table below, only 9 SED patients (9/54, 17% of ITT) had both pre- and post-treatment liver biopsies. Four of the 9 patients did not have an appreciable change in the four categories between the pre- and post-treatment. Two of the 9 patients had a pathologist-identified “Worse” in bridging fibrosis (“W+” in the Table). Four of the 9 SED patients had an identified “Improvement” (“I-” in the Table) in inflammation, necrosis and cholestasis.

Table 24: Comparative Analysis of Liver Biopsy from SED, ITT (N = 9)

PID	Bx Date	Pre-treatment				Bx Date	Post-treatment			
		Infln	Fibr	Necr	Chsts		Infln	Fibr	Necr	Chsts
009-S	11/15/90	+	+	n/a	+	11/7/96	+	W+	+	+
030-S	1/26/93	-	+	n/a	-	6/8/93	-	+	n/a	n/a
033-S	7/24/89	+	+	+	+	8/20/93	I-	W+	I-	I-
034-S	9/5/89	+	+	n/a	+	6/27/96	I-	++	n/a	I-
065-S	7/18/02	+	+	n/a	+	10/31/02	+	+	n/a	+
076-S	2/10/95	n/a	+	n/a	+	9/22/95	n/a	+	n/a	I-
079-S	10/9/96	+	++	+	n/a	12/5/97	+	++	I-	-
093-S	2/6/03	-	n/a	-	+	2/27/04	+	+	n/a	+
134-S	2/2/08	+	+	n/a	-	12/21/08	+	+	n/a	-

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From the Clinical Reviewer's notes of the Study Report (CAC91-10-10)

SED: single enzyme defect; Bx date: biopsy date; PID: patient ID; Infln: inflammation; Fibr: fibrosis; Necr: necrosis; Chsts: cholestasis; n/a: not assessed; + denotes presence; ++ denote extensive; - denotes absence; W+ denotes pathologist-identified worsening; I denotes pathologist-identified improvement.

As shown in the following Table, there were 13 PD patients who had both pre- and post-treatment liver biopsies (13/31, 42%). Eight of the 13 patients did not have appreciable changes in the four categories between pre- and post-treatment. Five of the 12 patients (5/13, 38%) had a pathologist-identified "Worse": 5 in bridging fibrosis, and 2 of them died; 1 in inflammation who survived. No one of the PD patients had pathologist-identified improvement by treatment.

In summary, the comparative analyses of liver biopsies show some improvements on the treatment in SED patients, but not in PD patients.

Table 27: Comparative Analysis of Liver Biopsy from PD, ITT (N = 12)

PID	Bx Date	Pre-treatment				Bx Date	Post-treatment			
		Infln	Fibr	Necr	Chsts		Infln	Fibr	Necr	Chsts
007-P	4/1/96	-	-	-	n/a	8/6/96	-	W+	n/a	n/a
011-P	4/4/00	+	+	n/a	+	4/18/01	-	+	n/a	n/a
012-P	4/27/96	+	+	+	n/a	4/18/97	+	W+	+	+
020-P	11/9/00	+	+	n/a	-	11/16/01	W+	W+	+	-
030-P	1/26/93	-	+	-	-	6/8/93	-	+	-	-
032-P	4/6/96	+	+	n/a	-	5/10/96	+	+	n/a	+
036-P	7/2/96	-	+	n/a	+	4/17/98	+	W+	n/a	-
037-P	5/23/95	-	+	+	n/a	9/22/95	n/a	W+	n/a	+
046-P	10/22/96	+	+	n/a	-	5/6/97	-	+	+	n/a
051-P	3/20/96	-	-	-	n/a	4/24/03	-	-	-	n/a
064-P	8/25/94	-	+	n/a	-	12/1/95	-	+	-	n/a
076-P	2/10/95	n/a	n/a	n/a	+	9/22/95	n/a	+	n/a	+
092-P	12/15/00	n/a	+	n/a	n/a	1/11/02	-	+	n/a	-

From the Clinical Reviewer's notes of the Study Report (CAC91-10-10)

PD: peroxisomal disorder; Bx date: biopsy date; PID: patient ID; Infln: inflammation; Fibr: fibrosis; Necr: necrosis; Chsts: cholestasis; n/a: not assessed; "+" denotes presence; "-" denotes absence; W+ denotes pathologist-identified worsening; I denotes pathologist-identified improvement.

Sensitivity Analyses of Efficacy Endpoints

Clinical Review
Wen-Yi Gao, M.D., Ph.D.
NDA 205-750/0
Cholbam (50 mg and 250 mg capsules)

Asklepiion submitted sensitivity analyses of the responses of SED and PD patients to efficacy end-points on June 20, 2014 (SN026, NDA 205,750).

The efficacy endpoints were compared between the “Median Baseline to Median Post-Treatment”, the “Mean Baseline to Mean Post-Treatment”, and the “Last Baseline to Last Post-Treatment”, respectively. Three types of single enzyme defects were examined: i.e., 3 β -hydroxy-5-C27-steroid dehydrogenase defect (3 β -HSD), Δ 4-3-oxosteroid 5 β -reductase defect (AKR1D1), and sterol 27-hydroxylase defect (CTX); and two types of peroxisomal disorder were examined: i.e., Zellweger syndrome (ZS) and neonatal adrenoleukodystrophy (NALD).

In the SED sensitivity study, the medians of ALT and AST on treatment were consistently improved in all the three sub-groups:

- ALT from 70.0 to 31.5 U/L, and AST from 74.0 to 42.0 U/L in the 3 β -HSD group; ALT from 253.5 to 52.0 U/L, and AST from 482.5 to 79.5 U/L in the AKR1D1 group; and ALT from 167.0 to 49.5 U/L, AST from 336 to 55 U/L in the CTX group, respectively.

The median of bilirubin shows the improvement in the 3 β -HSD group. However, the AKR1D1 data was unavailable, and the CTX data only had one patient.

In the height percentile analysis of SED, the median baseline to median post-treatment” was unchanged for the 3 β -HSD group (35.49 percentiles, n = 28, for the pre- and post-treatment, respectively). In the weight percentile analysis, the median was increased from 34.60 to 46.77 percentile (n = 28) for the 3 β -HSD group. The height percentile for the AKR1D1 group was not available, while the weight percentile was decreased from 42.91 percentile of the pre-treatment to 22.02 percentile of the post-treatment (n = 4). The medians of height and weight percentile of the CTX group were unchanged, 27.74 (n = 3) and 40.26 (n = 4) percentile, respectively.

In the PD sensitivity study, the median of ALT on treatment of the ZS group was improved from 97 to 82 U/L, and the median of AST improved from 373 to 202 U/L. However, the total bilirubin of ZS worsened from 3.1 to 5.6 mg/dL (n = 4, median baseline to median post-treatment), and 3.3 to 5.4 mg/dL (n = 4, last baseline to last post-treatment), respectively. The median of height percentile analysis of ZS had only one patient (27.45 percentile). The median of weight percentile of ZS group worsened from 5.83 to 0.18 percentile (n = 11).

In the neonatal adrenoleukodystrophy (NALD) group, the median of ALT (Median Baseline to Median Post-Treatment) were improved from 148 to 63 U/L, but the median of AST worsened from 164 to 186 U/L. The medians of total bilirubin of NALD patients pre- and post-treatment were within the normal range.

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The median of height percentile of NALD patients worsened from 6.06 to 1.33 percentile (n = 4), while the median of weight percentile worsened from 1.76 to 0.40 percentile (n = 8).

Table 28: SED Sub-type Analysis of CA Effectiveness Endpoints (ITT)

ITT (n=54)	ALT/AST	Bilirubin (Total)	Weight	Sibling Study	Survival ¹⁰ (Historical)
3β-HSD (n=35)	Imp ¹ (n=22)	Imp ⁴ (n=4)	Imp ⁵ (n=28)	Surv ⁹ (1 vs. 4)	96% ^{26/27} (100% ^{8/8})
AKR1D1 (n=10)	Imp ² (n=4)	N/A	Wnd ⁷ (n=4)	N/A	57% ^{4/7} (17% ^{1/6})
CTX (n=5)	Imp ³ (n=2)	Imp ⁶ (n=1)	Unch ⁸ (n=4)	N/A	100% ^{3/3} (86% ^{6/7})

From the clinical reviewer's notes based on Asklepiion Supplement SN028 (with no imputation) on July 7, 2014, and literature search for historical untreated control.

Imp¹: median of ALT of 3β-HSD improved from 70.0 to 31.5; median of AST also improved from 74.0 to 42.0;

Imp²: median of ALT of AKR1D1 improved from 253.5 to 52.0; Median of AST also improved from 482.5 to 79.5;

Imp³: median of ALT of CTX improved from 167.0 to 49.5; Median of AST also improved from 336.0 to 55.0;

Imp⁴: median of total bilirubin of 3β-HSD improved from 1.175 to 0.700;

Imp⁵: median of weight percentile of 3β-HSD improved from 34.60 to 46.77 percentile;

Imp⁶: median of total bilirubin of CTX (only 1 patient) improved from 6.400 to 0.200.

Wnd⁷: median of weight percentile of AKR1D1 worsened from 42.91 to 22.02 percentile;

Unch⁸: median of weight percentile of CTX was unchanged (i.e., 40.26 percentile, respectively).

Surv⁹: historical sibling study reported a 3β-HSD family: 4 of 5 siblings were untreated, and died; the fifth had CA treatment, and survived.

Survival¹⁰: the overall historical survival rate of SED=19/25 (76%); survival rate of SED on treatment=44/50 (88%).

Table 29: PD Sub-type Analysis of CA Effectiveness Endpoints (ITT)

ITT (n=31)	ALT/AST	Bilirubin (Total)	Weight	Sibling Study	Survival ⁸
Zellweger's (n=12)	Imp ¹ (n=8)	Wnd ⁴ (n=4)	Wnd ⁶ (n=11)	N/A	5/11 (45%)
Neonatal adrenoleukodystrophy (n=8)	ALT Imp ² (n=7) AST Wnd ³ (n=7)	Normal ⁵ (n=4)	Wnd ⁷ (n=8)	N/A	3/6 (50%)

From the clinical reviewer's notes based on Asklepiion Supplement SN028 (with on imputation) on July 7, 2014.

Imp¹: median of ALT of Zellweger's improved from 97 to 82; median of AST also improved from 373 to 202;

ALT Imp²: median of ALT of NALD improved from 148 to 63;

AST Wnd³: median of AST of NALD worsened from 164 to 186;

Wnd⁴: median of total bilirubin of Zellweger's worsened from 0.500 to 1.050;

Normal⁵: median of total bilirubin of NALD was in the normal range at baseline (0.825) and post-TMT (0.347), respectively;

Wnd⁶: median of weight percentile of Zellweger's worsened from 5.83 to 0.18 percentile;

Wnd⁷: median of weight percentile of NALD worsened from 1.76 to 0.40 percentile;

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Survival⁸: the overall historical survival rate of PD=10/31 (32%); the total PD on treatment=15/29 (52%); Sub-types historical control is not available.

Medical Officer Comments:

Because there was only small numbers of patients who had both pre- and post-treatment evaluations, the sensitivity analyses were considered to be explorative. However, the trend of SED sub-type analyses supports the clinical benefits of cholic acid therapy for SED patients.

In contrast, there was no consistent trend of biomarker analyses in PD; while the clinical weight and height percentile worsened on treatment for both ZS and NALD.

Review of Letters Addressing Quality of Life from Parents

Asklepiion submitted 24 letters from the parents of 17 patients to addressing quality of life on cholic acid therapy (SN029 of NDA 205,750, July 11, 2014). Eight of the 17 patients were selected among the companionate user who did not have a reviewable medical history. Nine of the patients (6 SED patients and 3 PD patients) were from Asklepiion-sponsored studies. The revised narratives to include the parent letters were submitted later (SNs 036 and 037 of NDA 205,750). The 9 patients are listed below.

Listing of Patients and Diagnosis for letters in SN029 (July 11, 2014)

Patient ID	Patient Diagnosis
012	Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy
033	3 β -hydroxy- Δ 5-C27-steroid oxidoreductase
034	3 β -hydroxy- Δ 5-C27-steroid oxidoreductase
068	Δ 4-3-oxosteroid 5 β -reductase
092	Peroxisomal Biogenesis Disorder: Generalized Peroxisomal Disorder
093	3 β -hydroxy- Δ 5-C27-steroid oxidoreductase
132	Peroxisomal Biogenesis Disorder: Zellwegers
176*	3 β -hydroxy- Δ 5-C27-steroid oxidoreductase
706*	3 β -hydroxy- Δ 5-C27-steroid oxidoreductase

*Initiated treatment with Cholic Acid after CAC-91-10-10 closed
From the Supplement 0029 of NDA 205750 on July 11, 2014.

The clinical dataset shows that the 3 PD patients (PIDs 012, 092, and 132) who did not have cholestasis at baseline are not responders to cholic acid treatment based on the criteria described. The letters of the 6 SED cases are also reviewed. The clinical data and responder analyses are consistent with the improvements of quality of life described by the parents.

7 Review of Safety

Highlights of safety findings by disease (Study CAC-91-10-10):

- A. Single enzyme defects (Safety Population): 50 patients
- Among them, 6 patients died during the study (6/50, 12%);
 - The untreated historical death rate was 24% (6/25).
 - Adverse events (AEs) were not recorded on a daily basis. Eight patients had a non-fatal serious adverse event (SAE) (8/50, 16%).
 - Six of the 8 patients had disease progression, MedDRA System Organ Class. Three of them died.
 - “Disease progression” was defined by the investigators as an increase of serum ALT/AST and/or bilirubin; or cholestasis in liver biopsy.
 - There were 7 patients who discontinued treatment (7/50, 14%), due to disease progression and death (6 patients) or disease progression and alive (one patient).
 - The most frequent treatment-emergent adverse events (TREA) were disease progression (6/50, 12%), followed by diarrhea (4/50, 8%), and jaundice/cholestasis (3/50, 6%).
 - Clinical and laboratory data included liver function test, serum bilirubin test, liver biopsy, and measurement of height/weight percentile.
- B. Peroxisomal disorders (Safety Population): 29 patients
- Among them, 14 patients died during the study (14/29, 48%); Seven of the 14 deaths did not have a clinical narrative.
 - In literature search by sponsor, the historical untreated death rate was 68% (21/31).
 - Twelve patients had a non-fatal serious adverse event (SAE) (12/29, 41%).
 - Four patients had disease progression, MedDRA System Organ Class. All of them died.
 - There were 14 patients who discontinued treatment (14/29, 48%), due to disease progression, convulsion, coagulopathy, GI hemorrhage and death.
 - There were 6 patients who were “lost to follow-up”.
 - Most frequent treatment-emergent adverse events (TREA) were disease progression (5/29, 17%) and convulsion (5/29, 17%), followed by diarrhea (3/29, 10%), gastroenteritis (3/29, 10%), and urinary tract infection (3/50, 6%).
 - Except liver function test, serum bilirubin test, liver biopsy, and measurement of height/weight percentile, no other clinical and laboratory examination was submitted.

Limitations of the available data:

The safety review is based on a single arm compassionate use trial for two rare diseases. The limitations of the submission are as follows:

- Small number of patients (50 patients with single enzyme defects and 29 patients with peroxisomal disorders, Safety Population).
- Incomplete narratives of patients who died during the study.
- Missing medical records and clinical laboratory data.
- Exposure to multiple types of primary bile acids: cholic acid, URSO (Ursodiol), and CDA (chenodeoxycholic acid) with different dosing regimens.
- More than 21 types of protocol deviations.
- Rates of lost-to-follow-up were high (11/50, 22% of SED patients and 6/29, 21%).

7.1 Methods

The primary safety review was based on an open-label, single arm trial (CAC-91-10-10 including sub-trial CAC-92-8-19) with 79 patients (50 patients with single enzyme defects, and 29 patients with peroxisomal disorders, Safety Population). Safety Population was defined as subjects who received at least one dose of Cholic Acid during the study. Table 30 provides an overview of the patient information.

A natural history control data was collected by the sponsor. The data included a) case reports; b) data from the pre-treatment phase of all patients with two or more years of pre-treatment history; and c) sibling data of SED where the diagnosis and treatment of an affected child had been preceded by the death of an elder sibling from the same disease. The historical reports were used as a control of the untreated deaths (see Tables 1 and 2 under Section 5.1).

A natural history study of PD by Poll-The et al. (Poll-The, 2004) was used as a comparator of untreated PD patients (age > 1 year old) (see Section 6.1.4 Table 15 and Figure 5).

Table 30: Primary Diagnosis by Disorder Type

Type of Disorder Primary Diagnosis	ITT (N = 85) N (%)	Safety (N = 79) N (%)	mITT (N = 70) N (%)
Single Enzyme Defect	54 (64)	50 (63)	43 (61)
3 β -hydroxy-5-C27-steroid oxidoreductase (3 β -hydroxy-5-C27-steroid dehydrogenase/isomerase or 3 β -HSD or HSD3B7)	35 (41)	35 (44)	32 (46)
Δ 4-3-oxosteroid 5 β -reductase (Δ 4-3-oxo-R or AKR1D1)	10 (12)	9 (11)	6 (9)
Sterol 27-hydroxylase (CTX)	5 (6)	3 (4)	3 (4)
2- (or a-) methylacyl-CoA racemase (AMACR)	1 (1)	1 (1)	1 (1)
Cholesterol 7 α -hydroxylase (CYP7A1)	1 (1)	1 (1)	0 (0)
Smith-Lemli-Opitz	1 (1)	1 (1)	1 (1)
Unknown	1 (1)	0 (0)	0 (0)
Peroxisomal Disorder	31 (36)	29 (37)	27 (39)
Peroxisomal Biogenesis Disorder: Zellweger's	12 (14)	11 (14)	9 (13)
Peroxisomal Biogenesis Disorder: Neonatal adrenoleukodystrophy	8 (9)	8 (10)	8 (11)
Peroxisomal Biogenesis Disorder: Type unknown	6 (7)	5 (6)	5 (7)
Peroxisomal Biogenesis Disorder: Refsum's	4 (5)	4 (5)	4 (6)
Peroxisomal Biogenesis Disorder: Generalized peroxisomal disorder	1 (1)	1 (1)	1 (1)

N = number of patients

Source: Tables 14.1.2.1, 14.1.2.3, 14.1.2.5, 14.1.2.8 to 14.1.2.10

From Section 11.2.2 Clinical Study Report CAC-91-10-10, Page 62.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation was primarily based on one open-label, single arm, and compassionate-use trial (CAC-91-10-10 including sub-study CAC-92-8-19) with 79 patients (50 with single enzyme defects and 29 with peroxisomal disorders, Safety Population).

Supportive studies included a therapeutic equivalency study (CAC-001-01) of currently used formulation vs. the to-be-marketed (16 patients with single enzyme deficiency), and a pharmacokinetic study (CAC-003-01, 18 healthy adults).

Literature search for the historical untreated controls was also reviewed.

7.1.2 Categorization of Adverse Events

The adverse events were correctly coded based on MedDRA.

Clinical Review
Wen-Yi Gao, M.D., Ph.D.
NDA 205-750/0
Cholbam (50 mg and 250 mg capsules)

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

7.1.3.1 Incidence of AEs in Study CAC-91-10-10

The overall incidence (at least 1 AE) of treatment-emergent adverse events (TEAEs) in Study CAC-91-10-10 (including sub-study CAC-92-8-19) was summarized in Table 31:

Table 31: Summary of Treatment-Emergent AEs by Disorder Type (Safety)

AE Type	Single Enzyme Defects (N = 50)			Peroxisomal Disorders (N = 29)		
	n	N	%	n	N	%
AE	41	22	44	85	21	72
SAE	9	8	16	25	12	41
Deaths	6	6	12	14	14	48
AEs Leading to Discontinuation	7	7	14	14	14	48

Note: n = number of adverse events, N = number of patients.

Source: The reviewer's notes based on Tables 14.3.1.1, 14.3.1.2 of Clinical Study Report CAC 91-10-10.

7.1.3.2 Incidence of AEs in Study CAC-101-01

Study CAC-101-01 was a small size, 30-day study. It compared the therapeutic equivalency of the currently used capsules with the To-Be-Marketed capsules. There were 16 patients with single enzyme defects in the study: no death, no SAE, and no discontinuation due to AE occurred. One subject (ID 159) experienced adverse events of vomiting and fever that resulted in hospitalization and IV fluids. Both events resolved were considered to be mild in intensity and considered to be unrelated with the study medication by the investigator.

There were 13 total adverse events from 9 patients (9/16, 56%). Four of the 13 patients had decreased vitamin D (4/16, 25%), and one had decreased vitamin A (1/16, 0.6%). In addition, one patient (1/16, 0.6%) had vomiting, fever, or abdominal muscle spasm, respectively. One patient with diarrhea and one patient with gastric reflux were considered to be treatment-related by the investigators.

7.1.3.3 Incidence of AEs in Study CAC-003-01

Study CAC-003-01 was a phase 1 single-center, open-label, three-way crossover study. The study was designed to assess the bioavailability/bioequivalence of a cholic acid 250 mg cGMP (Current Good Manufacturing Practice regulations by the US FDA) capsule relative to a 250 mg Pharmacy-Produced capsule and an oral 250 mg solution. Each administered twice daily (q 12h) PO for 4 days with 18 healthy male adults average age of 30.6 years old. There was no death, no SAE, and no discontinuation due to an AE.

Clinical Review
Wen-Yi Gao, M.D., Ph.D.
NDA 205-750/0
Cholbam (50 mg and 250 mg capsules)

The most common treatment-emergent AEs were diarrhea (17%, 3/18), Gastrointestinal Disorders, System Organ Class, followed by headache (11%, 2/18), Nervous System Disorders.

7.1.3.4 Incidence of Mortality from Literature Search

The natural historical control of SED and PD by literature search of case reports is listed at Tables 1 and 2 under Section 5.1. The overall mortality of the historical untreated control is 24% (6/25) and 68% (21/31) for SED and PD, respectively.

PD is a heterogeneous group of diseases; and the majority of the patients live longer than 1 year old. The mortality rate of these untreated patients is reported (29%, 9/31) by Poll-The, et al. (Poll-The, 2004).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety of cholic acid has been studied in 3 clinical studies (CAC91-10-10, CAC001-01, and CAC003-01) with a total of 66 patients with single enzyme defects, 29 patients with peroxisomal disorders, and 18 healthy adult patients.

There were 79 patients (50 patients with single enzyme defects; 29 patients with peroxisomal disorders) in the safety population of CAC91-10-10; there were 16 patients with single enzyme defects in CAC-001-01; and there were 18 healthy adults in CAC-003-01.

7.2.1.1 Drug exposure

Drug exposure in Study CAC-91-10-10

In the 18-year study, cholic acid was initially administered in combination with URSO (from 1992 to 2001); followed by using alone (from 2001 to 2009). There were multiple medication regimens of cholic acid as shown in the following Table. The majority patients received the cholic acid as a single agent.

Table 32: Medication Regimens (Safety Population)

Regimen 1	Regimen 2	Regimen 3	N	Percent
CA Only			40	47
CA & URSO			5	6
CA & CDA			1	1
CA Only	URSO only		16	19
CA Only	URSO only	CDA only	1	1
CA Only	URSO only	CA & URSO	4	5
CA Only	CA & URSO		4	5
CA Only	CDA Only		3	4
CA only	CA & CDA		1	1
CA Only	DHA only		3	4
CA Only	DHA only	DHA & Cholic	1	1
URSO only	CA & DHA		1	1

CA = cholic acid, CDA = chenodeoxycholic acid, DHA = docosahexenic acid, N = number of patients.

Source: Table 14.1.1.3

From the Study Report of CAC 91-10-10, Section 12.1, Page 91. DHA (Docosahexaenoid acid) is a polyunsaturated fatty acid that is used in the treatment of patients with peroxisomal disorders to support brain development.

The majority of patients received doses of about 15 mg/kg body weight per day. Twelve patients received daily doses greater than 20 mg/kg. Patients #79 and #65 received the highest doses with 61.5 and 58.1 mg/kg/day, respectively. The sponsor stated that the use of higher doses was because the patients' urinary bile acid or transaminase value increased.

The majority of patients received cholic acid treatment as a single agent; and on average for a duration of 145 weeks. One patient had received cholic acid for a maximum of 545 weeks. The mean treatment duration for URSO was 82 weeks.

Table 33: Treatment Duration (Safety Population)

Treatment Duration (in weeks) ^a	N	Mean	Std Dev	Median	Minimum	Maximum
With CA	53	145	155	73	0	545
With URSO	11	82	103	36	2	337
With DHA	2	217	59	217	175	259
With CDA	4	22	20	18	4	48

^aOnly calculated for patients with available treatment start and stop dates and at least information on the month available.

Source: Table 14.1.1.4

From the Study Report of CAC 91-10-10, Section 12.1, Page 96.

Drug exposure in Study CAC-001-01

There were 16 patients with single enzyme defect who received 10 to 15 mg To-Be-Marketed or currently used cholic acid per kg body weight per day for 30 days.

Drug exposure in Study CAC-003-01

Clinical Review
Wen-Yi Gao, M.D., Ph.D.
NDA 205-750/0
Cholbam (50 mg and 250 mg capsules)

There were 18 healthy adults who received cholic acid 250 mg/kg twice daily for 12 days. There were 3 dosing regimens. Treatment A consisted of a dosage of 250 mg oral capsule (Pharmacy formulation) administered twice daily under fasting conditions for 4 consecutive days. Treatment B consisted of a dosage of 250 mg oral capsule (cGMP formulation) administered twice daily for 4 consecutive days. Treatment C consisted of a dosage of 250 mg/mL solution (cGMP formulation) administered twice daily for 4 consecutive daily. There was no washout between each treatment.

7.2.1.2 Demographic and Other Characteristics of Study Population

Demography of Study CAC-91-10-10

Approximate 60% of patients were male, and 36% of female. The range of age at diagnosis varied from 0 to 13 years. Approximate half of patients (49%) were younger than 6 months of age at diagnosis. On average, the heights were in the 33% to 34% of height percentile; and the weights were 35% to 39% weight percentile.

Table 34: Demographic Profile of Safety Populations of Study CAC91-10-10

Characteristic		ITT (N = 85)	Safety (N = 79)	mITT (N = 70)
Gender [N (%)]	Female	31 (36)	29 (37)	25 (36)
	Male	50 (59)	48 (61)	45 (64)
	Unknown	4 (5)	2 (3)	0 (0)
Race [N (%)]	Arabic	1 (1)	1 (1)	1 (1)
	Asian Indian	2 (2)	2 (3)	2 (3)
	Black/African American	1 (1)	1 (1)	1 (1)
	Egyptian	1 (1)	1 (1)	1 (1)
	Haitian	1 (1)	1 (1)	1 (1)
	Hispanic	10 (12)	10 (13)	10 (14)
	Middle Eastern	7 (8)	7 (9)	6 (9)
	Persian/Iranian	1 (1)	1 (1)	1 (1)
	Portuguese	2 (2)	2 (3)	2 (3)
	UNK	29 (34)	23 (29)	16 (23)
	White	30 (35)	30 (38)	29 (41)
Age at diagnosis [years]	Mean ± SD	2 ± 4 (n = 74)	2 ± 4 (n = 71)	2 ± 4 (n = 62)
	Min, Max	0, 13 (n = 74)	0, 13 (n = 71)	0, 13 (n = 62)
Age group at diagnosis [N (%)]	<3 months		23 (27)	
	3-6 months		19 (22)	
	7-12 months	NA	13 (15)	NA
	13-36 months		12 (14)	
	>36 months		18 (21)	
Age at treatment start [years]	Mean ± SD	3 ± 4 (n = 77)	3 ± 4 (n = 77)	3 ± 4 (n = 68)
	Min, Max	0, 16 (n = 77)	0, 16 (n = 77)	0, 16 (n = 68)
Baseline height percentile	Mean ± SD	33 ± 31 (n = 16)	33 ± 31 (n = 16)	34 ± 31 (n = 15)
	Min, Max	0, 92 (n = 16)	0, 92	0, 92 (n = 15)
Baseline weight percentile	Mean ± SD	39 ± 36 (n = 16)	39 ± 36 (n = 16)	35 ± 35 (n = 15)
	Min, Max	0, 98 (n = 16)	0, 98 (n = 16)	0, 98 (n = 15)

N = number of patients, n = number of patients with data available, NA = not assessed, SD = standard deviation.

Source: Tables 14.1.2.1 to 14.1.2.7

From the Study Report of CAC-91-10-10, Section 11.2, Page 61.

Demography of Study CAC-001-01

The study enrolled 11 males and 5 females; and the ages ranged from 0.6 to 20 years old. The primary diagnosis included 11 patients with 3β-HSD defect, 3 patients with CTX defect, and 2 patients with AKR1D1 (5β-reductase) defect.

Table 35: Demographic Profile of Safety Populations of Study CAC-001-01

<i>Listing 1: DEMOGRAPHIC CHARACTERISTICS</i>												
Subject ID	Visit	Age	Gender	Race	Ethnicity	Diagnosis	Weight	Weight Percentile	Height	Height Percentile	Met Inc/Excl	Has Any Deviations
27	1	8.5	Male	White	Not Hispanic	CTX	23.70	23	124.0	15	Yes	No
	2	8.5	Male	White	Not Hispanic	CTX	23.50	23	128.0	35	Yes	Yes
57	1	11.0	Male	White	Not Hispanic	3beta-HSD	50.70	93	144.7	60	Yes	No
	2	11.0	Male	White	Not Hispanic	3beta-HSD	52.70	95	144.7	60	Yes	No
65	1	8.0	Male	White	Not Hispanic	CTX	21.00	10	126.0	37	Yes	No
	2	8.0	Male	White	Not Hispanic	CTX	21.30	10	127.0	37	Yes	No
68	1	20.0	Male	White	Not Hispanic	5beta-Reductase	73.30	63	173.5	38	Yes	No
	2	20.0	Male	White	Not Hispanic	5beta-Reductase	72.80	63	174.1	38	Yes	No
79	1	15.0	Male	White	Not Hispanic	3beta-HSD	80.60	96	175.5	75	Yes	No
	2	15.0	Male	White	Not Hispanic	3beta-HSD	84.50	97	172.0	70	Yes	No
86	1	11.0	Male	Black	Not Hispanic	CTX	45.20	80	148.0	75	Yes	Yes
	2	11.0	Male	Black	Not Hispanic	CTX	46.40	85	149.5	82	Yes	No
93	1	7.5	Female	White	Not Hispanic	3beta-HSD	27.80	80	128.6	75	Yes	No
	2	7.5	Female	White	Not Hispanic	3beta-HSD	28.40	85	129.4	80	Yes	No
95	1	6.8	Male	White	Not Hispanic	3beta-HSD	27.90	90	121.2	50	Yes	No
	2	6.5	Male	White	Not Hispanic	3beta-HSD	29.20	94	121.4	50	Yes	Yes
106	1	5.8	Male	White	Hispanic	3beta-HSD	18.50	25	104.8	3	Yes	No
	2	5.8	Male	White	Hispanic	3beta-HSD	19.10	37	105.3	3	Yes	No
133	1	3.5	Female	White	Not Hispanic	5beta-Reductase	10.00	3	82.9	3	Yes	No
	2	3.5	Female	White	Not Hispanic	5beta-Reductase	9.90	3	84.1	3	Yes	No
138	1	4.8	Female	White	Hispanic	3beta-HSD	15.10	10	94.0	1	Yes	No
	2	4.8	Female	White	Hispanic	3beta-HSD	15.60	17	95.4	1	Yes	Yes
145	1	3.5	Male	White	Hispanic	3beta-HSD	16.60	75	91.7	3	Yes	No
	2	3.5	Male	White	Hispanic	3beta-HSD	17.10	90	92.9	6	Yes	No
149	1	6.5	Female	White	Hispanic	3beta-HSD	26.80	88	116.5	37	Yes	No
	2	6.5	Female	White	Hispanic	3beta-HSD	27.80	93	117.2	49	Yes	No
159	1	4.5	Male	White	Hispanic	3beta-HSD	19.10	75	98.7	7	Yes	No
	2	4.5	Male	White	Hispanic	3beta-HSD	19.30	75	98.9	7	Yes	No
176	1	7.8	Male	Black	Not Hispanic	3beta-HSD	25.50	51	125.8	45	Yes	No
	2	7.8	Male	Black	Not Hispanic	3beta-HSD	26.70	62	126.7	50	Yes	No
177	1	0.6	Female	White	Not Hispanic	3beta-HSD	7.00	25	65.4	25	Yes	Yes
	2	0.6	Female	White	Not Hispanic	3beta-HSD	7.76	52	59.0	75	Yes	Yes

From the Study Report of CAC-001-01, Section 11.2, Page 28.

Demography of Study CAC-003-01

The study enrolled 18 healthy adults with an average of age 30.6 years old. None of them had a history of smoking.

Table 36: Demographic Profile of Safety Populations of Study CAC-003-01

Demographic Characteristics	N = 18
Race [n (%)]	
Caucasian Males	4 (22.2)
Black Males	14 (77.8)
Age (years)	
Mean	30.6
Standard Deviation	7.26
Median	27.5
Min, Max	22, 45
Height (cm)	
Mean	178.5
Standard Deviation	6.23
Median	178.5
Min, Max	170.0, 192.0
Weight (kg)	
Mean	79.2
Standard Deviation	7.32
Median	80.0
Min, Max	67.3, 93.2

Data source: [Appendix 16.2.4](#)

From the Study Report of CAC-003-01, Section 11.2, Page 36.

7.2.2 Explorations for Dose Response

Explorations for dose response were not performed in this NDA.

7.2.3 Special Animal and/or In Vitro Testing

Special animal testing and/or in vitro testing were not performed in this NDA.

7.2.4 Routine Clinical Testing

Routine clinical testing in the CAC-91-10-10 study included vital signs, physical examination, liver function tests, bilirubin and urinary FAB-MS atypical bile acid test. The AE safety nomenclature for this study was MedDRA.

7.2.5 Metabolic, Clearance, and Interaction Workup

Clinical Review
Wen-Yi Gao, M.D., Ph.D.
NDA 205-750/0
Cholbam (50 mg and 250 mg capsules)

Cholic acid is an endogenous primary bile acid. The pharmacokinetic parameters following multiple 250 mg oral doses of cholic acid were studied in healthy adults (see Summary of Study CAC-003-01, Section 9). The workup of drug-drug interaction was not submitted.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Cholic Acid is a primary bile acid. Information for potential adverse events based on similar primary bile acid drugs is not available.

Ursodexoycholic acid (URSO[®] & URSO Forte[®]), a secondary bile acid, was approved for the treatment of primary biliary cirrhosis (PBC) in December 1997 (NDA 20-675). FDA issued Warnings and Precautions of ursodiol in December 2012:

- Contraindications: contraindicate Urso in patients with complete biliary obstruction;
- Warnings and Precautions: warning regarding hepatotoxic effects, the need to maintain bile flow, and recommend liver function and bilirubin monitoring.

This regulatory action was based on the reports:

- In animal studies of bile duct obstruction, UDCA induced bile duct infarcts and bile leakage into the surrounding liver tissues.
- Safety database search by sponsor identified 215 case reports: There is strong temporal relationship between UDCA administration and sharp increase of ALT and AST tests in patients with biliary obstruction. On the other hand, withdrawal of UDCA improved the abnormal LFTs. Maintenance of the bile flow also improved the clinical signs.

(Also, see Section 2.4).

7.3 Major Safety Results

7.3.1 Deaths

Deaths in Single Enzyme Defects (Study CAC-91-10-10)

A total of 6 SED patients expired during the study. The death rate (12%, 6/50, Safety Population) of the study is numerically lower than the historical untreated control (24%, 6/25, Table 37). The causes of deaths were disease progression (6 deaths).

Table 37 shows that the average age of subjects at death is younger than the historical control (0.7 year old vs. 6.4 years old). This may be due to the requirement of selecting historical patients who had 2 or more years of pre-treatment history. Further review shows that all of the deaths were younger than 1 year old, and that they had severe cholestasis and being treated for 2 months to 1 year (Table 38).

Clinical Review
Wen-Yi Gao, M.D., Ph.D.
NDA 205-750/0
Cholbam (50 mg and 250 mg capsules)

Table 37: Deaths of SED on Treatment and Historical Untreated Control

Safety Population	SED on TMT	Historical Control
	N=50	N=25
Death	12% (6/50)	24% (6/25)
Age at Death	0.7 ±0.5	6.4 ±15.0
Age at Diagnosis	0.4 ±0.4	5.7 ±13.4

From the Study Report of CAC-91-10-10 and the Historical Control Summary of NDA submission.
SED: single enzyme defect; Age at Diagnosis denotes the age of the 6 deaths at diagnosis; TMT: treatment; ±0.5: standard deviation of age.

Table 38: Temporal Relationship of SED Post-TMT Cholestasis, Bilirubin and Death

PID	Age at Diagnosis	TMT	Post TMT	Urinary BA	Time to Death
#0	Neonate	CA	Severe cholestasis	Marked	2 mo
#16	Neonate	CA	Severe cholestasis	Marked	2 mo
#103	4 mo	CA	ALT 222 /AST 557 /Total Bili 30.5	Significant	3 mo
#127	5 mo	CA +URSO	Cholestasis	Slight	1 yr
#143	1 yr	CA +URSO	ALT 249 /AST 254 /Direct Bili 33.5	Slight	3 mo
#152	Neonate	CA	Severe cholestasis	Marked	3 mo

From the Study Report of CAC-91-10-10 of NDA submission.

PID: patient identification number; SED: single enzyme defect; TMT: treatment; Mo: month; yr: year; CA: Cholic Acid; URSO: ursodiol; and Bili: bilirubin.

Narratives of Death in SED Group of Study CAC-91-10-10

(1) Subject ID: #0

Disorder Type: Δ 4-3-oxosteroid 5 β -reductase (AKR1D1)

Subject #0, a 3 week old white male, was enrolled in Study CAC-91-10-10 on 4/11/1993. He received Cholic Acid (dosing level not submitted) from 4/11/1993 to (b) (6) (b) (6) weeks), and his condition was deteriorated. He had 3 post-treatment assessments during the first month of treatment. The elevation of bile acid excretion was marked. No liver function test was available. The treatment was terminated on (b) (6) due to "disease progression", and died subsequently. The subject was scheduled for a liver transplant.

(2) Subject ID: #16

Disorder Type: Cholesterol 7- α -hydroxylase (CYP7A1)

Subject #16, a neonate male, was enrolled in Study CAC-91-10-10 on 7/6/1996. He received Cholic Acid (dosing level not submitted) from 7/6/1996 to (b) (6). He had 6 post-treatment assessments. All bile acid excretion scores were either "significant" or "marked". No liver function test values are available. The treatment was stopped due to worsening of the disease (disease progression) and the need for a liver transplantation. The patient died (b) (6) days after the liver transplantation.

(3) Subject ID: #103

Disorder Type: Δ 4-3-oxosteroid 5 β -reductase (AKR1D1)

Clinical Review
Wen-Yi Gao, M.D., Ph.D.
NDA 205-750/0
Cholbam (50 mg and 250 mg capsules)

Subject #103, a 4 months old male, was enrolled in Study CAC-91-10-10 on 8/16/2006. He received Cholic Acid (dose level not submitted) on 8/16/2006 and had at least 2 months of treatment. During the treatment, he had 4 assessments. The last liver function test values on 9/19/2006 were ALT 222 IU/L, AST 557 IU/L, and total bilirubin 30.5 mg/dL. Two non-serious AEs (ascites and nose bleed) were reported. The patient died [REDACTED] (b) (6) and “disease progression” was likely responsible for the death.

(4) Subject ID: #127

Disorder Type: Smith-Lemli-Opitz

Subject #127, a 5-month old male, was enrolled in Study CAC-91-10-10 in July 2005. He received Cholic Acid and URSO (dosing regimen not submitted) from 7/2005 to 11/2005. He had 10 assessments during Month 1 to Month 13 of treatment. His serum bilirubin was 8.7 mg/dL, and by report, he had “modestly elevated serum ALT and AST”. Despite treatment with Cholic Acid, his serum bilirubin continued to climb. His serum bilirubin rose to 14.2 mg/dL and his AST/ALT were in the “400 range”. He was restarted on ursodeoxycholic acid with Cholic Acid because of perceived poor response to Cholic Acid. One adverse event “cholestasis” was documented for the patient. Given his decline in liver function, Cholic Acid was discontinued in 11/2005. He died on [REDACTED] (b) (6). His FAB-MS assessment was “Slight” on 7/17/2006.

(5) Subject ID: #143

Disorder Type: 3 β -hydroxy- Δ 5-C27-steroid oxidoreductase (3 β -HSD)

Subject #143, a 9 months old male, enrolled in Study CAC-91-10-10 in March 2008. He received Cholic Acid and URSO from 3/2008 to [REDACTED] (b) (6) (dosing regimen not submitted). He had two post-treatment assessments: the urinary bile excretion score was “Slight” on 3/3/2008, and on 3/8/2008, the ALT was 249 IU/L, AST 254 IU/L, and direct bilirubin 335.9 μ mol/L, respectively. The patient died due to “severe disease progression” on [REDACTED] (b) (6).

(6) Subject ID: #152

Disorder Type: Δ 4-3-oxosteroid 5 β -reductase (AKR1D1)

Subject #152, a 2 month old baby (gender not known), enrolled in Study CAC-91-10-10 in January 2008. The patient received Cholic Acid therapy (dose level not submitted) from 1/2008 to [REDACTED] (b) (6). The patients had two post-treatment assessments during the month of treatment. The urinary bile acid excretion score was “marked”. No liver function test values were submitted. SAE reported “disease progression”. The patient died on [REDACTED] (b) (6), due to “severe disease progression”. Postmortem examination revealed “neonatal hemochromatosis” (a form of fulminant hepatic failure due to injury to the perinatal liver) with very few viable hepatocytes.

Medical Officer Comments:

Infants with SED appear to be more susceptible to cholic acid treatment than the adult patients. Precautions should be taken against drug-induced cholestasis in these patients.

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A Day 120-Safety Update Report was reviewed (See Appendix 9.6 for details)

Deaths in Peroxisomal Disorders (Study CAC-91-10-10)

A total of 14 PD patients expired during the study. The death rate (48%, 14/29, Safety Population) is numerically lower than the historical untreated control (68%, 21/31). The most frequent cause of death was “disease progression” (6 deaths) and “unknown causes” (6 deaths). Table 39 shows that the average age of subjects at death is comparable to the historical control. Table 40 shows that 7 of the 14 PD patients who died during the study (50%, 7/14) had abnormal LFT tests, serum bilirubin, or cholestasis on biopsy prior to deaths, but the urine abnormal bile acid score were normal or close to normal.

Table 39: Deaths of PD on Treatment and Historical Untreated Control

Safety Population	PD on TMT	Historical Control
	N=29	N=31
Death	48% (14/29)	68% (21/31)
Age at Death	1.6 ±1.7	0.7 ±0.8
Age at Diagnosis	0.5 ±0.8	0.6 ±0.7

From the Study Report of CAC-91-10-10 and the Historical Control Summary of NDA submission. PD: peroxisomal disorder; Age at Diagnosis denotes the age of the 14 deaths at diagnosis; TMT: treatment; ±1.7: standard deviation of age.

Table 40: Temporal Relationship of PD Post-TMT Cholestasis, Bilirubin and Death

PID	Age at Diagnosis	TMT	Pre TMT	Post TMT	Urinary BA	Age at Death
#13	Neonate	CA/URSO	Bx Chltasis	ALT 51/ AST 108/ Direct Bili 0.6	Normal	1 yr 5 mo
#19	Neonate	CA/URSO	No Bx	ALT 96/ AST 409	Normal	4 mo
#36	Neonate	CA	Bx Chlstasis	ALT 35 /AST 94 /Total Bili 1.1	Normal	1 yr 9 mo
#37	Neonate	CA +DHA	Bx No Chltasis	ALT 119/ AST 483/ direct Bili 4.2/ Bx Chlstasis	Normal	1 yr 1 mo
#72	1 yr	CA	Bx No Chlstasis	ALT 165	Normal	2 yr 4 mo
#80	Neonate	CA/URSO	Bx Chlstasis	ALT 69/ AST 276/ Total Bili 19.8	Slight	3 mo
#17	Neonate	URSO/CA/DHA	No Bx	ALT 307/ AST 505/ Total Bili 7.8/ Direct Bili 5.6	Normal	1 yr 6 mo

From the Study Report of CAC-91-10-10, NDA 205,750.

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PID: patient identification number; PD: peroxisomal disorders; TMT: treatment; Mo: month; yr: year; CA: Cholic Acid; URSO: ursodiol; DHA: docosahexenic acid, a polyunsaturated fatty acid used in the treatment of PD patients with brain disorders); Urinary BA: urine abnormal bile acid test score; Bili: bilirubin. Bx ChlStasis: biopsy showed Cholestasis; ALT and AST: IU/L; Bilirubin mg/dL.

Medical Officer Comments:

PD is a heterogeneous group of diseases. The death rate of patients who were older than 1 year of age appears to be lower than the natural history study by Poll-The (40% vs. 71%). The 4-year survival rate is also lower than the natural history study (60% vs. 77%) (Table 15).

7.3.2 Nonfatal Serious Adverse Events

7.3.2.1 Nonfatal SAEs in Study CAC-91-10-10 Safety Population

Nonfatal SAEs in Single Enzyme Defect Patients

Nonfatal treatment-emergent SAEs occurred in 4 SED patients (8%, 4/50) (Table 41). They had 6 SAEs: disease progression, jaundice, respiratory disorder, urinary tract infection, coagulopathy, and hyperammonemia (Table 41). Disease progression was defined as increase of serum ALT/AST, increase of bilirubin, or identifying cholestasis on biopsy.

Table 41: Nonfatal Serious Adverse Events SED Patients (Safety Population)

PID	Preferred Term	Outcome
#31	Disease progression	Discontinued
#76	Respiratory disorder; Urinary tract infection	Recovered
#106	Coagulopathy; hyperammonemia	Recovered
#159	Jaundice	Recovered

From the Study Report of CAC-91-10-10, Section 5.3.5.1, Pages 286-288

Nonfatal SAEs in Peroxisomal Disorder Patients

Nonfatal treatment-emergent SAEs occurred in 8 PD patients (28%, 8/29) with 14 nonfatal SAEs. The SAEs with more than two reports were diarrhea, gastroenteritis, dehydration, and urinary tract infection (Table 42).

Table 42: Nonfatal Serious Adverse Events in PD Patients (Safety Population)

PID	Preferred Term	Outcome
#12	Dehydration	Recovered
#29	Gastric ulcer	NA
#37	Nasopharyngitis; abnormal nutritional condition; urinary tract infection; gastroenteritis;	Recovered

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#46	Gastroenteritis	Recovered
#69	Respiratory distress; epistaxis; urinary tract infection	Recovered
#72	Pneumoperitoneum	Recovered
#92	Diarrhea	Recovered
#128	Diarrhea; dehydration	Recovered

From the Study Report of CAC-91-10-10, Section 5.3.5.1, Pages 286-288

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Discontinuations in Study CAC-91-10-10

Discontinuations in SED Patients

There were 7 discontinuations of treatment in SED patients due to an AE. The most common discontinuation due to AE was “disease progression” that occurred in 5 patients (Table 43).

Table 43: SED Patients with TEAEs Resulting in Discontinuation of Study Medication (Safety Population)

PID (SED)	Preferred Term	Outcome
#0	Disease progression	Discontinued, died
#16	Disease progression	Discontinued, died
#31	Disease progression	Discontinued, alive
#103	Disease progression	Discontinued, died
#127	Cholestasis	Discontinued, died
#143	Disease progression	Discontinued, died
#152	Jaundice	Discontinued, died

From the Study Report of CAC-91-10-10, Section 5.3.5.1, Pages 289-316

Disease progression was defined as increase of serum ALT/AST, increase of bilirubin, or identifying cholestasis on biopsy.

Discontinuations in PD Patients

There were 14 discontinuations of treatment in PD patients due to an AE. The most common discontinuation was “disease progression” that took place in 6 patients (Table 44).

Table 44: PD Patients with TEAEs Resulting in Discontinuation of Study Medication (Safety Population)

PID (PD)	Preferred Term	Outcome
#13	Disease progression	Discontinued, died
#17	Unknown	Discontinued, died
#19	Disease progression	Discontinued, died
#29	Disease progression	Discontinued, died
#36	Disease progression	Discontinued, died
#37	Disease progression	Discontinued, died

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#59	Convulsion	Discontinued, died
#69	Coagulopathy	Discontinued, died
#72	Unknown	Discontinued, died
#80	Disease progression	Discontinued, died
#87	Unknown	Discontinued, died
#91	Unknown	Discontinued, died
#123	Unknown	Discontinued, died
#130	Unknown	Discontinued, died

From the Study Report of CAC-91-10-10, Section 5.3.5.1, Pages 289-316
Disease progression was defined as increase of serum ALT/AST, increase of bilirubin, or identifying cholestasis on biopsy.

7.3.4 Significant Adverse Events

“Disease progression” was the most frequent reported adverse events (SED: 5; PD: 6) in Study CAC-91-10-10. The definition was “increase of serum ALT/AST, increase of bilirubin, or identifying cholestasis on biopsy”. Two SED patients and 6 PD patients died. Both the underlying diseases and the cholic acid overexposure can attribute to the “disease progression”.

7.3.5 Submission Specific Primary Safety Concerns

There are two primary safety concerns of cholic acid treatment as follows:

(1) Mitochondria toxicity of bile acids:

Pre-clinical studies show that bile acids may inhibit mitochondrial respiration function in a dose-dependent manner (Palmeira, 2004). The mechanism may involve detergent effects against plasma membrane of cells. Bile acids may damage hepatocytes in two mechanisms: At higher concentrations (≥ 250 mcM), bile acids cause hepatocellular necrosis, and at lower concentrations (≤ 100 mcM), bile acids trigger apoptosis of hepatocytes (Palmerira, 2004).

(2) Exacerbation of pre-existing cholestasis:

SED patients:

In patients with single enzyme defects, cholic acid overdosing may cause cholestasis damaging hepatic cells. Drug-induced cholestasis may occur in patients with pre-existing biliary obstruction.

PD patients:

It is known that patients with peroxisomal disorders have pre-existing severe mitochondrial and peroxisomal defects (Goldfischer, 1973; Hughes, 1990; Mooi, 1983; Baumgart, 2001; Dirkx, 2005; Keane, 2007). Bile acid therapy may exacerbate the severe mitochondria defects.

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Cholic acid fed PD mice experienced micro-vesicular steatosis on liver biopsies; while the untreated control did not (Keane, 2006). This pathology is associated with the interruption of β -oxidation of fatty acids at mitochondria (Burt, 1998; Mautekeete, 1990). Clinically, Reye's syndrome shows the picture on liver biopsies, and is associated with drug-induced delayed mitochondria toxicity.

Medical Officer Comments:

Cholic acid treatment may benefit SED patients who do not have biliary obstruction. Liver function tests (γ -GT, alkaline phosphatase, AST, ALT) and bilirubin level should be monitored during the treatment. Discontinuation should be considered if the parameters increase to a level considered clinically significant. Caution has to be exercised to maintain the bile flow of the patients who take cholic acid.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Common AEs in Study CAC-91-10-10

There were only small numbers of common AEs reported from the 18-year study. Adverse events were recorded at the time of study visits. Commonly reported treatment emergent AEs (TEAE) are defined as those reported at ≥ 2 subjects in the treated groups. Diarrhea was the most frequent common treatment emergent AEs in both the single enzyme defects and peroxisomal disorders groups.

Common AEs in Single Enzyme Defects

The most common AEs in SED group were pyrexia and diarrhea.

Table 45: Single Enzyme Defects: TEAEs Occurrence ≥ 2 Subjects (Safety Population)

MedDRA Preferred Term	SED, n=50
Pyrexia	4
Diarrhea	3
Jaundice	2
Abdominal pain	2
Respiratory tract infection	2
Epistaxis	2

From the Study Report of CAC-91-10-10, NDA 205,750.

Common AEs in Peroxisomal Disorders

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NDA 205-750/0
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The most common AEs were convulsion, respiratory tract infection, and diarrhea. There were 7 convulsion AEs in 5 patients, 5 fracture AEs in 3 patients, and 3 dehydration AEs in 3 patients.

Table 46: Peroxisomal Disorder TEAEs Occurrence ≥ 2 Subjects (Safety Population)

MedDRA Preferred Term	PD, n=29
Convulsion	5
Respiratory tract infection	4
Diarrhea	3
Gastroenteritis	3
Pyrexia	3
Fracture	3
Dehydration	3
Vomiting	2
Pneumonia	2
Urinary tract infection	2
Weight decrease	2
Lethargy	2

From the Study Report of CAC-91-10-10.

7.4.1.2 Common AEs in Study CAC-001-01

The numbers of adverse events reported were small (Table 47). There were two AEs (mild gastric reflux and moderate diarrhea), which were possibly related to the study drug.

Table 47: Adverse Events with Patient ID in Study CAC-001-01

Body System	Mild			Moderate		Severe		Total	Possibly Related	Total (%)	
	Unlikely Related	Possibly Related	Not Related	Possibly Related	Not Related	Related	Not Related				
General											
Decreased Vit A					159			1		1 (7.7%)	
Decreased/low 25OH/Vit D			68, 95,106, 145, 159					4		4 (30.7%)	
Fever								1		1 (7.7%)	
EENT											
Nosebleed					176			1		1 (7.7%)	
Gastrointestinal											
Diarrhea				149					1	1 (7.7%)	
Reflux		79							1	1 (7.7%)	
Vomiting			159					1		1 (7.7%)	
Hepatobiliary											
Increased ALT	133							1		1 (7.7%)	
Increased AST	133							1		1 (7.7%)	
Musculo-Skeletal											
Muscle Spasm					79			1		1 (7.7%)	
Total	2	1	6	1	3	0	0	0	11	2	13 (100)

From the Study Report (CAC-001-01), Section 12.2, Page 40.

7.4.1.3 Common AEs in Study CAC-003-01

There were 18 healthy adults (male) who received Cholic Acid 250 mg twice daily for 4 days (3 different formulations: a) pharmacy capsule, b) new cGMP capsule, and c) Cholic Acid solution).

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A total of 13 AEs were reported in 6 subjects (33%, 6/18). The most common AEs were diarrhea (3/18), and headache (2/18).

Table 48: Adverse Events with Patient ID in Study CAC-003-01

System Organ Class Preferred Term	Treat A N=18	Treat B N=18	Treat C N=18	Total N=18
SUBJECTS WITH ANY ADVERSE EVENTS	1	1 (6%)	5 (28%)	6 (33%)
Gastrointestinal disorders	1 (6%)	1 (6%)	1 (6%)	3 (17%)
Diarrhoea	1 (6%)	1 (6%)	1 (6%)	3 (17%)
Eructation	0	0	1 (6%)	1 (6%)
General disorders and administration site conditions	0	1 (6%)	0	1 (6%)
Feeling hot	0	1 (6%)	0	1 (6%)
Investigations	0	0	1 (6%)	1 (6%)
Blood glucose increased	0	0	1 (6%)	1 (6%)
Nervous system disorders	0	1 (6%)	2 (11%)	3 (17%)
Dizziness	0	0	1 (6%)	1 (6%)
Headache	0	1 (6%)	1 (6%)	2 (11%)
Renal and urinary disorders	0	0	2 (11%)	2 (11%)
Glycosuria	0	0	1 (6%)	1 (6%)
Leukocyturia	0	0	1 (6%)	1 (6%)

Data source: [Appendix 16.2.7.3](#)

From the Study Report (CAC-003-01), Section 12.2, Page 48.

7.4.2 Laboratory Findings

The clinical laboratory data of Study CAC-91-10-10 consisting of liver function tests (serum transaminases) and bilirubin are analyzed as efficacy endpoints. The results are presented in Section 6.1.8. No other clinical laboratory data were submitted.

The clinical laboratory data of Studies CAC-001-01 and CAC-003-01 did not show overall inconsistent outcomes to the treatment.

7.4.3 Vital Signs

The vital signs of Study CAC-91-10-10 were examined at study visits, and the outcomes were briefly mentioned in the narratives.

The mean changes of vital signs of Studies CAC-001-01 and CAC-003-01 from baseline to end of study were small, and did not show overall inconsistency to the treatment.

7.4.4 Electrocardiograms (ECGs)

ECG examination data of Study CAC-91-10-10 were not submitted. ECG examination was not conducted in Study CAC-001-01.

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In Study CAC-003-01, one subject had sinus bradycardia and QT interval prolongation at the Cycle 3 (Oral Solution). The investigator determined the abnormal ECG unrelated.

Medical Officer Comments:

Cholic acid is one of the endogenous bile acid, and the subject is a healthy volunteer without underlying disease. Literature search by the reviewer did not find a similar case associated with bile acid treatment. These results support that the “unrelated” conclusion by the investigator is acceptable.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials were conducted.

7.4.6 Immunogenicity

Immunogenicity studies were not part of the Cholic Acid development plan.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Cholic Acid is one of the primary bile acid. Dose dependency for clinical adverse events was not studied.

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was not studied.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not studied.

7.5.4 Drug-Disease Interactions

Detailed drug-disease interactions were not studied.

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not studied.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

(b) (4) Carcinogenicity and genetic toxicity to human were not studied.

7.6.2 Human Reproduction and Pregnancy Data

Adequate and well-controlled studies were not conducted in pregnant women. In the literature, four pregnancies in two women taking cholic acid for 3 β -HSD deficiency resulted in healthy infants (Gonzales, 2009).

Furthermore, animal reproduction studies have not been conducted. It is not known whether cholic acid treatment can cause fetal harm.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of cholic acid in neonates has not been established. The safety and effectiveness of cholic acid in 66 SED pediatric patients age from 3 weeks to 16 years have been studied. Detailed effects on growth have not been studied.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose and drug abuse potential were not studied in this submission.

7.7 Additional Submissions / Safety Issues

There was no additional submission of safety issue.

8 Postmarket Experience

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Cholic Acid has not been approved in the United States. A similar product Cholic Acid FGK for treatment of inborn errors in primary bile acid synthesis was approved by EMA (European Medicines Agency) in January 2014. Postmarketing safety data is not available.

In the literature, the development of symptomatic cholelithiasis has been reported in a patient with 3 β -HSD deficiency (Gonzales, 2009).

9 Appendices

9.1 Literature Review/References

Literature Review

Literature review focuses on the safety and effectiveness of cholic acid treatment in SED and PD patients.

SED Paper (Gonzales, 2009):

Gonzales and his colleagues reported a 12-year cholic acid study in 15 SED patients (13 patients with 3 β -HSD deficiency and 2 patients with AKR1D1 deficiency):

- Jaundice disappeared within weeks during the treatment and steatorrhea improved;
- Growth (weight and height) improved
- Hepatosplenomegaly improved
- Liver biopsy (after \geq 5 years of treatment) showed no cholestasis in 14 patients.
- Normal sexual maturation in all patients. Four of them had normal pregnancies.
- Six of the patients were from Study CAC-91-10-10.

PD Papers

- Severe mitochondria defect is the primary pathology of PD. It has been demonstrated in both clinical case reports and animal studies (Goldfischer, 1973; Mathis, 1980; Hughes, 1990; Baumgart, 2001; Dirkx, 2005).
- Study by Keane et al. show that cholic acid and UDCA-fed PD mice developed hepatic steatosis similar to “microvesicular steatosis” and hepatocellular damages. Bile acids exposure worsened the conjugation and transportation of bile acids in the PD liver (Keane, 2007).

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NDA 205-750/0

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Wen-Yi Gao, M.D., Ph.D.

NDA 205-750/0

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9.2 Labeling Recommendations

Labeling underwent extensive negotiations between the Applicant and FDA. See the final negotiated labeling.

9.3 Advisory Committee Meeting

There was no advisory committee meeting held for this original NDA.

9.4 Summary of Study CAC-001-01

Title of Study: An Open-Label, Single-Center, Nonrandomized Study to Compare the Therapeutic Efficacy of To-Be-Marketed (TBM) Cholic Acid Capsules with that of the Currently Used (CU) Formulation of Cholic Acid Capsules Used to Treat Children with Inborn Errors of Bile Acid Synthesis (Phase 3)

Study Center: Cincinnati Children's Hospital Medical Center (CCHMC)

Study Objectives:

Efficacy Variables: Therapeutic effect on TBM cholic acid capsules, compared with the effect of the CU formulation of cholic acid, on 1) serum transaminases and 2) suppression of synthesis of atypical bile acids, as measured by urine and serum bile acid analysis using mass spectrometry.

Safety Variables: Safety and tolerability of TBM cholic acid capsules were assessed by vital signs, physical examinations, clinical laboratory tests, and adverse events.

Methodology: Open-label, nonrandomized, single center, cohort comparative study (30 days) of two formulations using each patient as his/her own control. Cross-over treatment from the currently used CU cholic acid to the manufactured TBM cholic acid:

- Total of 16 patients were 3 β -HSD: 11, AKR1D1: 2, and CTX: 3.
- TBM capsules, each containing 50 or 250 mg of cholic acid. Dosage: 10-15 mg/kg body weight/day.

Main Inclusion Criteria:

- Patient must have stable transaminase levels within 2 times the upper limits of the normal range.
- Patient must have a diagnosis of an inborn error of bile acid synthesis.
- Patient must be currently receiving CU cholic acid therapy under IND 45,470.

Appendix Table 1: Schedule of Study CAC-001-01

Assessment or Procedure	Visit Day	Visit 1 Day 1	Phone Day 14-17 ^a	Visit 2 Day 30+/- 3
Confirm eligibility (patient meets study criteria)		x		
Obtain written informed consent from patient and/or parent/legal guardian		x		
Collect demographic data and disease and medication history, including family history		x		
Obtain body weight		x		x
Record concomitant medications		x	x	x
Record adverse events		x	x	x
Obtain blood and urine samples for laboratory tests		x		x
Review study procedures with patient and/or legal guardian/Confirm compliance		x	x	
Place patient on continuation protocol ^b				x

From the Study Report of CAC-001-01, NDA 205,750

Efficacy Results:

The results show that there were no clinically meaningful changes in LFTs between the two dosing formulations. One subject (ID 133) had higher values of AST and ALT with both dosing formulation. Thus, the sponsor states that the apparent therapeutic equivalence was 93% (15/16) (Appendix Table 2).

Appendix Table 2: Summary of Liver Function Tests

<i>Listing 2: LFT TESTS, BY VISIT</i>										
Subject ID	Visit	ALT	AST	ALP	GGT	Creatinine	Total Bilirubin	Total Protein	Direct Bilirubin	Albumin
27	1	32	64	259	20	0.5	0.3	7.8	0	5.1
	2	26	46	272	17	0.5	0.2	7.8	0	5.0
57	1	28	46	270	29	0.6	0.1	7.1	0	4.4
	2	27	42	264	30	0.6	0.1	6.4	0	4.2
65	1	17	57	213	22	0.5	0.1	8.3	0	5.1
	2	15	54	206	22	0.4	0.1	7.4	0	4.8
68	1	98	101	81	25	1.0	0.4	6.9	0	4.5
	2	54	53	92	31	1.0	0.6	7.3	0	4.6
79	1	22	37	139	19	0.8	0.5	6.8	0	4.4
	2	27	50	131	24	0.7	0.4	6.6	0	4.3
86	1	23	37	353	28	0.5	0.1	7.3	0	4.3
	2	32	38	382	32	0.5	0.4	7.0	0	4.0
93	1	6	49	201	17	0.4	0.1	7.2	0	4.5
	2	23	50	208	17	0.4	0.1	7.6	0	4.5
95	1	20	36	169	19	0.4	0.3	8.2	0	4.5
	2	6	43	193	20	0.3	0.3	6.9	0	4.2
106	1	26	52	383	30	0.3	1.0	8.3	0	5.1
	2	11	54	278	23	0.3	0.9	8.3	0	5.0
133	1	47	111	602	45	0.4	0.1	6.2	0	4.0
	2	100	195	457	70	0.4	0.2	6.7	0	4.0
138	1	24	70	246	20	0.3	0.4	7.9	0	4.9
	2	12	96	270	29	0.3	0.2	7.8	0	4.6
145	1	51	59	235	22	0.3	0.1	7.7	0	4.4
	2	49	50	239	18	0.3	0.1	7.4	0	4.3
149	1	20	39	261	.	0.4	0.1	7.8	0	4.7
	2	14	54	285	23	0.4	0.2	7.9	0	4.6
159	1	18	73	239	54	0.3	1.4	8.1	0	4.7
	2	34	48	184	41	0.3	0.9	8.6	0	4.8
176	1	19	49	465	30	0.4	0.3	7.8	0	4.8
	2	10	65	424	29	0.4	0.1	7.3	0	4.6
177	1	52	123	182	24	0.2	0.3	7.8	0	4.3
	2	54	102	167	.	.	.	6.9	0	4.7

From the Study Report of CAC-001-01; GGT: Gamma-glutamyl transpeptidase

Safety Evaluation:

There were no death, no SAEs, and no discontinuation of treatment in the study. Physical examinations, vital signs, and clinical laboratory tests were unremarkable at baseline and follow-up. Two non-serious AEs, reflux and diarrhea, possibly related to the study drug were reported.

Medical Officer Comment:

The sponsor's statement of therapeutic equivalence between the to-be-marketed and the currently used formulations is acceptable.

9.5 Summary of Study CAC-003-01

Title of Study: Comparative Bioavailability of Three Formulations of Cholic Acid in Healthy Male Subjects Using a Multiple Dose Repeated Measures Approach

Study Center: Frontage Clinical Services, Hackensack, NJ 07601

Objectives: To evaluate the relative bioavailability/bioequivalence and pharmacokinetics of multiple oral doses of a new cGMP (current Good Manufacturing Practice) produced cholic acid capsule formulation in comparison to a previously used pharmacy capsule formulation and an oral solution or suspension (250 mg) in 18 healthy male volunteers. Given the potential for endogenous cholic acid being present, a repeated measures approach without washout was employed. In addition, the safety of cholic acid, following multiple dose administration of cholic acid was also assessed.

Methodology: This was a phase 1, randomized, three-way crossover study with dosing under fasting conditions. Eighteen healthy adult male volunteers were screened and randomized to receive 3 multiple oral dose regimens (250 mg) of cholic acid without a washout period between each successive dose.

Treatment A (pharmacy cholic acid capsules) were supplied as:

- Cholic acid 250.00 mg
- (b) (4)
- White, opaque, gelatin (b) (4) capsule.

Treatment B (cGMP Cholic Acid capsules) were supplied as:

- Cholic acid 250.00 mg
- Silicified Microcrystalline Cellulose/USP (b) (4)
- Magnesium Stearate/USP (b) (4)
- Hard Gelatin Capsules/USP Size #0.

Treatment C (cholic acid oral solution) was supplied as:

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- Cholic acid 250.00 mg in 25 mL (10 mg/mL)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

Subjects who were eligible were enrolled and randomized to 1 of 6 dosing schedule regimens (ABC, ACB, BAC, BCA, CBA, or CAB) where regimen A consisted of a cholic acid Pharmacy prepared 250 mg capsule formulation, regimen B consisted of a cGMP prepared cholic acid 250 capsule formulation, and regimen C consisted of a cGMP prepared cholic acid 250 mg/25 mL solution. During each of the 3 dosing periods, 6 subjects were assigned to each dosing regimen. Each had a dosing regimen of twice daily under fasting conditions for 4 consecutive days. During the first treatment cycle, samples of venous blood were obtained on Days 1, 3 and 4. During the second cycle, samples were obtained on Days 7 and 8. During the third cycle, samples were obtained on Days 9, 11 and 12.

Safety evaluations included assessment of adverse events, vital signs, 12-lead electrocardiogram, and clinical laboratory results (hematology, serum chemistry, and urinalysis).

Main Inclusion Criteria:

Subjects included were healthy male subjects between the ages of 18 and 45 years of age who met stringent weight criteria (≥ 132 lbs and ≤ 220 lbs), were non-smokers, did not have any known hypersensitivities or allergies to cholic acid, and no clinically significant laboratory abnormality, and were negative for hepatitis B surface antigen, anti-hepatitis C antibody, or human immunodeficiency virus.

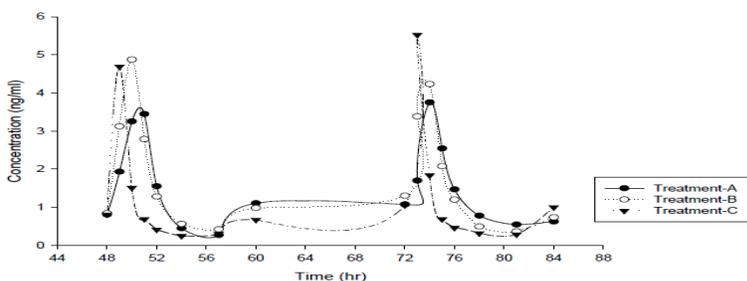
Summary of Findings:

Pharmacokinetic Findings:

The following concentration vs. time analysis shows the 3 formulations appears to be similar (Appendix Figure 1). The sponsor states that comparison of Treatment B (cGMP capsule formulation) to Treatment A (Pharmacy formulation) shows slight differences in bioavailability. Comparison of the two oral 250 mg capsule formulations with the oral 250 solution (Treatment C) shows numerically greater bioavailability for the capsules relative to the solution.

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Appendix Figure 1: Geometric Mean Concentrations of Cholic Acid in Healthy Subjects Following Oral Administration of 250 mg of 3 Different Dosage Forms



From the Study Report of CAC-003-01

Appendix Table 3: Pharmacokinetic Parameters of Cholic Acid Following Multiple Oral Doses

	Treatment A (N = 17)		Treatment B (N = 18)		Treatment C (N = 17)	
	Mean	SD	Mean	SD	Mean	SD
Day 3						
PK Parameter						
T _{max} (hr)	2.3	0.77	1.7	0.669	1.0	0.0
C _{max} (ng/mL)	6.02	3.75	7.13	3.21	5.01	2.01
AUC _{tau} (ng•hr/mL)	21.54	14.13	23.66	10.81	12.87	5.36
C _{min} (ng/mL)	1.76	1.41	2.11	2.40	1.15	0.95
K _{el} (hr ⁻¹)	0.410	0.196	0.321	0.172	0.298	0.132
Elim. t _{1/2} (hr)	2.13	1.08	2.96	1.77	3.22	2.73
Cl/F (L/hr)	15.01	6.486	12.86	5.806	22.77	9.142
Vd _{ss} /F (L)	48.766	30.276	56.87	45.164	106.26	83.211
Day 4						
PK Parameter						
T _{max} (hr)	3.1	2.50	1.6	0.85	1.6	2.67
C _{max} (ng/mL)	5.26	2.64	6.26	2.40	6.37	2.60
AUC _{tau} (ng•hr/mL)	21.57	12.35	20.52	6.21	15.78	7.34
C _{min} (nMol/mL)	1.56	1.57	1.88	1.54	1.78	1.44
K _{el} (hr ⁻¹)	0.30	0.108	0.333	0.114	0.308	0.119
Elim. t _{1/2} (hr)	3.11	2.91	2.39	1.01	2.78	1.675
Cl/F (L/hr)	14.56	6.145	13.57	5.31	19.90	10.38
Vd _{ss} /F (L)	54.87	19.23	48.10	35.385	120.32	116.80

Data source: Appendix 16.2.6.1A, Appendix 16.2.6.1B and Appendix 16.2.6.5

From the Study Report of CAC-003-01

Safety Findings:

Eighteen male subjects received cholic acid in 3 different formulations twice daily for 4 days under fasting conditions. There was no deaths occurred during the study. No subject experienced a SAE. None of the subjects withdrew from the study due to AEs. A summary of the AEs is located at Section 7.4.1.3.

Medical Officer Comments:

In the healthy adults, the PK parameters of the 3 formulations appear to be similar. In SED or PD patients, endogenous cholic acid levels are expected to be lower than the

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healthy subjects, and the PK parameters may be different. Furthermore, PD patients with deficiencies in transportation and conjugation of bile acids may have different PK parameters.

9.6 Summary of 120-Day Safety Update Report

The 120-day safety update report covered the period of 3 years 11 months (from January 1, 2010 to November 30, 2013) based on the continuation of study CAC-002-01.

A total of 46 patients were enrolled (up to November 30, 2013): 31 of them transitioned from CAC-91-10-10 to CAC-002-01 (SED 21, PD 10); and 15 of them were treatment naïve (SED 13, PD 2).

The subtypes PIDs of the treatment naïve patients enrolled on CAC-002-01 were as follows:

- 3 β -HSD: 176, 700, 705, 706, 707, 709^Δ, 711^Δ, 713^Δ;
- AKR1D1: 701, 704;
- CTX: 708, 712^Δ;
- Zellweger's: 702, 703;
- No defect confirmed: 710^Δ

Note: PID^Δ denotes patients included only in the 120-day safety update report, not in the interim study report of CAC-002-01.

Sponsor reported 120-day safety update:

- There were 5 deaths (2 SED; 3 PD). The investigator stated “None of them were related to the study drug.”

Appendix Table 4: Deaths in Study CAC-002-01 (120-day safety report)

PID	Defect Type	Treatment	Cause of Death
057	3 β -HSD	Experienced	Suicide secondary to depression
128	PD-Refsum's	Experienced	Liver failure
132	PD-Zellweger's	Experienced	Sepsis
702	PD-Zellweger's	Naïve	Worsening of disease
704	AKR1D1	Naïve	Thrombosis subcortical brain

From the 120-day safety report, SN011.

Medical Officer Comments:

- I agree with the investigator in that the deaths of SED patients (IDs 057 and 704) may not be related to the cholic acid treatment.
- I also agree the death of PD patient (ID 132) not related. The patient had a dramatic deterioration following a pamidronate infusion prior to death.
- I cannot rule out the possibility of the contributions of cholic acid treatment to the two deaths of PD patients (PIDs 128 and 702):

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- Patient 128 was a 9 years old female diagnosed with PD. Her ALT and AST tests were normal during Study CAC-91-10-10. She developed severe cholestasis (b) (6) day after the entry of CAC-002-01, and died. At the time of death, she received 225 mg of cholic acid per day.
- Patient 702 was a 6 months female diagnosed with PD. She was lost to follow-up. No post baseline study data are available for the safety evaluation.
- Death of PID 130 (PD) was not included in the 120-day safety update, but in the interim study report (CAC-002-01) (see MO comments at the interim safety section).

- There were 31 SAEs occurred in 31 patients (Table 5). Disease progression was the most frequently reported SAE, followed by coagulopathy, encephalopathy and influenza/pneumonia. All SAEs occurred in single patients only. None of the SAEs were considered related to study medication by the Investigator.

Appendix Table 5: Treatment-Emergent SAEs (Study CAC-002-01, N=46)

MedDRA ^a System Organ Class	Preferred Term	N	Percent
Blood and lymphatic system disorders		3	7
	Coagulopathy	3	7
Cardiac Disorders		1	2
	Cardiac Arrest	1	2
Gastrointestinal disorders		1	2
	Abdominal Distention	1	2
General disorders and administration site conditions		5	11
	Disease progression	4	9
	Pyrexia	1	2
Hepatobiliary disorders		3	7
	Hepatic artery thrombosis	1	2
	Hepatic failure	1	2
	Hyperbilirubinaemia	1	2
Infections and infestations		6	13
	Bacteraemia	1	2
	Influenza	2	4
	Pneumonia	2	4
	Sepsis	1	2
	Upper respiratory tract infection	1	2
Injury, poisoning, and procedural complications		1	2
	Fracture	1	2
Metabolism and nutrition disorders		3	7
	Hypoalbuminaemia	1	2
	Hypocalcaemia	1	2
	Hypokalaemia	1	2
Nervous system disorders		2	4
	Encephalopathy	2	4
Psychiatric disorders		1	2
	Completed suicide	1	2
Respiratory, thoracic and mediastinal disorders		2	4
	Hypoxia	1	2
	Respiratory distress	1	2
	Respiratory failure	1	2
Uncoded^b		1	2
	Uncoded	1	2
Vascular Disorders		1	2
	Thrombosis	1	2

^a MedDRA version 11.0. Subjects with multiple events for a given outcome were counted once only for each outcome.

^bUncoded SAE was hospitalization for adenoidectomy secondary to tonsillar hypertrophy in patient #703
N = number of patients.

- There were 3 patients who discontinued the study due to an adverse event (Table 6).

Appendix Table 6: Discontinuations Due to Adverse Events in Study CAC-002-01 (Interim Report)

PID	Defect Type	Treatment	Preferred Term
175	SED	Experienced	Peripheral neuropathy

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701	SED	Naïve	Disease progression
704	SED	Naive	Disease progression

From the 120-day safety report, SN011.

- Common adverse events: there were 4 patients who experienced diarrhea. None of them was considered to be serious by the investigator.
- Clinical laboratory findings (CAC-002-01) were not submitted to the 120-day safety report.
- Sponsor conclusions: Cholic acid has a beneficial effect in patients with inborn errors of primary bile acid synthesis. No serious treatment related adverse reactions to cholic acid have been reported in the clinical program.

Medical Officer Comments:

The safety outcomes of the 120-day safety report are consistent with the Study CAC-91-10-10. No new safety issue was identified.

9.7 Summary of Interim Study Report of CAC-002-01

The interim study report covered the period of 2 years 9 months (from January 1, 2010 to September 30, 2012).

Study title: An Open-Label, Single-Center, Non-Randomized Continuation Study of Cholic Acid Capsules in Subjects with Inborn Errors of Bile Acid Synthesis

Primary Objective:

The primary objective of this study was to evaluate the therapeutic efficacy of cholic acid in subjects with identified inborn errors of bile acid metabolism on (1) serum transaminases and (2) suppression of bile acid synthesis of atypical bile acids, as measured by urine and/or serum bile acid analysis using mass spectrometry.

Secondary Objective:

The secondary objective of the study was to assess the safety and tolerability of CA capsules. The incidence and severity of adverse events (AEs) compared with baseline and clinical laboratory test and physical examination results were to be assessed when available.

Cholic Acid Treatments:

The oral doses administered were 10 to 15 mg/kg body weight/day. It included the CCHMC formulation and the to-be-marketed formulation of CA capsules. In addition, some subjects had used a liquid formulation of 15 mg/mL.

Appendix Table 4: Assessment Schedule of CAC-002-01

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Assessment or Procedure	Baseline (new subjects)	Treatment start (new subjects)	On-treatment 6 to 12 months (all subjects)
Check eligibility	x		
Written informed consent	x		
Demographic data	x		
Disease and medication history (optional)			
Physical examination (optional)	x		x
Initiate study drug therapy		x	
Blood and/or urine samples for FAB-MS	x ^{a,b}		x ^e
Blood samples for LFT ^c analysis	x		x
Height and weight ^d	x		x
Adverse events ^d	x		x
Monitor study drug therapy and adjust dose as needed			x

^a May have been obtained through diagnostic screening.

^b Serum was only analyzed by gas-liquid chromatography-mass spectrometry if urine analysis was inconclusive.

^c Included ALT and AST, and if available total/direct bilirubin, alkaline phosphatase, GGT, prothrombin time with INR.

^d Collected via telephone.

^e Every 6 to 12 months or when clinically indicated.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, GC-MS = gas chromatography mass-spectrometry, GGT = gamma glutamyltransferase, INR = international normalized ratio, LC-MS = liquid chromatography-mass spectrometry, LFT = liver function tests, LSMIS = liquid secondary ion mass spectrometry.

Inclusion Criteria:

The study included subjects who had completed Studies 91-10-10 or CAC-001-01, and subjects newly diagnosed with an inborn error of bile acid synthesis.

Requirements for inclusion were:

- Informed consent prior to study start for treatment naive subjects. Subjects who had participated in protocols conducted under IND 45,470 were re-consented to this continuation protocol.
- The subject was required to have a diagnosis of an inborn error of bile acid synthesis.
- The subject was required to be willing and able to comply with all study assessments and procedures.
- Subjects with other organ dysfunction were not excluded.

Exclusion Criteria:

No exclusion criteria were used for the study.

Efficacy Evaluation:

A total of 41 patients were enrolled in the study and underwent at least one round of study evaluations (ITT population). Among them, 29 patients were diagnosed with SED and 12 patients with PD. The majority of the patients were continued from Study CAC-91-10-10 (31 patients: SED 21 and PD 10). In addition, there were 10 patients (SED 8 and PD 2) who were treatment naïve.

- Effects of Cholic Acid on Continuation of SED Patients

There were 21 SED patients previously treated under protocol CAC-91-10-10. Seventeen of them were responders to cholic acid treatment. Sixteen of them continued to be responsive to the treatment during CAC-002-01; while 1 patient (PID 175) cannot be assessed due to lack of data (Table 5). One responder (PID 057) died from suicide secondary to depression.

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Four SED patients who were not responders in CAC-91-10-10 due to lack of data became responders during CAC-002-01 (PIDs 106, 159, 177, and 133; Table 5) based on the additional data.

The values of alkaline phosphatase were high in 14 patients. The rest was in the normal ranges (ALK, GGT, PT, total protein, and albumin were examined; Table 5).

Appendix Table 5: Responder Analysis of SED Patients Continued in CAC-002-01 (Interim Report)

SED/PID#	Continuation of CA Treatment at CAC-002-01					
	Responder [#]	Alkaline Phosphatase	GGT	Prothrombin Time	Total Protein	Albumin
SED: 21	20/21=95%					
3β-HSD: 16	15/16=93%					
#033 ^v	+(E, B) [#]	Normal	Normal	N/A	Normal	Normal
#034 ^v	+(E, B) [#]	Normal	Normal	N/A	Normal	Normal
#057 ^{v*}	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#079 ^v	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#090 ^v	+(E, B, W) [#]	Normal	Normal	Normal	Normal	Normal
#093 ^v	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#095 ^v	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#100 ^v	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#106	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#138 ^v	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#145 ^v	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#149 ^v	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#157 ^v	+(E, B, W) [#]	N/A	Normal	N/A	N/A	N/A
#159	+(E, W) [#]	High	Normal	Normal	Normal	Normal
#175 ^v	+W; (EBN)	N/A	N/A	N/A	N/A	N/A
#177	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
AKR1D1: 2	2/2=100%					
#068 ^v	+(E, B, W) [#]	Normal	Normal	Normal	Normal	Normal
#133	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
CTX: 3	3/3=100%					
#027 ^v	+(E, B, W) [#]	Normal	Normal	Normal	Normal	Normal
#065 ^v	+(E, B) [#]	High	Normal	Normal	Normal	Normal
#086 ^v	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
	Responder	Alkaline Phosphatase	GGT	Prothrombin Time	Total Protein	Albumin

From the interim study report of CAC-002-01 (SN045). The purpose of the analysis is to identify (1) the number of patients who were responders in CAC-91-10-10 had sustained improvements during CAC-002-01; and (2) the number of patients who were not responders in CAC-91-10-10 became responders in CAC-002-01. Four criteria are chosen for the determination of Cholic acid responder, because the treatment targets at intrahepatic cholestasis, and should improve survival and growing. The 4 criteria are: 1) ALT/AST values reduced to <50 U/L, or baseline levels reduced by 80%; 2) total bilirubin values

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reduced to ≤ 1 mg/dL; 3) body weight increase by 10%, or stable at >50 weight percentile; and 4) patient alive at the cut-off date of the interim study. The responder must meet at least two criteria of the biomarkers plus the clinical survival; or at least one criterion of the biomarker plus two clinical criteria: i.e., weight percentile increase and survival.

Note: PID^v: Responder to cholic acid treatment at CAC-91-10-10; +()[#]: Responder at CAC-002-01; N: Normal value; E: ALT/AST; B: Total bilirubin; EBN: Both ALT/AST and bilirubin being normal; W: body weight increase by 10%, or stable at >50 weight percentile; (EBN): patient had normal ALT/AST and bilirubin at CAC-91-10-10; N/A: data not available; GGT: Gamma-glutamyl transferase. Normal reference ranges: alkaline phosphatase <100 IU/L; GGT <100 IU/L; prothrombin time <15 seconds; serum total protein >6.0 g/dL; and albumin >3.5 g/dL.

• Effects of Cholic Acid on Continuation of PD Patients

There were 10 PD patients who were previously treated (CAC-91-10-10). One of the patients (PID 021) responded to cholic acid treatment according to the responder criteria (Table 6). Three patients died during the study CAC-002-01 (PIDs 128, 130, 132). Three patients (PIDs 020, 030, 046) had normal transaminases and total bilirubin at baseline of CAC-91-10-10, and had no data to support the response in CAC-002-01. Two patients (PIDs 012, 092) had abnormal transaminases and normal bilirubin at baseline of CAC-91-10-10, and had no improvement of transaminases in CAC-002-01. One patient (PID 173) had only body weight data.

The values of alkaline phosphatase were high in 8 PD patients. The values of prothrombin time were abnormal in 2 patients. The value of GGT was abnormal in 1 patient (Table 6).

Appendix Table 6: Responder Analysis of PD Patients Continued in CAC-002-01 (Interim Report)

PD/PID#	Continuation of CA Treatment at CAC-002-01					
	Responder [#]	Alkaline Phosphatase	GGT	Prothrombin Time	Total Protein	Albumin
PD: 10	1/10=10%					
Zellweger's: 3						
#046	N/A	High	Normal	N/A	Normal	Normal
#132*	+ALT	High	Normal	Normal	Normal	Normal
#173	+W	N/A	N/A	N/A	N/A	N/A
NALD: 2						
#012	(B)	High	High	Normal	Normal	Normal
#030	Wt 0	N/A	N/A	N/A	N/A	N/A
Unknown: 1						
#130*	Abnormal EB	High	N/A	Abnormal	Normal	Normal
Refsum's: 3						
#020	+E (B)	High	Normal	Normal	Normal	Normal
#021	+(E, W) [#] (B)	High	Normal	N/A	Normal	Normal
#128*	+ALT-B	High	Normal	Abnormal	Normal	Abnormal

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Generalized: 1						
#092	+W (B) Responder	High Alkaline Phosphatase	Normal GGT	N/A Prothrombin Time	Normal Total Protein	Normal Albumin

From the interim study report of CAC-002-01 (SN045). The purpose of the analysis is to identify (1) the number of patients who were responders in CAC-91-10-10 had sustained improvements during CAC-002-01; and (2) the number of patients who were not responders in CAC-91-10-10 became responders in CAC-002-01. Four criteria are chosen for the determination of Cholic acid responder, because the treatment targets at intrahepatic cholestasis, and should improve survival and growing. The 4 criteria are: 1) ALT/AST values reduced to <50 U/L, or baseline levels reduced by 80%; 2) total bilirubin values reduced to ≤1 mg/dL; 3) body weight increase by 10%, or stable at >50 weight percentile; and 4) patient alive at the cut-off date of the interim study. The responder must meet at least two criteria of the biomarkers plus the clinical survival; or at least one criterion of the biomarker plus two clinical criteria: i.e., weight percentile increase and survival.

Note: +(#): Responder at CAC-002-01; PID*: patient dead during the study; N: Normal value; E: ALT/AST; B: Total bilirubin; EBN: Both ALT/AST and bilirubin being normal; W: body weight increase by 10%, or stable at >50 weight percentile; (EBN): patient had normal ALT/AST and bilirubin at CAC-91-10-10; (B): patient had normal bilirubin at baseline of CAC-91-10-10; -B: total bilirubin worsened at CAC-002-01; PID*: patient dead; Abnormal EB: patient dead with abnormal ALT/AST and total bilirubin; Wt 0: weight percentile being 0; N/A: data not available; GGT: Gamma-glutamyl transferase. Normal reference range: alkaline phosphatase <100 IU/L; GGT <100 IU/L; prothrombin time <15 seconds; serum total protein >6.0 g/dL; and albumin >3.5 g/dL.

- Effects of Cholic Acid in Treatment Naive Patients

Five of the 8 treatment naïve SED patients responded to cholic acid treatment, while 1 of the 2 treatment naïve PD patients responded to the treatment according to the responder criteria (Table 7).

Appendix Table 7: Summary of Responder Analysis of Treatment Naive Patients in CAC-002-01 Interim Report

SED/PID#	Continuation of CA Treatment at CAC-002-01					
	Responder [#]	Alkaline Phosphatase	GGT	Prothrombin Time	Total Protein	Albumin
SED: 8						
3β-HSD: 5						
#176	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#700	+(E, B, W) [#]	High	Normal	Normal	Normal	Normal
#705	+(E, B) [#]	High	Normal	Abnormal	Normal	Normal
#706	+(E, B, W) [#]	High	Normal	Normal	N/A	Normal
#707	+(E, B) [#]	High	Normal	N/A	Normal	Normal
AKR1D1: 2						
#701	N/A	High	N/A	N/A	N/A	N/A
#704*	N/A	N/A	Normal	N/A	N/A	Abnormal
CTX: 1						
#708	+W (EB N/A)	N/A	N/A	N/A	N/A	N/A
PD: 2						

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ZS: 2						
#702*	Wt 0.1	N/A	N/A	N/A	N/A	N/A
#703	+(ALT, B, W) [#]	High	High	Normal	Normal	Normal

From the interim study report of CAC-002-01 (SN045). The purpose of the analysis is to identify the responses of treatment naïve patients to cholic acid therapy. Four criteria are chosen for the determination of Cholic acid responder, because the treatment targets at intrahepatic cholestasis, and should improve survival and growing. The 4 criteria are: 1) ALT/AST values reduced to <50 U/L, or baseline levels reduced by 80%; 2) total bilirubin values reduced to ≤1 mg/dL; 3) body weight increase by 10%, or stable at >50 weight percentile; and 4) patient alive at the cut-off date of the interim study. The responder must meet at least two criteria of the biomarkers plus the clinical survival; or at least one criterion of the biomarker plus two clinical criteria: i.e., weight percentile increase and survival.
 Note: +()[#]: Responder to cholic acid treatment at CAC-002-01; PID*: patient dead during the study; E: ALT/AST; B: Total bilirubin; W: body weight increase by 10%, or stable at >50 weight percentile; N/A: data not available; Wt 0.1: only had one measurement of weight percentile = 0.1; +W (EB N/A): patient did not have ALT/AST and total bilirubin data, but had data of weight percentile improvement; GGT: Gamma-glutamyl transferase. Normal reference ranges: alkaline phosphatase <100 IU/L; GGT <100 IU/L; prothrombin time <15 seconds; serum total protein >6.0 g/dL; and albumin >3.5 g/dL.

Medical Officer Comment:

The overall efficacy report of CAC-002-01 is consistent to the CAC-91-10-10.

Safety Evaluation:

Safety variables include:

- AEs and SAEs
- Clinical laboratory evaluations
- Physical examination findings

There were 3 patients who died during the reported period: 1/1/2010-9/30/2012.

Appendix Table 8: Deaths (Safety Population, N=41)

PID	Disorder Type	Treatment Start	Treatment Stop	Date of Death	Cause of Death	Relationship
130	PD	01Jan2010*	24Oct2010	24Oct2010	Disease progression (multisystem failure secondary to primary disease)	unrelated
702	PD	22Oct2010	Unknown	Unknown	Disease progression (worsening of disease under study)	unrelated
704	SED	03Feb2012	19Feb2012	28Feb2012	Thrombosis (cortical and subcortical brain injury secondary to thrombosis)	unrelated

*Patient transitioned from study CAC-91-10-10 and was thus on CA at study start. Event occurred while on CCHMC formulation.

SED = single enzyme defect, PID = patient identity, PD = peroxisomal disorder.

Source: Table 14.3.2.1

Medical Officer Comments:

- Investigator stated “the death of PID 704 (SED) not related to cholic acid treatment”. The clinical reviewer agreed.
- Investigator stated “the deaths of PIDs 130 and 702 (PD) not related”. The reviewer cannot rule out the possibility of “related” for the following reasons:

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Cholbam (50 mg and 250 mg capsules)

- Patient 130 was a 4 years old male diagnosed with peroxisomal biogenesis disorder (type unknown). His body weight was 50 percentile, ALT 33, AST 63, total bilirubin 0.2 prior to the cholic acid treatment. He received unknown doses of cholic acid at CAC-91-10-10 and CAC-002-02. In 4 years on cholic acid treatment, his body weight decreased from 50 percentile to 1.7 percentile; his transaminases, total bilirubin, and prothrombin time became abnormal (ALT 81, AST 318, total bilirubin 1.9, and PT 20.5 prior to death). He died (b) (6) after entry of CAC-002-01. The sponsor did not provide convincing evidence to rule out the possibility of cholic acid toxicity.
- Patient 702 did not have post baseline study data for the evaluation, and was lost to follow-up.

There were 13 SAEs occurred in 13 patients. Disease progression was the most frequently reported SAE (Table 9).

Appendix Table 9: Treatment-emergent SAEs (Safety Population, N=41)

MedDRA ^a System Organ Class Preferred Term	n	N	%
Blood and lymphatic system disorders	1	1	2
Coagulopathy	1	1	2
General disorders and administration site conditions	4	4	10
Disease progression	4	4	10
Hepatobiliary disorders	2	2	5
Hepatic artery thrombosis	1	1	2
Hyperbilirubinaemia	1	1	2
Infections and infestations	3	3	7
Bacteraemia	1	1	2
Pneumonia	1	1	2
Upper respiratory tract infection	1	1	2
Nervous system disorders	1	1	2
Encephalopathy	1	1	2
Respiratory, thoracic and mediastinal disorders	1	1	2
Respiratory distress	1	1	2
Vascular disorders	1	1	2
Thrombosis	1	1	2

^a MedDRA version 11.1.

AE = adverse event, MedDRA = medical dictionary for drug regulatory affairs, n = number of events, N = number of subjects.

Source: [Table 14.3.1.9](#)

There were 4 patients who had an AE leading to study discontinuation. These were disease progression in 3 patients and peripheral neuropathy in 1 patient.

Appendix Table 10: Treatment-emergent AEs leading to study discontinuation (Safety Population, N=41)

PID	Disorder Type	Treatment Start	AE leading to discontinuation (PT, verbatim term)	AE Start date	AE Stop date	Intensity	Relationship
130*	PD	01Jan2010	Disease progression, multisystem failure secondary to primary disease	Unknown*	24Oct2010	severe	unrelated
175	SED	01Jan2010	Neurophathy peripheral, head and hands tingling	Mar2010*	Apr2010	mild	possibly
701	SED	16Aug2010	Disease progression, secondary to liver transplantation	Sep2010*	13Sep2010	severe	unrelated
704	SED	03Feb2012	Disease progression, worsening of disease under study resulting in liver transplant	2012	20Feb2012	severe	unrelated

* Event occurred while on CCHMC formulation.

* Although this patient died due to this AE, the investigator reported no action with respect to study medication. This patient is thus not included in the analysis for Table 14.3.1.10, which lists only patients for whom the Investigator reported that study medication was prematurely discontinued.

SED = single enzyme defect, PID = patient identity, PT = preferred term.

Source: Listings 16.2.3.2, 16.2.7

- Common adverse events: there were 4 patients who experienced diarrhea.
- Clinical laboratory findings included liver function tests, bilirubin, alkaline phosphatase, gamma-glutamyl transferase, prothrombin time, serum total protein, and albumin (see efficacy evaluation).

Medical Officer Comments:

The report of effectiveness and safety of cholic acid treatment of CAC-002-01 were consistent with the report of CAC-91-10-10. No new safety issue was identified.

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/s/

WEN-YI GAO
03/11/2015

LARA DIMICK-SANTOS
03/11/2015

MEMORANDUM

DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS

DATE: January 28, 2014

TO: DIVISION FILES: **NDA 205-750/000**
Cholbam (Cholic acid)
[Sponsor: Asklepiion Pharmaceuticals, LLC.]

FROM: Wen-Yi Gao, MD, PhD
Medical Officer
DGIEP/ODE3 (HFD-180)

SUBJECT: **Addendum of the potential review issues to be forwarded to the Applicant in the 74-day letter**

I. RECOMMEDATIONS

The reviewer has additional concerns from the initial review of the NDA application:

1. The sponsor has included two different populations in this application, single enzyme defects and peroxisome disorders. Because these diseases have different phenotypes and outcomes, they may require separate applications.
2. The primary efficacy endpoint is a biomarker, not a clinically meaningful endpoint. This would be considered a surrogate. This may not be acceptable for regular approval. This was discussed with the sponsor in the meetings (dated January 25, 2010 and July 25, 2012) prior to the application.
3. The primary endpoints are not pre-specified. Non-pre-specified primary endpoints may not serve as supporting evidence for efficacy evaluation.
 - a. The (b) (4) methodology was not discussed with the FDA prior to the application. This methodology may not be acceptable for responder criteria.
4. The historical control data were collected from the literature. These data provided valuable information for FDA review. However, they may not be

adequate to serve as qualified controls because the baseline characteristics of the historical control and the treatment groups may not match.

5. The narratives of patients who died during Study CAC-91-10-10 do not have adequate detailed clinical information for the FDA review.

In summary, the reviewer agreed to file this NDA application for further evaluation, and may request further information for the on-going review.

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/s/

WEN-YI GAO
01/28/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 205-750/000
Applicant: Asklepiion Pharmaceuticals, LLC.
Stamp Date: November 21, 2013
Drug Name: Cholic Acid
NDA/BLA Type: 505 (b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			The Application is a 505(b)(2). The reference drug is endogenous cholic acid.
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? There were no dose-ranging studies. The dosing regimen was similar to other bile acid products, i.e., chenodeoxycholic acid (CDA, 15 mg/kg/body weight) and ursodeoxycholic acid (URSO, 10 to 15 mg/kg/body weight).		X		
EFFICACY					
14.	Do there appear to be the requisite number of adequate and			X	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>well-controlled studies in the application? This application is for treatment of rare disease. The Division recommended at least one trial using natural history control with supportive evidence. The Applicant submitted a natural history control summary. The pivotal study is an open-label, uncontrolled study (with two protocols for two different rare diseases):</p> <ul style="list-style-type: none"> ■ <u>Pivotal Study Protocol #1</u>: CAC-91-10-10 ■ <u>Indication</u>: Treatment of inborn errors of bile acid metabolism ■ <u>Pivotal Study Protocol #2</u>: CAC-92-8-19 ■ <u>Indication</u>: Treatment of inborn errors of peroxisomal disorders affecting bile acid metabolism 				
15.	<p>Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?</p> <p>Yes. DGIEP requested at Type C meeting on July 25, 2012 that “To gain approval for cholic acid you will need to demonstrate in at least one adequate and well controlled trial with supportive evidence that cholic acid is safe and effective for a specific target population.” The Applicant submitted one pivotal efficacy study within current divisional policies.</p>	X			
16.	<p>Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</p>	X			
17.	<p>Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?</p> <p>No. There was no statement regarding a rationale for assuming the applicability of foreign data to U.S. population / practice of medicine in the submission.</p>		X		
SAFETY					
18.	<p>Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?</p>	X			
19.	<p>Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?</p> <p>No. Information to assess the arrhythmogenic potential of CA was not submitted.</p>		X		
20.	<p>Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?</p>	X			
21.	<p>For chronically administered drugs, have an adequate</p>		X		

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>number of patients (based on ICH guidelines for exposure¹) been exposed at the dose (or dose range) believed to be efficacious?</p> <p>No. The inborn error of bile acid metabolism is a rare disease. Efficacy of CA has not been demonstrated in a controlled trial. Although the compassionate use trial continued for 17 years, only 85 patients were studied.</p>				
22.	<p>For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?</p> <p>N/A</p>			X	
23.	<p>Has the applicant submitted the coding dictionary² used for mapping investigator verbatim terms to preferred terms?</p> <p>No. The applicant has not submitted the coding dictionary.</p>		X		
24.	<p>Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?</p> <p>No. The new drug belongs to the drug class bile acid. Recent labeling change of one bile acid, UDCA (NDA 20675-S22), warns that UDCA is contraindicated in patients with complete biliary obstruction.</p> <p>There were 22 deaths (22/85) during the trial of the new drug (CAC-91-10-10). The effect of cholic acid in patients with biliary obstruction has not been adequately evaluated.</p>		X		
25.	<p>Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?</p> <p>Yes, narrative summaries of deaths are submitted, but, narratives of serious adverse events and adverse dropouts are not submitted.</p> <p>After the study closed, CRF was created and documents were transferred from the Principal Investigators to Asklepiion in November 2010.</p>	X			
OTHER STUDIES					
26.	<p>Has the applicant submitted all special studies/data requested by the Division during pre-submission</p>			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? As cholic acid has been granted orphan designation for the treatment of inborn errors of bile acid synthesis, Pediatric Research Equity Act (PREA) does not apply.			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? No. The Applicant did not submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? Case Report Forms of deaths is submitted. Case Report Forms of serious adverse events and adverse dropouts are not submitted.	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? There is no additional Case Report Forms previously requested.			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information? Yes. The applicant has submitted FDA Form 3455. Each of the two principal investigators, (b) (6)	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	(b) (6) respectively.				
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? No. There is no statement of Good Clinical Practice. However, the original CAC-91-10-10 study protocol and informed consent form were reviewed and approved by the Cincinnati Children’s Hospital Medical Center.		X		

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? **YES.**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. The application is not fileable for the following reasons:

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- **Provide efficacy data (summary tables and original data) of liver function test (LFT) and bilirubin test (direct, total, and indirect bilirubin) in patients with single enzyme defect.**
- **Provide detailed narratives of the PIDs 0, 16, 103, 127, 143, 152, and 181.**
- **On page 20 of your clinical overview you state that you prepared a revised clinical study report to address the EMA comments. Please provide a copy of the EMA comments and clarify how you revised the study report to address these comments.**

Sponsor should be requested to provide the “coding dictionary” consisting of a list of all investigator verbatim terms and the preferred terms to which they were mapped.

{See appended electronic signature page}

Reviewing Medical Officer Date

{See appended electronic signature page}

Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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/s/

WEN-YI GAO
01/17/2014

LARA DIMICK-SANTOS
01/17/2014