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*APPLICATION NUMBER:*

**205750Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

NDA 205,750 - Cholic acid

The submitted studies in NDA 205,750 were single arm trials in which on-treatment measurements of efficacy were compared to baseline measurements. The reference to these studies as “uncontrolled” on page 32 of my previous review dated March 17<sup>th</sup>, 2015, should not be construed that efficacy was assessed as isolated measurements, without comparison to a baseline measurements.

Lara Dimick-Santos, MD

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LARA DIMICK-SANTOS  
03/23/2015

### Cross-Discipline Team Leader Review

<b>Date</b>	2/10/2015
<b>From</b>	Lara Dimick-Santos, MD, FACS – Medical Team Leader
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	202-750
<b>Supplement#</b>	0
<b>Applicant</b>	Asklepiion Pharmaceuticals, LLC
<b>Date of Submission</b>	11/21/2013
<b>PDUFA Goal Date</b>	7/21/2014 major amendment 10/21/2014
<b>Proprietary Name / Established (USAN) names</b>	CHOLBAM Cholic acid
<b>Dosage forms / Strength</b>	Capsules 50mg and 250mg
<b>Proposed Indication(s)</b>	1. Treatment of <span style="background-color: #cccccc; padding: 0 5px;">(b) (4)</span> bile acid synthesis in two populations Single enzyme defects and Peroxisomal disorders including Zellwegers spectrum disorders
<b>Recommended:</b>	Regular Approval for single enzyme defect and peroxisomal biogenesis disorder (including Zellwegers spectrum disorders) populations

<b>Material Reviewed/Consulted</b>	<b>Names of Discipline Reviewers</b>
Clinical Review - DGIEP	Wen-Yi Gao, MD
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Biostatistics Reviewer - primary - team lead	Benjamin P Vali, MS Yeh-Fong Chen, PhD
Maternal and Pediatrics – labeling review - primary reviewer - team leader	Tamara Johnson, MD Carrie Ceresa, PharmD
Labeling Reviewers – DMEPA, OMEPRM	Matthew Barlow, RN, BSN Kendra Worthy, PharmD
Nonclinical Reviewers - primary reviewer - team leader - director	Ke Zhang, PhD David Joseph, PhD Abigail Jacobs, PhD
Compliance Reviewer - DSI	Susan Leibenhaut, MD
Bioequivalence and GLP Compliance - primary reviewer - director	Gajendiran Mahadevan, PhD William H. Taylor, Ph.D.
CMC - primary reviewer - Team leader	Gene Holbert, PhD Marie Kowblansky, PhD
Biopharmaceuticals Reviewer - Primary reviewer - team leader	Kareen Riviere, PhD Tapash Ghosh, PhD
Microbiology Reviewer	Bryan S. Riley, Ph.D.
Project Manager	Anissa Davis, CDR Brian Strongin

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## Cross Discipline Team Leader Review Template

### 1. Introduction

The Applicant, Asklepiion Pharmaceuticals, submitted an NDA for the treatment of two rare disorders of bile acid synthesis involving single enzyme defects (SED) and peroxisomal biogenesis disorders (PD), including Zellwegers spectrum disorders. The product, cholic acid (Cholbam), is a new molecular entity.

This review assesses the effectiveness and safety, primarily based on an open-label, single arm, treatment (expanded access) trial (CAC-91-10-10). The study was conducted for 18 years, and the data were collected from 54 SED patients and 31 PD patients (ITT population, 85 patients). There were multiple gaps in data collection with missing records for many efficacy parameters and missing data to confirm compliance. Literature was also reviewed and a thorough analysis of the mechanism of action of cholic acid in patients was undertaken and is discussed in Section 5.

Though the applicant submitted the application with both populations and primarily analyzed the data for the two populations together, these are in reality very different diseases with different phenotypic expressions and different outcomes. Single Enzyme Defects (SEDs) have primarily hepatic pathology (with the exception of Cerebrotendinous Xanthomatosis [CTX] disease, which has systemic and neurological manifestations). However, peroxisomal disorders, including Zellweger's Spectrum Disorders, are systemic diseases that affect multiple organs and have prominent neurological manifestations.

The clinical review team did not agree with the applicant's analysis methods and the medical officer (MO) devised a Post-Hoc analysis method that defined a "responder criteria" based on 3 biomarkers (AST/ALT, total bilirubin, and histologic lack of cholestasis) and two clinical criteria (weight and survival). By this method the MO evaluated efficacy in the SED population and determined there was evidence of efficacy for this population.

On initial review of the data from trial CAC-91-10-10 by the Medical Officer, Wen-Yi Gao, MD did not show efficacy in the PD population by his initial responder criteria. However, the MO did not initially review the data from the extension trial CAC-002-01 that was submitted very late in the review. Subsequently, he did review the data for the extension trial, but he did not agree with the other MDs on the team about the responder analysis. When the data from the extension trial are included, as well as including improvements in coagulopathy, there are 11 of 24 responders in the PD population. See discussion of these issues in Section 7g - Efficacy Summary on page 54.

Additionally, I do not agree with Dr. Gao's conclusion that survival is significantly worse in the trial population than in the historical control data submitted by the applicant or in the paper reviewed by Dr. Gao. See my discussion of this issue in Section 7e - Historical Control on page 47. The other main issue with this application is the poor quality of the bioequivalence study performed to bridge the cholic acid formulation used in the initial trials with the to-be-marketed formulation. The study was not well-designed and an inspection found that [REDACTED]<sup>(b) (4)</sup>; therefore these data could not be accepted for review. However, the phase 3 study, CAC-001-01, and the extension trial provided adequate data to assure bioequivalence between the formulations.

## 2. Background

### *a. Normal Pathophysiology of Bile Acid Synthesis and Bile Flow*

This section is copied from the excellent summary of bile acid metabolism presented by Dr. Julie Beitz, Director, Office of Drug Evaluation 3, in her review.

#### General Overview

Cholic acid, one of two primary bile acids, is synthesized de novo in the liver from cholesterol; the rate limiting enzyme involved is CYP7A1 (cholesterol 7- hydroxylase). In the liver, cholic acid is conjugated with glycine and/or taurine and actively secreted into bile by transporters localized in the canalicular membrane, notably BSEP (bile salt export pump), and then released into the small intestine. The canalicular secretion of bile acids via BSEP is the rate-limiting step in enterohepatic circulation.

In the intestine, bile acids modulate the release of pancreatic secretions and gastrointestinal peptides, and activate enzymes required for the absorption of fat-soluble vitamins. The detergent effects of bile acids also assist in the solubilization of cholesterol and dietary fats in the intestine.

Intraluminal bile acids are absorbed in the ileum, returned to the liver via the portal circulation and taken up by hepatocytes via transporters localized in the sinusoidal membrane, notably NCTP

(Na<sup>+</sup>/taurocholate cotransporting polypeptide) and OATP (organic anion transport protein), thus forming an enterohepatic circuit. See Figure 1 below from Wanders and Ferdinandusse (2012).<sup>1</sup>

Under normal conditions, the levels of bile acids in the liver are kept low in order to prevent deleterious effects of bile acid intermediates on hepatocellular processes. The expression of CYP7A1 and BSEP is coordinately regulated by multiple transactivation

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<sup>1</sup> Wanders RJA and Ferdinandusse S. Peroxisomes, peroxisomal diseases, and the hepatotoxicity induced by peroxisomal metabolites. Current Drug Metabolism 2012; 13:1401-1411.

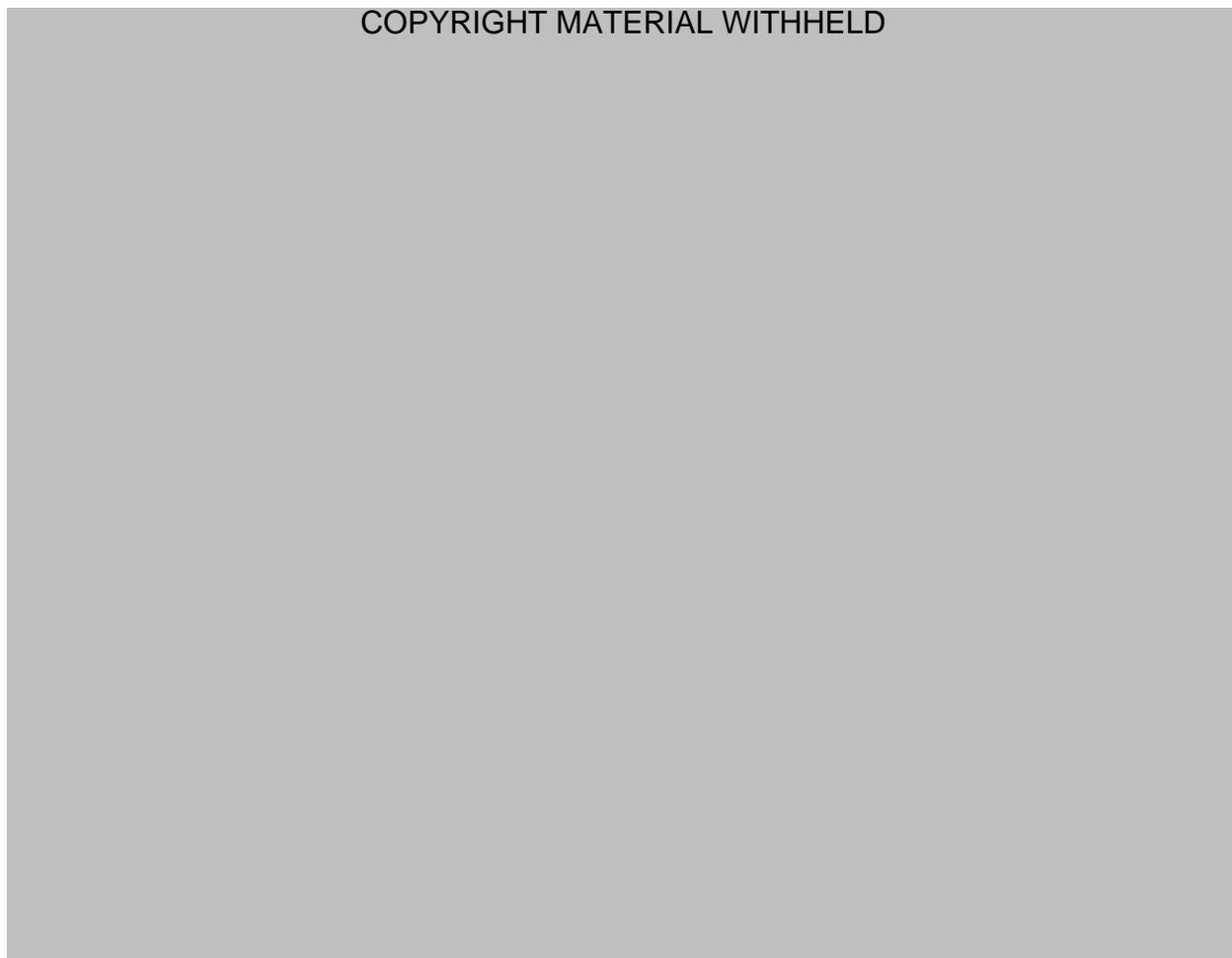
pathways, notably the bile acid/farnesoid X receptor (FXR) signaling pathway. Bile acids, acting as FXR agonists, strongly repress CYP7A1 expression through a negative feedback circuit involving SHP and LHR1,<sup>2</sup> whereas bile acids markedly induce BSEP expression by activating FXR. Such coordinated feedback and feed-forward regulation of CYP7A1 and BSEP by bile acids prevent excessive accumulation of toxic bile acid intermediates in hepatocytes and promote excretion of bile acids into the bile thereby stimulating bile flow (Song et al. 2008).<sup>3</sup>

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<sup>2</sup> The “classical” negative feedback cascade involves bile acids binding to FXR which in turn activates transcription of SHP (short heterodimeric partner). SHP then inhibits transcription of LHR1, the gene coding for the liver receptor homologue 1. LHR1 normally transactivates CYP7A1.

<sup>3</sup> Song X, Kaimal R, Yan B, Deng R. Liver receptor homolog 1 transcriptionally regulates human bile salt export pump expression. *J Lipid Res* 2008; 49(5):973-84.

**Figure 1**



An alternate mechanism by which bile acids down-regulate their own synthesis involves the intestinal enterocyte. Here, binding of bile acids to FXR leads to the production of fibroblast growth factor 15

(FGF15). FGF15 is transported to the liver via the circulation; intracellular signaling pathways triggered in the liver give rise to inhibition of CYP7A1 gene transcription.

Expression of the sinusoidal transporter, NTCP, is down-regulated by bile acid intermediates thereby decreasing uptake of bile acids by hepatocytes.

#### Bile Acid Synthesis Pathways

In the “classical” pathway, bile acid synthesis begins with the conversion of cholesterol to 7 $\alpha$ -hydroxycholesterol by cholesterol 7 $\alpha$ -hydroxylase or CYP7A1. This microsomal cytochrome P450 enzyme is localized exclusively in the liver and its expression is highly regulated. The classical pathway accounts for 90% of total bile acid synthesis.<sup>4</sup>

The next step in bile acid synthesis is catalyzed by the microsomal HSD3B7 (3 $\beta$ -hydroxy- $\Delta^5$ -C<sub>27</sub>-steroid oxidoreductase) which can only handle 7 $\alpha$ -hydroxylated intermediates. At this point, any intermediates acted upon by sterol 12 $\alpha$ -hydroxylase or CYP8B1, another microsomal cytochrome P450, are destined to become cholic acid, otherwise they will go on to form chenodeoxycholic acid.

After a series of additional enzymatic reactions, mitochondrial CYP27A1 catalyzes the formation of the R isomers of the C<sub>27</sub>-bile acid intermediates, THCA and DHCA.<sup>5</sup> The R isomers are transported into the peroxisome and converted to their respective S isomers by 2-methylacyl-CoA racemase (AMACR), a peroxisomal enzyme; the S isomers are then subjected to beta-oxidation in the peroxisome.

The final step in bile acid synthesis involves conjugation with an amino acid (taurine or glycine) catalyzed by BAAT (bile acyl-CoA: amino acid N-acyltransferase). BAAT is localized in peroxisomes and the cytosol. Thus, peroxisomal BAAT is responsible for conjugation of newly synthesized primary bile acids in the peroxisome, whereas cytosolic BAAT is involved in the reconjugation of the recycled bile acids that were deconjugated in the intestine. Conjugated bile acids are more hydrophilic and less cytotoxic than their unconjugated forms. Under normal conditions, unconjugated bile acids make up only a small proportion of bile acids in bile.

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<sup>4</sup> The alternative “acidic” pathway is responsible for the remainder of bile acid synthesis; oxysterols rather than cholesterol serve as substrates for 7 $\beta$ -hydroxylation. Enzymes involved in this pathway include sterol 27-hydroxylase or CYP27A1. This pathway produces mainly chenodeoxycholic acid, is the major pathway for bile acid synthesis in the first year of life, and is involved in the control of cholesterol levels in extrahepatic tissues, particularly in the nervous system.

<sup>5</sup> THCA is (25R)3 $\alpha$ ,7 $\beta$ ,12 $\beta$ -trihydroxy-5 $\beta$ -cholestanoic acid; DHCA is (25R)3 $\alpha$ ,7 $\beta$ ,12 $\beta$ -dihydroxy-5 $\Delta$ -cholestanoic acid.

After conjugation, “mature” C<sub>24</sub>-bile acids are transported out of the peroxisome, and then out of the hepatocyte into bile via BSEP. In livers of normal subjects, total C<sub>27</sub>-bile acid intermediates amounted to only 2 nmol/gr wet weight vs. a total mature C<sub>24</sub>-bile acid wet weight of 52 nmol/gr.<sup>6</sup>

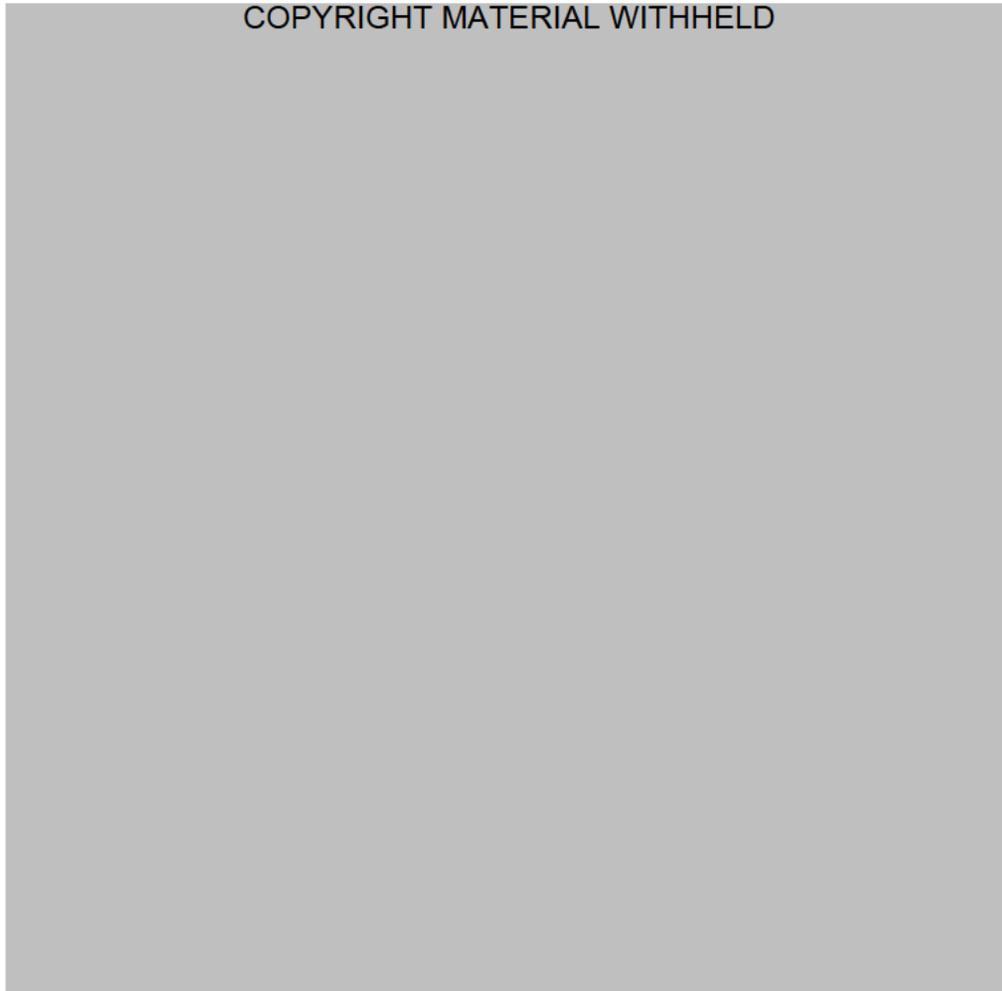
The schematic below adapted from Ferdinandusse and Houten (2006) depicts the enzymatic pathways involved in bile acid synthesis.<sup>7</sup> Known enzyme defects are shown by solid bars over the arrows. Atypical bile acid intermediates specific to each defect form above the block. In patients with non-functional peroxisomes, or defects in peroxisomal enzymes, C<sub>27</sub>-bile acid intermediates (THCA and DHCA) can accumulate.

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<sup>6</sup> Ferdinandusse, et al. Bile Acids: the Role of Peroxisomes. *Journal of Lipid Research*. Nov 2009;50:11:2139-2147

<sup>7</sup> Ferdinandusse S and Houten SM. Peroxisomes and bile acid synthesis. *Biochimica et Biophysica Acta* 2006; 1763:1427-1440.

**Figure 2**



## ***b. Bile Acid Deficiency States***

### Pathophysiology

Patients with inherited single enzyme defects in bile acid synthesis and those with peroxisomal disorders (involving peroxisomal enzyme defects or non-functional peroxisomes) fail to synthesize the primary bile acids (cholic acid and chenodeoxycholic acid). This can lead to:

- Reduction in bile flow. The secretion of bile by the liver is driven by the pumping of bile acids into the canaliculi. When there is a failure to synthesize the primary bile acids, bile flow is reduced leading to cholestasis and retention of compounds normally excreted in the bile, such as conjugated bilirubin.
- Fat malabsorption. Bile acids are detergents and are needed in the intestine for digestion and absorption of fat and fat-soluble vitamins. In this role, the taurine and glycine conjugates of cholic acid and chenodeoxycholic acid are more efficient than other bile acids. Fat malabsorption can lead to steatorrhea, failure to thrive and deficiencies of fat-soluble vitamins (most commonly rickets, and vitamin E and K deficiencies).
- Lack of the physiologic down-regulation of bile acid synthesis. Atypical bile acids that accumulate as a result of single enzyme defects may function poorly as FXR agonists, failing to repress CYP7A1 expression allowing for the sustained production of high concentrations of atypical bile acid intermediates.

As a result, there is:

- Accumulation of potentially hepatotoxic atypical bile acid intermediates in the liver. Liver pathology usually involves giant cell hepatitis and steatosis; extramedullary hematopoiesis may be present. Limited information is available<sup>8</sup> to establish the role of atypical bile acids in clinical manifestation in patients. In a study using rat liver canalicular membrane vesicles, taurine conjugate of 3 $\beta$ ,7 $\alpha$ -dihydroxy-5-cholenoic acid and 7 $\alpha$ -hydroxy-3-oxo-4-cholenoic acid which are detectable in patients with deficiency in HSD3 $\beta$ 7 and 5 $\beta$ -reductase, respectively inhibited the transport of taurocholic acid suggesting a potential role of these bile acids in cholestasis. No information is available for atypical bile acids found in patients with deficiency in other enzymes. While the information is limited, the potential contributions of these atypical bile acids to clinical symptoms cannot be ruled out.

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<sup>8</sup> Stieger B et al. Differential interaction of bile acids from patients with inborn errors of bile acid synthesis with hepatocellular bile acid transporters. Eur. J. Biochem. 1997; 244: 39-44; Stieger et al. (1994) Transport of taurine conjugates of 7 $\alpha$ -hydroxy-3-oxo-4-cholenoic acid and 3 $\beta$ ,7 $\alpha$ -dihydroxy-5-cholenoic acid in rat liver plasma membrane vesicles, in Cholestatic liver diseases: 82-87

- Accumulation of atypical bile acid intermediates in extrahepatic tissues. Conversion of atypical bile acid intermediates to cholestanol in extrahepatic tissues can lead to excess deposition in various organs, including the CNS, as seen in patients with defects in sterol 27-hydroxylase (CYP27A1) function (also known as CTX or Cerebrotendinous Xanthomatosis).
- Accumulation of very long chain fatty acids in the CNS. In patients with neonatal adrenoleukodystrophy, peroxisomal function is impaired leading to in neuronal cell membranes and neurologic injury.

### Single Enzyme Defects of Bile Acid Synthesis

3 $\beta$ -hydroxy- $\Delta^5$ -C<sub>27</sub>-steroid oxidoreductase (3 $\beta$ -HSD) and  $\Delta^4$ -3-oxosteroid 5 $\beta$ -reductase ( $\Delta^4$ -3-oxo-R or AKR1D1) defects. These are rare autosomal recessive diseases and the most frequent inborn errors of primary bile acid synthesis causing early cirrhosis and liver failure. They result from dysfunction of HSD3B7 and AKR1D1, respectively, which leads to the hepatic accumulation of abnormal (“atypical”) bile acid intermediates that cannot be transported across the canalicular membrane; rather they are excreted in urine. The presence of atypical bile acid intermediates, specific for each defect, concomitant with a lack of primary bile acids in the urine and serum is the basis for diagnosis of these genetic defects. Of note, pruritus is absent, and serum  $\gamma$ -glutamyltransferase (GGT) activity is normal.<sup>9</sup> Thus, there is both a failure to synthesize adequate amounts of cholic acid, and unregulated production of cholestatic atypical bile acid intermediates that accumulate proximal to the enzyme defect. Recently, two of the atypical bile acid intermediates arising from a defect in HSD3B7 function were shown to be unable to function as FXR agonists and exert the hepato-protective effects which are efficiently coordinated by primary bile acids under normal conditions. Their inability to repress CYP7A1 expression could account for the sustained production of high concentrations of atypical bile acid intermediates (Gioiello et al. 2014).<sup>10</sup> As already noted, steatorrhea and fat-soluble vitamin deficiencies result from the reduced levels of intraluminal cholic acid in these patients (Gonzales et al. 2009).<sup>11</sup>

Cerebrotendinous xanthomatosis (CTX). This is a rare autosomal recessive disease caused by a defect in CYP27A1 (sterol 27-hydroxylase) function in mitochondria, which results in reduced bile acid synthesis and tissue accumulation of cholestanol. The mitochondrial location of this defect makes it different from the other SEDs in that patients can have systemic disease and neurological outcomes. Patients presenting in early infancy can have cholestatic liver disease which may be fatal. Clinical manifestations in older children are related to the presence of cholestanol deposits and can include tendon xanthomas, learning

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<sup>9</sup> Bile acids facilitate the detachment of GGT from the canalicular membrane. Thus, if there are reduced amounts of bile acids entering the canaliculi, as in disorders of bile acid synthesis (unlike other causes of cholestasis), soluble GGT is not released and plasma GGT is not elevated.

<sup>10</sup> Gioiello A, Cerra B, Zhang W, Vallerini GP, Constantino G, DeFranco F, Passeri D, Pellicciari R, Setchell KD. Synthesis of atypical bile acids for use as investigative tools for the genetic defect of 3 $\beta$ -hydroxy- $\Delta^5$ -C<sub>27</sub>-steroid oxidoreductase deficiency. *J Steroid Biochemistry & Molecular Biology* 2014; 144:348-360.

<sup>11</sup> Gonzales E, Gerhardt MF, Fabre M, Setchell KD, Davit-Spraul A, Vincent I, Heubi JE, Bernard O, Jacquemin E. Oral cholic acid for hereditary effects of primary bile acid synthesis: A safe and effective long-term therapy. *Gastroenterology* 2009; 137:1310-1320.

difficulties (low IQ) or psychiatric illness. Adults may present with spastic paraparesis (due to spinal xanthomas), falling IQ and frank dementia with ataxia and seizures or peripheral neuropathy. Adults may also experience premature atherosclerosis and coronary heart disease, and early onset osteoporosis.

### Peroxisomal Single Enzyme Defects

AMACR defect. Although most patients with a defect in AMACR function present in adolescence with a neuropathy resembling that of Refsum disease, two siblings presenting in the first weeks of life have been described (Setchell et al. 2003).<sup>12</sup> The index (female) patient presented with cholestatic liver disease, coagulopathy and malabsorption of fat-soluble vitamins; the deceased (male) patient presented with cholestatic liver disease, coagulopathy and died of a subdural hematoma. His liver was harvested for orthotopic transplantation; the recipient developed the same urinary bile acid profile (elevated levels of THCA) as the donor's sister.

A defect in AMACR function results in accumulation of the R isomers of C<sub>27</sub>-bile acid intermediates (THCA and DHCA) which are more hydrophobic than their C<sub>24</sub>-products, and less efficiently conjugated and excreted into the bile. These factors contribute to the retention of these intermediates in the liver, cholestasis and, consequently, to hepatic injury. Moreover, C<sub>27</sub>-bile acid intermediates are more hepatotoxic than mature C<sub>24</sub>-bile acids<sup>6</sup>. In addition, the primary bile acid substrates for BSEP are low in concentration, thus limiting bile flow; concentrations of C<sub>24</sub>-bile acid measured from duodenal aspirates are decreased. Reduced intraluminal bile acid concentrations, in turn, lead to malabsorption of dietary fat and fat-soluble vitamins.

### Zellweger Spectrum Disorders

These inherited disorders include Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD) and have overlapping clinical, biochemical and genetic phenotypes. The failure to form functional peroxisomes is common to all these disorders. Clinically, patients have cognitive and motor dysfunction, retinopathy, sensorineural hearing impairment, hepatic involvement, and growth failure.

A report of the natural history of 31 patients with Zellweger spectrum disorders who survived beyond one year found that long-term survival was possible. Nine patients died at a mean age of 8 years (1.2 to 22.5 years) from a variety of causes including respiratory problems, dehydration and shock, and renal failure. One patient died of liver failure and another from gastrointestinal bleeding due to gastric varices (Poll-The et al. 2004).<sup>13</sup>

### Zellweger syndrome (ZS)

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<sup>12</sup> Setchell KDR, Heubi JE, Bove KE, O'Connell NC, Brewsaugh T, Steinberg SJ, Moser A, Squires Jr RH. Liver disease caused by failure to racemize trihydrocholestanic acid: Gene mutation and effect of bile acid therapy. *Gastroenterology* 2003; 124:217-232.

<sup>13</sup> Poll-The BT, Gootjes J, Duran M, de Klerk JBC, Maillette de Buy Wenniger-Prick LJ, Admiraal RJC, Waterham HR, Wanders RJA, Barth PG. Peroxisome biogenesis disorders with prolonged survival. *American Journal of Medical Genetics* 2004; 126A:333-338.

Patients diagnosed with Zellweger syndrome exhibit a wide variety of abnormalities involving multiple organs, including the liver. Hepatomegaly was reported in 78% of 114 patients; histology varied from near normal to diffuse fibrosis and micronodular cirrhosis depending on the age of the patient (Wanders 1988). Invariably, there is distortion of mitochondria and either total absence or a severe reduction in peroxisomes in the liver. There is accumulation of hepatotoxic R and S isomers of C27-bile acid intermediates, due to the block in beta-oxidation to mature C24-bile acids. In livers of ZS patients, total C27-bile acid intermediates amounted to 63.5 nmol/gr wet weight vs. a total C24-bile acid wet weight of 16.7 nmol/gr.<sup>6</sup> As noted above, C27-bile acid intermediates are less efficiently conjugated and excreted into the bile, and more hepatotoxic than mature C24-bile acids.

Accumulation of C27-bile acid intermediates also occurs in other organs, including the brain. Serum levels of these intermediates range from normal to levels that are 50-fold higher than normal; urine levels are also elevated. In contrast, biliary bile acid concentrations measured in duodenal aspirates is decreased.

#### Neonatal adrenoleukodystrophy (NALD) and infantile Refsum disease (IRD)

NALD and IRD are considered milder forms of the Zellweger disease spectrum. Patients with NALD, IRD and less severe presentations of ZS (i.e., patients surviving more than 1 year) have generally lower serum levels of C27-bile acid intermediates and less cholestasis (Ferdinandusse and Houten 2006).<sup>14</sup>

NALD is characterized by the accumulation of very-long-chain fatty acids (VLCFA) resulting from a  $\beta$ -oxidation defect caused by mutations in the ABCD1 gene, the gene encoding the peroxisomal enzyme ABCD1 (ATP-binding cassette [ABC] transporter subfamily D member 1). ABCD1 transports CoA-activated VLCFA from the cytosol into the peroxisome for degradation.

While dysfunction of peroxisomal beta-oxidation results in accumulation of VLCFA in all tissues, clinically NALD primarily affects the nervous system and the adrenal glands. The typical manifestation of mutations in ABCD1 is adrenomyeloneuropathy, a slowly progressive dying-back axonopathy affecting both ascending and descending spinal cord tracts as well as in some cases, a peripheral neuropathy. In about 60% of male patients, either in childhood (35-40%) or in adulthood (20%), an initial, clinically silent, myelin destabilization results in conversion to a devastating, rapidly progressive form of cerebral inflammatory demyelination.

In IRD the function of peroxisomal enzyme, phytanoyl-CoA 2-hydroxylase, which catalyzes the conversion of phytanic acid to pristanic acid, is defective; phytanic acid accumulates in tissues. The clinical signs of the disease include retinitis pigmentosa, cerebellar ataxia and polyneuropathy, whereas liver abnormalities are rarely reported.

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<sup>14</sup> Ferdinandusse, et al. Peroxisomes and bile acid biosynthesis. *Biochimica Et Biophysica acta-molecular cell research*, 2006; 1763;12:1427-1440.

### ***c. Regulatory History***

Cholbam was studied under an open-label, non-randomized, single-arm treatment IND (#45,470) submitted in June 1994 by two academic investigators at Cincinnati Children’s Hospital Medical Center (CCHMC). On 27 Jan 1992, about 1 month after the protocol to study CAC-91-10-10 was approved; the Principal Investigator sent a request to the IRB to include patients with peroxisomal disorders. A separate protocol (CAC-92-8-19) was submitted and approved by the IRB on 8 September 1992. Study CAC-92-8-19 was based on a different funding source and was considered a sub-study to CAC-91-10-10, but specifically addressed patients with peroxisomal disorders, while study CAC-91-10-10 mainly addressed patients with single enzyme defects, but also enrolled a small number of patients with peroxisomal disorders. Study CAC-92-8-19 was essentially identical to study CAC-91-10-10, and included the same drug treatment and study procedures (see below). These trials were closed for data analysis December 31, 2009 and patients from study CAC-92-8-19 and CAC-91-10-10 continued treatment with CA under CAC-91-1010 until trial CAC-002-10 the extension trial was operational in 2002. Additional patients were also enrolled into the extension trial.

The IND was transferred to Asklepiion Pharmaceuticals, LLC in May 2007 for the purpose of commercializing the product. In 2010, the new applicant defined a data collection cut-off date of 31 December 2009 for study CAC-91-10-10. The clinical data cut-off was set to officially determine a data collection endpoint and to enable clinical data analysis and preparation of the CSR, as well as MAA/NDA reporting. In the meantime, the clinical program, including further data collection and shipment of CA, was continuing under protocol CAC-91-10-10 and several amendments to the protocol and/or the ICF were submitted.

On July 18, 2003, Cholbam was granted Orphan designation for “treatment of inborn errors of cholesterol and bile acid synthesis and metabolism”.

The continuous treatment of patients and data collection under the ongoing clinical program was formally described in the continuation study protocol CAC-002-01, which was approved by the IRB in 12 December 2011. At that time there was a request to retrospectively collect data as of 31 December 2009 to avoid any gaps in data collection. Data collected during the period from 1 January 2010 until consenting to CAC-002-01 was then approved by the IRB to be included in the CAC-002-01 continuation study. All data collected from 1 January 2010 onwards will thus be reported in the CAC-002-01 CSR. The CAC-002-01 CSR will include a description of any amendments to the study program after 1 January 2010 and will identify dates for patient informed consent signatures. Asklepiion reported that since November 2010 it has performed auditing and monitoring programs as well as onsite training to enhance the quality of data collection over previous efforts which did not meet ICH Good Clinical Practice (GCP) guidelines.

Asklepiion retrospectively devised a case report form from a chart review of the patients treated under the IND. For analysis and writing of this CSR, data from both studies CAC-91-10-10 and its sub-study CAC-92-8-19 are combined. They also retrospectively reviewed literature to construct a historical control. In late 2013, Asklepiion submitted a marketing Authorization Application to the European Medicines Agency (EMA) for Cholic Acid FGK for the treatment of Single Enzyme Defects in bile acid synthesis.

Asklepiion did not submit data on the PD population to the EMA because the EMA did not have an orphan designation for the PD population. During the course of this review (b) (4) Asklepiion conducted extensive re-monitoring of study data (including patient charts, screening logs, adverse events, laboratory findings, and study medications) with the result that additional patients could be included in analyses of efficacy and safety. In January 2014, the CHMP adopted a positive opinion for granting a Marketing Authorization under exceptional circumstances to cholic acid FGK for the treatment of patients diagnosed with sterol 27-hydroxylase (CTX), AMACR and CYP7A1 deficiencies based on the results of Study CAC-91-10-10 and interim data from CAC-002-01, supported by literature reports. The product has been marketed since April 2014.

In Europe, Laboratories CTRS' cholic acid capsules (trade name Orphacol) received marketing authorization in September 2013 for the treatment of patients diagnosed with 3 $\beta$ -HSD and AKR1D1 deficiencies based on safety and efficacy information obtained from literature reports.

The applicant is conducting a Registry Study in the EMA as part of its post-marketing requirements. See the Primary MO review by Dr. Wen-Yi Gao for full regulatory history details.

### **3. CMC/Device**

#### **a. Overview**

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

Sufficient information regarding raw materials, manufacturing process and controls, and stability has been submitted to ensure that the drug substance and drug product have been adequately characterized.

Gene Holbert, PhD, reported no issues with the CMC review and recommended approval.

#### **b. Bioequivalence with To-Be-Marketed Formulation**

In study CAC-91-10-10, pharmacy prepared capsule or oral liquid formulation was used until the proposed to-be-marketed (TBM) capsule formulation became available in April 2010. As such the clinical efficacy and safety data collected were with the pharmacy prepared capsule or oral liquid formulation.

In accordance with advice provided by FDA that an *in vivo* bioequivalence study would be needed to compare the pharmacokinetic profiles of the clinical formulations and to-be-marketed (TBM) formulations of cholic acid, Asklepiion contracted with Frontage Clinical Services, Inc., to conduct Study CAC-003-01 in healthy male volunteers. This was a Phase I single center study conducted to compare the Cincinnati Children's Hospital (CCHMC) Pharmacy formulation used in Study CAC-91-10-10 to an oral solution and to the TBM formulation.

The biopharmaceutical reviewer, Kareen Riviere, PhD, noted several issues with the design and conduct of Study CAC-003-01, in particular, the study is (b) (4)

However, a Form 483 was issued following OSI's inspection of the study site for CAC-003-01 conducted May 12 to 20, 2014. Inspectors found that the study site was in violation of 21 CFR (b) (4)

Nevertheless, OSI has recommended that data generated by Frontage for Study CAC-003-01 not be accepted for Agency review.

In 2010, bridging Study CAC-001-01 was conducted in 16 patients with single enzyme defects (15 previously enrolled in Study CAC-91-10-10 and one treatment naive patient diagnosed with 3 $\beta$ -HSD) to assess the short-term impact on efficacy and safety of switching from the CCHMC formulation to the TBM formulation of cholic acid. Patients were switched to the TBM from either pharmacy prepared capsule (n=9) or oral liquid (n=6). There were no significant safety issues noted during 30 days after switch-over to TBM formulation from pharmacy prepared capsule or oral liquid formulation.

Dr. Riviere concluded that although BE Study CAC-003-01 study was not acceptable to bridge the pharmacy and to-be marketed formulations; it could be used as evidence of bioavailability of the to-be marketed formulation. Also, the phase 3 Study CAC-001-01 can be used for purposes of demonstrating bioavailability or bioequivalence of the proposed drug product according to 21CFR 320.24(b)(4) and 21CFR320.24 (b)(6), therefore, the phase 3 Study CAC-001-01 was deemed adequate to support the bridging of the pharmacy and to-be marketed formulations.

Safety information is available on a total of 45 patients, who took the TBM formulation in the extension trial (CAC-002-10), including:

- 1) 16 patients previously enrolled on CAC-001-01
- 2) 16 additional patients previously treated with the CCHMC formulation on Study CAC-91-10-10 (n = 6) or Study CAC-92-8-19 (n = 10)

3) 13 additional treatment naïve patients (11 with single enzyme defects and 2 with peroxisomal disorders).

*CDTL Comments:*

*While the bioequivalence study was not adequate alone to prove bioequivalence between the formulation used in the initial studies and the TBM formulation the clinical team agree with the Dr. Riviere that there was adequate data and clinical experience with the TBM formulation in trial CAC-001-01 and trial CAC-002-01 to assess the safety and efficacy of the TBM formulation.*

*The stability of the product in infant formula was not specifically tested, however it was stable in applesauce (b) (4) and stable when (b) (4) therefore the CMC reviewer Gene Holbert was in agreement with the labeling recommendations to mix with formula or applesauce.*

#### **4. Nonclinical Pharmacology/Toxicology**

Dr. Zhang, the Preclinical Pharmacology and Toxicology reviewer 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 applicant 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”. David Joseph, PhD, the Lead Pharmacologist agreed with Dr. Zhang. 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)

*CDTL Comment:*

*The Keane article, discussed below, generated concerns about use of cholic acid in the PD population. The following is a presentation of the article contents and then the conclusions of a review of the article by Prakash Jha, MD, MPH, Medical Officer/Pathologist, CDRH/OIR/DMGP, and a discussion of the conclusions of Wen-Yi Gao, MD, PhD, Medical Officer/DGIEP. This is followed by my conclusions.*

The PEX2<sup>-/-</sup> mouse model of Zellweger syndrome offers the opportunity to characterize biochemically the progression of hepatic disease and the effects of bile acid feeding. Feeding with a combination of cholic acid and ursodeoxycholic acid normalized C24 bile acid concentrations in bile to that of untreated control animals. Although growth was only mildly improved, there was near complete

normalization of stool fat content, resolution of steatorrhea, and improved survival. Bile acid feeding reduced the number of cholestatic deposits in bile ducts and alleviated cholangitis, but exacerbated the degree of hepatic steatosis and mitochondrial and cellular damage in the peroxisome-deficient livers of these animals.<sup>15</sup>

Total hepatic lipids analysis found a 1.75-fold increase in untreated PEX2<sup>-/-</sup> mouse livers compared with control animals, but an additional 2-fold increase in bile acid-fed mutants. PEX2<sup>-/-</sup> mouse livers demonstrated mitochondrial abnormalities which persisted with bile acid feeding. The efficacy of bile acid feeding in these animals is limited by changes in bile acid transporter (BSEP) expression that limit hepatic excretion of bile acids, persistent canalicular damage, and limits to bile acid conjugation capacity. There can be increased mitochondrial autophagy and hepatocellular necrosis. Compared to mice deficient in the peroxisomal enzyme, *3-methylacyl-CoA racemase (AMACR)*, which have a similar degree of accumulation of C27-bile acid intermediates and have C27 conjugation defects, PEX2<sup>-/-</sup> mice have more widespread peroxisomal defects that can produce more severe biochemical disturbances and increase the potential for greater toxicity to bile acid feeding.

The following is taken from the review of the Keane et al. 2007 paper by Prakash Jha, MD, MPH, Medical Officer/Pathologist, CDRH/OIR/DMGP

“The paper under review acknowledges markedly improved clinical picture produced by bile acid therapy by showing prolonged survival, mildly improved growth, alleviated intrahepatic cholestasis and intestinal malabsorption, reduced trihydrocholestanic acid and dihydrocholestanic acid levels, temporarily normalized hepatic primary bile acid levels and protected older mutants from developing steatohepatitis. However they also noted that the therapy exacerbated the degree of hepatic steatosis and worsened the already severe mitochondrial and cellular damage and the persistence of significantly increased mitochondrial autophagy and increased matrix density in older mutants.

I agree with the sponsors that the treated homozygous mice actually do significantly better clinically however their interpretation of significant increase in the steatosis as being benign or reversible is questionable. Severe steatosis has been shown to lead to cirrhosis and this question has not been settled yet.

The second point regarding the mouse model and the assertion of the sponsor regarding extrapolating findings from rodent models to humans needs to be addressed. It is true that rodent models are being developed to mimic human liver disease. However, no model to date can completely recapitulate the “corresponding” human disorder. Limiting factors are the time frame required in humans to

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<sup>15</sup> Keane MH, Overmars H, Wikander TM, Ferdinandusse S, Duran M, Wanders RJA, Faust PL. Bile acid treatment alters hepatic disease and bile acid transport in peroxisome-deficient PEX2 Zellweger mice. *Hepatology* 2007; 45:982-997.

establish a certain liver disease and the fact that rodents possess a distinct immune system compared with humans and have different metabolic rates affecting liver homeostasis.

In conclusion, given the improvement of clinical picture both in the animal model (with caution in extrapolating findings from rodent models to humans) as well as similar finding of improvement seen in the human studies I don't have much concern on the long-term effectiveness and safety of the drug, however marked increase in steatosis is a concern and need to be monitored.”

*CDTL Comment:*

*Dr. Gao, who is trained as a pathologist, noted that the picture of histopathology in the article was consistent with a picture of microvesicular steatosis. However, the author noted only an increase in steatosis; therefore this concern would need further investigation with the primary author or examination of the histopathology from the mice to verify that microvesicular steatosis is indeed a feature. In addition, if additional information from this mice study showed microvesicular steatosis to be a concern then the study would need to be repeated with cholic acid alone.*

*Though there is some concern about findings of exacerbation of hepatic steatosis and mitochondrial and cellular damage in the PD deficient mice model, the overall clinical picture is of improvement. However, the relevance of the mice model to the human population is always debatable and the fact that these mice received both UDCA and cholic acid further confounds the interpretation of the relevance of this data. From a safety perspective, if it is the patients with the more severe peroxisomal defects that may be more susceptible to the toxic effects of cholic acid, because changes in bile acid transporter (BSEP) expression that limit hepatic excretion of bile acids, persistent canalicular damage, and limits to bile acid conjugation capacity, then close screening at the initiation of treatment should show worsening of liver function and treatment should be stopped. For patients that are treated long term, screening for early onset hepatic steatosis may be considered. Though there is no treatment currently available to treat steatosis, steatohepatitis or liver fibrosis there are currently several drugs under investigation for these indications. The post-marketing Registry trial should allow more information to be gathered to assess the implications for treatment in the PD population.*

## 5. Clinical Pharmacology/Biopharmaceutics

### a. Overview

Please see Section 2 –Background - Pathophysiology for a discussion of enterohepatic circulation and distribution and elimination of bile acids, on page 6.

#### *CDTL Comment:*

*PK of orally administered cholic acid was studied in the bioequivalence study in healthy subjects but not studied in patients whose endogenous levels of primary bile acids i.e. cholic acid and chenodeoxycholic acid, are expected to be low. However, it is expected that the enterohepatic circulation will be the same in both endogenous and administered cholic acid in this population.*

#### Selection of Doses in the Study

The enterohepatic circulation leads to an accumulation of bile acids, termed the bile acid pool that amounts to about 2-3 g in normal adults. Because the pool cycles several times with each meal, the effective pool size is much greater, exposing the intestine daily to about 20-30 g of bile acids. Only about 0.3 g per day are lost and made up by newly synthesized bile acids (Hofmann, 2009).

The proposed dose was determined empirically under the treatment IND without an evaluation of dose-response relationship. The applicant postulates that in order to substitute a pool of bile acids in patients with defects in bile acid synthesis it is necessary to at least administer an amount equivalent to, or above the daily synthesis rate of the primary bile acids. As the fractional absorption of bile acids is not 100% and, in addition, there will be some conversion by intestinal bacteria to the secondary bile acid deoxycholic acid, therefore, a therapeutic dose of 15 mg/kg/day was chosen to enable substitution of a normal bile acid pool.

The CA dose administered was also guided by the available dosage regimens of similar bile acids: chenodeoxycholic acid (CDA) (15 mg/kg/body weight) and URSO (10 to 15 mg/kg/body weight).

For each patient, the CA dose was adjusted, if necessary, based on changes in serum transaminases results as well as on the extent of reduction or disappearance of atypical metabolites in urine measured by fast atom bombardment (FAB-MS) analysis. In addition, changes in the patient's height or weight might have necessitated dose adjustments. See section 5b, on page 24, for a discussion of FAB/MS.

The study drug was administered orally in divided doses (as determined by the investigator) for a total daily dose of about 15 mg/kg body weight.

Study CAC-91-10-10 which included 85 patients either with single enzyme defects (SED) or peroxisomal disorders (PD), the dosing information is available from a subset of patients. In patients whose dosing information is available, the mean dose level on Day 1 was 10.5 mg/kg and 11.4 mg/kg for PD and SED, respectively and the dose level ranged from 3.3 to 26 mg/kg on Day 1. The change of doses over time was documented for some patients. The last documented dose also varied significantly ranging from 3.27 mg/kg to 24.56 mg/kg.

*CDTL Comment:*

*The applicant's justification for the dose of 10-15mg/kg is rational and they have accumulated years of clinical data with this dose range. The applicant states that the dose was adjusted based on changes in serum transaminases and bilirubin and the extent of reduction of atypical bile acids in urine. However, the documentation on the dosage adjustment with relevant clinical observations and biomarkers at the time of dosage adjustment was not adequate for review.* (b) (4)

*The labeling will reflect the dose as 10-15mg/kg and (u) (4) instructions for monitoring patients and discontinuing cholic acid for evidence of deteriorating hepatic function. Further data on dose and adjustment of dose using quantitative methods of measurement of urinary bile acids will be requested from the applicant as a part of the post-marketing registry. See discussion of the FAB-MS use for dose adjustment below.*

The proposed dosing frequency is once a day. However the dosage regimen varied among patients. In some patients, a change in dose and frequency was also noted over time. In CAC-91-10-10 cholic acid was administered mostly once or twice daily, while it was administered once daily in the switch-over study (CAC-001-01) and twice daily in the BE study (CAC-003-01).

*CDTL Comment:*

*The labeling will reflect instructions for dosing once or twice daily.*

Hepatic impairment

No PK study was done in patients with hepatic impairment. The target patient populations have a varying degree of progressive liver disease. The dosage adjustment should be based on clinical observations as well as relevant pharmacodynamic biomarkers rather than the systemic exposure to exogenous cholic acid.

Renal impairment

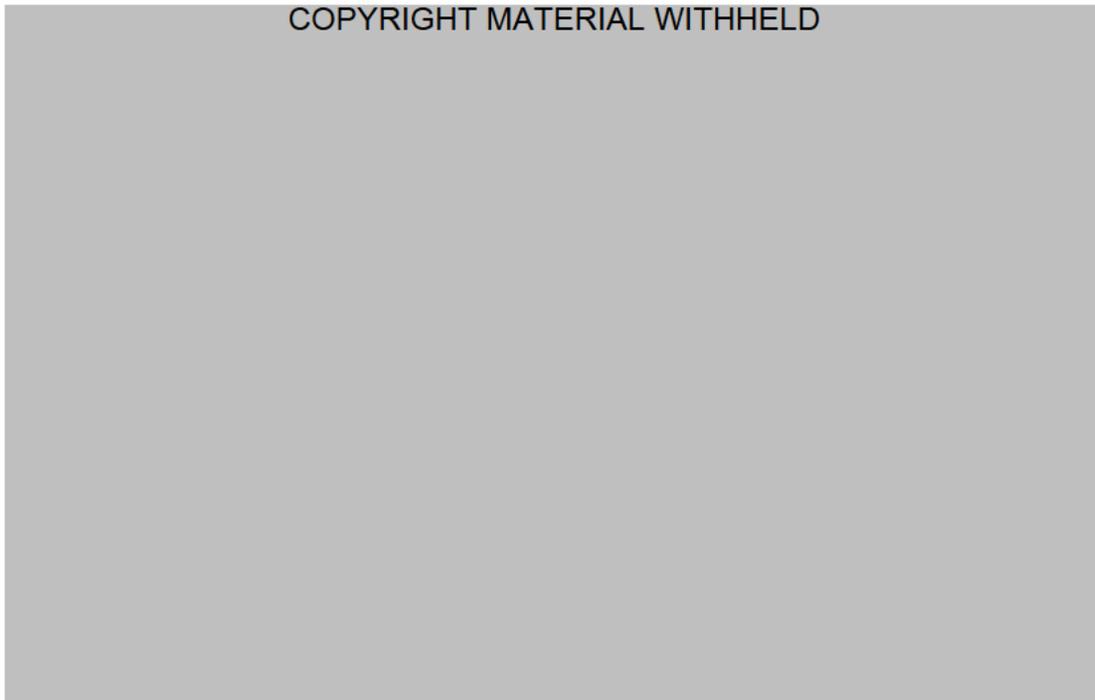
In patients with renal impairment, the urinary excretion of atypical bile acids may be reduced. No PK study was done in patients with renal impairment.

**b. Urinary Bile Acid Measurement- FAB-MS**

Investigators for this trial developed a qualitative assay using FAB-MS (fast atom bombardment mass spectrometry) to detect bile acids in spot urine samples. The bile acid profile or imprint of patient samples was compared to that of normal controls to discern whether abnormal bile acid metabolites are present. See Figure 3.

Individual bile acids of interest were subsequently identified by molecular structure prediction based on mass fragmentation pattern, thereby permitting diagnosis of specific enzyme defects. The FAB-MS assays as performed <sup>(b) (4)</sup> are based on methods validated, certified and accredited by the Centers for Medicare and Medicaid Services Clinical Laboratory Improvement Amendments (CLIA) and by the College of American Pathologists.

**Figure 3: Typical negative ion FAB-MS of the urine from a patient with 3β-hydroxy-C27-steroid dehydrogenase**



From: Setchell and O’Connell, (2007) “Disorders of bile acid synthesis and metabolism: a metabolic basis for liver disease”

*CDTL Comment:*

*The FAB-MS methodology is acceptable for identifying abnormal bile acids in urine samples and is accurate for diagnosing specific defects in bile acid synthesis by the profile of the abnormal bile acid metabolites.*

[Redacted] (b) (4)

See **Table 1.**

*Because the FAB-MS method was originally developed to be a qualitative analysis to aid the diagnosis of a specific enzyme defect, the assay was not validated as a quantitative assay method.* (b) (4)

[Redacted]

**Table 1: Categorization of elevation of atypical bile acids in urine**

[Redacted] (b) (4)

*To partly address these concerns, Asklepiion submitted information obtained using a liquid chromatography-mass spectrometry (LC-MS) assay. Although LC-MS was not used for the analysis of urine samples from patients enrolled in the submitted studies, it was performed with synthesized standards; results supported the identities of mass peak characteristics of atypical bile acid intermediates found in the urine from patients with 3β-HSD deficiency.*

*The clinical pharmacology reviewer, Dr. Insook Kim, noted that “a change in atypical bile acids upon cholic acid treatment in patients with defect in bile acid synthesis is considered as a reasonable pharmacodynamic biomarker to assess the early response to the treatment. This is based on the underlying mechanism of disease i.e. enzyme deficiency to accumulate intermediate bile acids<sup>16</sup> and the negative feedback mechanism mediated by cholic acid for the repression of bile acid synthesis from cholesterol<sup>17,18</sup>.”*

*She also noted that “the longitudinal data for urinary bile acids were not initially submitted and the information was requested along with the individual mass spectra. Significant variability on the signal-to-noise ratio was noted within and between patients. It is unknown how much the assay contributed to the variability as the assay was not adequately validated for quantitative analysis.”*

*In addition, ursodeoxycholic acid was administered in some patients. The information on the dose and treatment duration of ursodeoxycholic acid is mostly missing preventing the evaluation of effects of cholic acid treatment alone.*

*Unfortunately, the applicant was unable to provide actual data to match urinary bile acid scores to dose adjustments made in the clinical trials, therefore the significance of reduction of atypical bile acids to the clinical outcome and usefulness for dose adjustment will need to be further established. In addition, the team did not agree* [REDACTED] (b) (4)

[REDACTED] (b) (4)  
*The applicant has verbally committed to developing and appropriate method to quantitatively measure urine bile acids (e.g. liquid chromatography) and we will request data on urinary bile acid measurements and dose adjustments as part of the post-marketing registry data.*

## 6. Clinical Microbiology

The Product Quality, microbiology reviewer, Bryan S. Riley, Ph.D., noted that the Microbial Limits specification for Cholic Acid Capsules (50 mg and 250 mg) were acceptable from a Product Quality Microbiology perspective, and recommend approval.

<sup>16</sup> Sundaram et al. (2008) Mechanisms of Disease: inborn errors of bile acid synthesis, Gastroenterology & Hepatology, 5 (8): 456

<sup>17</sup> Hofmann AL (2007) Biliary secretion and excretion in health and disease: Current concepts, Annals of Hepatology 6(1): January-March: 15-27

<sup>18</sup> Wang et al. (1999) Endogenous Bile Acids Are Ligands for the Nuclear Receptor FXR/BAR, Molecular Cell, Vol. 3, 543–553

## 7. Clinical/Statistical - Efficacy

### **a. Introduction**

The Medical Officer Review by Dr. Wen-Yi Gao is in favor of accelerated approval of Cholbam for the SED population but recommends a complete response for the PD population. This reviewer is in favor of full approval for both populations. In team meetings, the three other Medical Doctors on the team, Andrew Mulberg, Julie Beitz and I disagreed with Dr. Gao’s interpretation of the data and interpretation of responder criteria. This is discussed in the CDTL Comment on page 34.

I will review the summary data on the SED and PD populations, but please refer to the MO primary review for the details of the efficacy evaluation in trials CAC-91-10-10 and CAC 92-8-19. The data will be reviewed, as noted below by first, combining data from the two main efficacy trials and the extension trial, and then reviewing the other supportive studies. Third, I will review the historical control data and discuss the differences in our approach to interpretation of the historical control data submitted and historical control data from the literature. Fourth, I will review of the relevant literature. In the summary, I will discuss the differences in the outcomes of the efficacy evaluation of the PD population and the difference in approach and conclusions between us.

### **b. Sources of Clinical Data**

#### Key Studies Submitted

- Primary Study: Study CAC-91-10-10 including sub-study CAC-92-8-19
- Extension Trial CAC-02-01

#### Other Supportive Studies Submitted

- 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 Review

### **c. Clinical Trial Design**

#### **Design of Study CAC91-10-10 and Study CAC-92-8-19**

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.

Study CAC-92-8-19 was started a year later to include patients with peroxisomal disorders in the trial and the trial design was the same. See Dr. Gao's review for analysis of the data from just these two primary trials; however the **data analysis below combines the data from these of the two primary trials and the data from the extension trial CAC-002-01, that included both patient groups.**

The extension trial, CAC-002-01 added an additional 2 years 11 months of safety data and additional 1 year, 9 months of efficacy data. In addition, data collection was much better in the extension trial and more information was available to evaluate efficacy. CAC-002-01 was also performed with the to-be-marketed formulation.

The original study objectives/hypothesis is listed below:

1. The initiating or perpetuating factor in the pathogenesis of cholestasis and liver injury in the inborn errors of bile acid metabolism or in peroxisomal disorders affecting bile acid metabolism is the intracellular accumulation of potentially hepatotoxic bile acids synthesized in response to the enzyme deficiency accompanied by extremely small primary bile acid pools.
2. Down-regulation in endogenous bile acid synthesis by the oral administration of primary bile acids will provide an effective therapy by increasing the primary bile acid pool size and reducing the production of hepatotoxic bile acid intermediates.
3. Administration of oral bile acids may have a palliative effect on the patient's clinical course leading to improved growth and potentially prolonged life (hypothesis specified in sub-study in PD patients [CAC-92-8-19]).

Therapeutic efficacy was proposed to be evaluated by assessing the effects of the administration of Cholic acid (CA) on:

1. Suppression of synthesis of atypical bile acids as measured by urine bile acid analysis using mass spectrometry,
2. Serum transaminases and bilirubin (see below)
3. Height/weight gain
4. Change in liver histology (for patients in whom biopsy was performed).

*CDTL Comment:*

*Bilirubin was not an original endpoint in the trial, it was added later, and data on bilirubin was only collected sporadically. In addition, other clinical data such as coagulopathy, hepatosplenomegaly, steatorrhea and presence of other systemic symptoms were not collected in a systemic fashion and data on these clinically relevant endpoints are available for only a few patients, though data collection is better in the extension trial (CAC-002-01).*

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).

In 2005, study CAC-91-10-10 was expanded to patients outside of CCHMC so that compassionate treatment could be provided to additional patients who had been identified with inborn errors of bile metabolism through the center's screening/diagnostic program. After enrollment and start of treatment, only blood and urine monitoring on a regular basis was required. No visits to the CCHMC were necessary. Systematic collection of AE information was not done on these outpatients.

*CDTL Comment:*

*The outside patients were frequently from other countries and data collection on these patients was especially poor with little verification of source data available.*

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);

- 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.

No patients were removed from therapy or assessment by the investigators, but due to the distributed nature of the study with patients located across the world and being treated by their local physician, some patients were lost to follow-up.

#### 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.

#### Discussion of Transition from combination URSO and CA to CA alone

In the original study protocol approved on 3 Jan 1992, a combination of URSO and CA was stipulated as study medication. Since URSO does not down regulate cholesterol and bile acid synthesis, it was initially combined with CA, which as a primary bile acid has the required inhibitory effect on cholesterol synthesis. However, analysis of urinary bile acids by FAB-MS or gas chromatography mass spectrometry (GC-MS) indicated incomplete down regulation of endogenous bile acid synthesis under combined URSO/CA therapy and the experience of Drs. Heubi and Setchell at CCHMC suggested that URSO could possibly interfere with intestinal absorption of CA. After administration of CA alone, a greater down-regulation of bile acid synthesis was obtained as evidenced from a strong decrease or almost complete disappearance of bile acid precursors (Jacquemin et al. 2001). Similarly, in a report on 15 children with genetic defects in primary bile acid synthesis (Gonzalez et al, 2009), marked reductions in  $\Delta^4$ -3-oxo bile acids and in total urinary bile acid excretion after CA therapy were described, while optimal suppression of metabolite synthesis was not achieved with URSO and CA therapy. The authors concluded that URSO in the long-term treatment of a bile acid synthesis defects was seldom useful.

Hence, monotherapy with CA was considered by the investigators the most appropriate therapeutic strategy to treat inborn errors in bile acid synthesis, because it provides a stimulus for bile flow and secretion, it inhibits endogenous production and accumulation of potentially hepatotoxic and cholestatic bile acid precursors, and it facilitates fat absorption without persisting disadvantageous or toxic side effects at therapeutic doses. In accordance with this evolving awareness for CA efficacy, URSO was removed as study

medication in the ICF version from 12 June 2001. However, it should be noted that for several patients URSO had been deleted in the individual ICFs prior to this date.

Cholic acid and URSO at a dose of 15 mg/kg each was to be administered orally, once a day. Following termination of URSO as study medication, only CA at a dose of 15 mg/kg was to be administered.

### Study Drug

Prior to August 1998 study medication compounding was completed in the Mass Spectrometry Laboratory by or under the direction of Dr. Setchell using active pharmaceutical ingredient (API) provided by the manufacturers.

Since August 1998, the CCHMC Investigational Drug Service (IDS) has been involved in the study drug handling. Until June 2008, the IDS compounded the (b) (4) capsules and distributed them in bulk to the staff of the Mass Spectrometry Laboratory. The laboratory staff then dispensed the study medication in individual bottles. The production, packaging and labeling of the liquid formulation was performed in the Laboratory as of August 1998.

As of July 2008 the IDS prepared the CA capsules as well as the liquid formulation. The study drug was then prescribed per patient and the IDS maintained a log of preparation, labeling and dispensing to the PI in addition to inventory logs for capsules, liquid (b) (4). The drug was then distributed to the patients by the PI. Different sources for the drug substance were used over the long period of the study.

The to-be-marketed formulation was introduced in April of 2010. See discussion of bioequivalence with the study drug in Section 2b on page 17.

### Compliance

Treatment compliance was monitored by the study personnel based upon timing of resupply requests and urine FAB-MS results.

During the monitoring period from November 2010 to

February 2011, a CRF was created to collect any study medication data available from patient records. During the re-monitoring from November 2012 through January 2013, any available data including shipping logs as well as air bill receipts were reviewed. However, even the analysis of all available study treatment data did not permit a complete, uninterrupted assessment of time of treatment with investigational drugs and dosing of study drug. To the extent that compliance can be determined, there were several patients who might have been without study drug for varying periods of time.

### **CAC-002-01 Extension Trial**

The study protocol for CAC-002-01 was essentially the same as for the primary trials. Study CAC-002-01 was initiated as a continuation study to allow patients to receive treatment with the TBM formulation. Safety data is available from the 120-day safety update for 2 years and 11 months from January 1<sup>st</sup>, 2010 to November 30<sup>th</sup>, 2013. Efficacy data is available for 21 months from January 1, 2010 to September 30, 2012, from the draft study report submitted to the Agency on January 7<sup>st</sup>, 2015. Asklepiion reported that since November 2010 it has performed auditing and monitoring programs as well as onsite training to enhance the quality of data collection over previous efforts which did not meet ICH Good Clinical Practice (GCP) guidelines.

*CDTL Comments:*

*The trial was not designed as a placebo-controlled trial as the investigators believed in the hypothesis and felt it would be unethical to withhold drug from any patient. Originally there was no control at all however when the Asklepiion purchased rights to cholic acid and began a drug development program they performed a literature search to attempt to establish historical control data. This effort was only partly successful. See discussion on historical control in Section 7e on page 47.*

#### **d. Review of Efficacy Data**

*CDTL Comment:*

*The efficacy data review presented here is based on the combination of data from the main study CAC-91-10-10 and the substudy CAC-02-01 as well as data from the draft study report for extension trial CAC-02-01.*

Exposure:

Exogenous oral cholic acid therapy (10-15 mg/kg daily) has been administered to 62 patients with single enzyme defects and 31 patients with Zellweger spectrum disorders (peroxisomal disorders) in a series of uncontrolled studies beginning in 1992. Pre- and on-treatment laboratory and clinical parameters were assessed in Study CAC-91-10-10 (n=50 patients with single enzyme defects), in Study CAC-92-8-19 (n=29 patients with Zellweger spectrum disorders), and in the continuation Study CAC-002-01 that included both patient groups (n=33 patients with single enzyme defects and n=12 with Zellweger spectrum disorders).

In anticipation of commercialization, Asklepiion introduced a new capsule formulation of cholic acid in 2010. Fifteen patients with single enzyme defects initially enrolled in Study CAC-91-10-10 were enrolled in crossover study CAC-001-01 that assessed the safety and efficacy of switching from the CCHMC formulation to the To-Be-Marketed (TBM) formulation after 30 days; one additional treatment naïve patient was also enrolled. No substantive changes in efficacy or safety were noted as a result of the formulation switch. See discussion on bioequivalence in Section 3b on page 17.

These 16 patients, along with 6 additional patients from Study CAC-91-10-10, 10 from CAC-92-8-19, and 9 additional treatment naïve patients were enrolled on continuation study CAC-002-01 as of the September 30, 2012 cut-off date for the interim report of Study CAC-002-01. As of this date, a total of 36 patients had received the TBM formulation (n=27 patients with single enzyme defects and 9 patients with Zellweger spectrum disorders). Four additional treatment naïve patients with single enzyme defects were enrolled on Study CAC-002-01 by the November 30, 2012 data cut-off date for the 120-day safety report. Subject disposition is shown below.



*The applicant also performed efficacy analyses on transaminases*

(b) (4)

*It is clear from this response and the responder analysis performed by the team, that there is 'greater' efficacy in the SED population than the PD population. The interpretation of this for the PD population is discussed below.*

(b) (4)

*Please see Dr. Gao's review for complete presentation of the applicant's initial analysis of data.*

(b) (4)

*After review of the data Dr. Gao presented a post-hoc method to assess efficacy in these populations using the limited amount of data that was available to us. His method used a combination of improvements in transaminases and bilirubin and resolution of cholestasis on histology, and the clinical outcomes of survival and weight gain. This method was accepted by the team as being a reasonable approach to analysis of the available data. However, the statistical team stated that because of the lack of real placebo data and no prespecified statistical plan for this trial, that no statistical analysis were valid and the interpretation of these data relied on clinical judgment.*

*The original method to assess efficacy was modified when data on prothrombin time became available with the better data collection in the extension trial. The final post-hoc method used to determine efficacy in both subpopulations is listed below, and the analysis of the two populations presented below is based on the combined data from the three trials and the assessment of efficacy using this method.*

*Of note, there was a significant amount of missing data on patients in the original trials. However, in the extension trial data was available on many of the patients who rolled over to the extension trial that was not presented in the original data sets. This new data on these patients significantly impacts the efficacy evaluation, esp. in the PD population.*

Laboratory criteria:

- ALT or AST values reduced to < 50 U/L, or baseline levels reduced by 80%
- total bilirubin values reduced to < 1 mg/L

- normalization of prothrombin time
- no evidence of cholestasis on liver biopsy

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, as well as body weight and survival criteria

*CDTL Comment:*

*During the final review of the responder analysis with the sponsor and the team, it became apparent that there were differences in interpretation of the criteria by different members of the team and by the Applicant. Therefore, clarifications were made in the definitions and these are presented below. Additionally, several patients were included in the original ITT population by the sponsor because they has adequate data, however for this responder criteria more data was necessary so additional patients were eliminated as “not enough data to be evaluable” and the final mITT population for efficacy included only the “evaluate” patients.*

*Laboratory criteria:*

- *ALT or AST values reduced to < 50 U/L, or baseline levels reduced by 80%*
- *Total bilirubin values reduced to < 1 mg/L*
- *Normalization of prothrombin time*
  - *For all three laboratory criteria above – the baseline must be elevated to qualify as a responder, baseline is last value before treatment, and post-treatment is best value*
- *No evidence of cholestasis on liver biopsy (must have baseline cholestasis)*

*Clinical Criteria:*

- *Body weight increased by 10% or stable at > 50th percentile*
- ***changed to:*** *survival for at least 3 years on treatment, or alive at the end of CAC-002-01*

***i. Single Enzyme Defect Population Efficacy Analysis***

Overall, 28 of the 44 patients with single enzyme defects (64%) were responders by the above criteria.

**Table 3: Response by Type of Enzyme Defect**

Single Enzyme Defect	Number of Responders/Number Treated
3 $\beta$ -HSD	22/37
AKR1D1	3/4
CTX	2/2
AMACR	1/1
CYP7A1	N/A
Smith-Lemli-Opitz	N/A

N/A indicates no evaluable patients in the defect subgroup

**Table 4: SED Responders**

PID	Primary Dz.	BL ALT	BL AST	Responder	BL Bilirubin	Responder	PT (CAC-002-01 only)	PT Responder (CAC-002-01 only)	Cholesterol (91-10-10 only)	BL Wt.	Responder	Alive	Responder in 91-10-10	Responder in CAC-002-01	Overall Responder
9	3β-hydroxy-Δ5-C27-steroid oxidoreductase	59	73	YES	4.39	NO			UNK	15.30	YES	YES	YES	NA	YES
33	3β-hydroxy-Δ5-C27-steroid oxidoreductase	58	49	YES	0.90	NO	-	UNK	UNK	33.50	YES	YES	YES	YES	YES
34	3β-hydroxy-Δ5-C27-steroid oxidoreductase	92	135	YES	10.20	YES	-	UNK	UNK	32.10	NC	YES	YES	YES	YES
47	3β-hydroxy-Δ5-C27-steroid oxidoreductase	298	264	YES	1.93	YES			UNK	12.80	YES	YES	YES	NA	YES
57	3β-hydroxy-Δ5-C27-	505	871	YES	17.50	YES	-	NC	UNK	-	YES	NO	YES	YES	YES

	steroid oxidoreductase														
65	Sterol 27-hydroxylase (CTX)	422	481	YES	6.40	YES	-	NC	NO	2.39	YES	YES	YES	YES	YES
68	$\Delta$ 4-3-oxosteroid 5 $\beta$ -reductase ( $\Delta$ 4-3-oxo-R or AKR1D1)	590	668	YES	15.00	YES	-	NC	UNK	9.53	NC	YES	YES	YES	YES
76	2- (or $\alpha$ -) methylacetyl-CoA racemase (AMACR)	223	199	YES	4.20	YES			YES	3.37	YES	YES	YES	NA	YES
79	3 $\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase	48	101	YES	0.70	YES	-	NC	UNK	12.20	YES	YES	YES	YES	YES
86	Sterol 27-hydroxylase (CTX)	99	-	YES	22.80	YES	-	NO	UNK	-	YES	YES	YES	YES	YES
90	3 $\beta$ -hydroxy- $\Delta$ 5-C27-steroid oxidoreductase	41	54	YES	1.20	YES	-	NC	UNK	15.00	NC	YES	YES	YES	YES
93	3 $\beta$ -hydroxy-	398	305	YES	-	YES	-	NC	NO	8.00	YES	YES	YES	YES	YES

	Δ5-C27-steroid oxidoreductase														
95	3β-hydroxy-Δ5-C27-steroid oxidoreductase	921	967	YES	13.50	YES	-	NC	UNK	6.67	YES	YES	YES	YES	YES
100	3β-hydroxy-Δ5-C27-steroid oxidoreductase	354	676	YES	1.40	YES	-	NC	UNK	6.10	YES	YES	YES	YES	YES
102	Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1)	284	487	YES		YES			UNK	5.10	YES	YES	YES	NA	YES
106	3β-hydroxy-Δ5-C27-steroid oxidoreductase	118	145	YES	3.50	YES	-	NC	UNK	10.09	YES	YES	YES	YES	YES
107	3β-hydroxy-Δ5-C27-steroid oxidoreductase	60		YES	3.88	YES			UNK	38.50	UNK	YES	YES	NA	YES
133	Δ4-3-oxosteroid 5β-	154	191	YES	0.01	YES	-	NC	UNK	4.49	YES	YES	YES	YES	YES

	reductase ( $\Delta^4$ -3-oxo-R or AKR1D1)														
138	3 $\beta$ -hydroxy- $\Delta^5$ -C27-steroid oxidoreductase	68	73	YES	2.30	YES	-	NC	UNK	-	YES	YES	NO	YES	YES
145	3 $\beta$ -hydroxy- $\Delta^5$ -C27-steroid oxidoreductase	120	92	YES	1.00	YES	-	NC	UNK	7.80	YES	YES	YES	YES	YES
157	3 $\beta$ -hydroxy- $\Delta^5$ -C27-steroid oxidoreductase	308	291	YES	7.31	YES	-	UNK	UNK	-	YES	YES	YES	YES	YES
175	3 $\beta$ -hydroxy- $\Delta^5$ -C27-steroid oxidoreductase	58	77	YES	3.20	YES	-	UNK	UNK	75.70	NO	YES	YES	NE	YES
176	3 $\beta$ -hydroxy- $\Delta^5$ -C27-steroid oxidoreductase	126	109	YES	0.60	YES	-	NC		25.00	YES	YES	NA	YES	YES
177	3 $\beta$ -hydroxy- $\Delta^5$ -C27-steroid	20	60	YES	10.30	YES	-	UNK	UNK	-	NO	YES	NO	YES	YES

	oxidored uctase														
700	3β- hydroxy- Δ5-C27- steroid oxidored uctase	150	202	YES	5.8 0	YES	-	NC			NO	YE S	NA	YES	YES
705	3β- hydroxy- Δ5-C27- steroid oxidored uctase	43	51	YES	0.7 0	YES	-	NC		7.00	YES	YE S	NA	YES	YES
706	3β- hydroxy- Δ5-C27- steroid oxidored uctase	106	91	YES	2.3 9	YES	-	NC		13.0 0	YES	YE S	NA	YES	YES
707	3β- hydroxy- Δ5-C27- steroid oxidored uctase	41	71	YES	0.9 2	YES	-	NC		15.8 0	YES	YE S	NA	YES	YES

**ii. Peroxisomal Disorders**

Overall, 11 of 24 patients (46%) in the PD population were responders by the criteria as outlined above.

**Table 5: Response by Type of Disorder**

Peroxisomal Disorder	Number of Responders/Number Treated
Zellweger Syndrome	3/8
Neonatal Adrenoleukodystrophy	3/6
Infantile Refsum Disease	3/4
Generalized Peroxisomal Disorder	1/1
Peroxisomal Disorder, Type Unknown	1/5
Total	11/24

**Table 6: Peroxisomal Disorder Responders**

PID	Primary Diagnosis	BL ALT	BL AST	Responder	BL Bilirubin	Responder	Prot hrombin Time (CAC-002-01 only)	PT Responder (CAC-002-01 only)	Cholestasis (91-10-10 only)	BL Weight	Responder	Alive	Responder in 91-10-10	Responder in CAC-002-01	Overall Responder
12	Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy	312	470	YES	0.80	YES	-	NC	UNK	3.49	YES	YES	YES	YES	YES
20	Peroxisomal Biogenesis Disorder: Refsum's	119	320	YES	0.60	YES	-	UNK	UNK	9.28	YES	YES	YES	YES	YES
21	Peroxisomal Biogenesis Disorder: Refsum's	72	78	NO	0.10	YES	-	UNK	UNK	11.30	YES	YES	NC	YES	YES
30	Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy	119	148	YES	1.40	YES	-	UNK	UNK	9.60	NO	YES	YES	NE	YES

	kodystrophy														
46	Peroxisomal Biogenesis Disorder: Zellwegers	56	86	YES	0.30	YES	-	NC	UNK	3.77	YES	YES	NO	YES	YES
51	Peroxisomal Biogenesis Disorder: Type unknown	18	68	YES	0.30	NC			UNK	26.70	YES	YES	YES	NA	YES
64	Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy	90	135	YES	0.40	NC			UNK	8.00	YES	YES	YES	NA	YES
92	Peroxisomal Biogenesis Disorder: Generalized Peroxisomal Disorder	83	130	NO	0.30	YES	-	NC	UNK	12.06	YES	YES	NO	YES	YES
128	Peroxisomal Biogenesis	396	449	YES		UNK	-	NO	UNK	10.40	YES	YES	YES	NO	YES

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	s Disorder: Refsum's														
132	Peroxisom al Biogenesi s Disorder: Zellweger s	282	639	YES		NO	-	NO	UNK	3.03	NO	YES	YES	NO	YES
703	Peroxisom al Biogenesi s Disorder: Zellweger s	165	290	YES	3.30	YES	-	UNK		3.90	YES	YES	NA	YES	YES

In addition, Zellweger syndrome patient 132 responded in terms of increased weight, transaminase criteria, and improvement in cognition and mental abilities, but died due to causes unrelated to the underlying disease (sepsis, complications following pamidronate infusion).

### ***e. Historical Control***

#### Applicant's submitted "historical control" data:

The Applicant provided a literature search for SED patients who had  $\geq 2$  years of untreated history. They also included 10 cases of SED sibling data.

- SED history control

A total of 18 papers were identified, which provided 25 cases of historical control across 4 disorders ( $3\beta$ -HSD, AKR1D1, CTX, and Smith-Lemli-Opitz disease).

- SED sibling control

A total of 10 sibling cases:  $3\beta$ -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. Literature search for PD patients did not have the requirement of  $\geq 2$  years of untreated history. 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.

#### Analysis from Applicant on Peroxisomal Disorders (PD): 91-10-10 compared to Historical Controls

Askleion 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). The applicant concludes that cholic acid treatment benefits the SED and PD patients by increasing the survival time as compared with the historical untreated control.

In terms of overall death rate, the 91-10-10 patients had a lower rate of death (48% compared to 68%), however, the difference does not reach statistical significance, Fisher's exact p-value=0.183. Adding in the patients with incomplete survival information improves the rate of death slightly (45%) but still not enough to achieve statistical significance (p=0.124). The time to death for the 91-10-10 patients is significantly longer than the historical control patients; 129 months vs. 9 months, log-rank p-value=0.01. The statistical conclusions do not change when the patients with incomplete censoring information are added in.

#### *CDTL Comment:*

*Dr. Gao concludes that the Kaplan-Meier method of analysis is likely not appropriate to this literature review data, and therefore the clinical relevance was not clear. I agree with his assessment.*

Discussion of the historical control data from “Poll-The” paper:

*CDTL Comment:*

*Dr. Gao reviewed a publication from 2004 in which the PD patients who survived greater than 1 year were noted to have a milder phenotype and he used this data to compare to the patients in the clinical trial who survived greater than one year.*

From the Poll-The paper:

“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).”

This report shows that a) it is not new that milder PD patients can have prolonged survivals; 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%).

Dr Gao concluded that “these data do not support the statement that cholic acid treatment brings about long-term survival benefit to the PD patients.” See Table 7: Comparison of Survival Rates of PD Patients Age > 1 Year Old (CAC-91-10-10, Historical Control, and Natural History Control).

He 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) when reviewing only the data available in this trial.

**Table 7: 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 Table 15 in Dr. Gao’s review

*CDTL Comment:*

*Unfortunately growth (weight) data was very poorly recorded in the main efficacy trial, however in the extension trial growth data was available for the 10 patients who crossed over to this trial, which documents weight gain that was not documented in the original data submitted by the applicant. When the data for growth and data on coagulopathy that are found in the extension trial data are included in the responder analysis there are 10 responders in the PD population.*

*I disagree that the comparison of survival in the Poll-The paper is significantly different or clinically meaningful for several reasons. First is the misclassification of patient #11 as unknown, review of this patient’s narrative show that the patient survived beyond age 4 (see Table 8 on page 51). This would make the comparison of survival between the two groups 77% vs. 65%. In addition, patient #130 died just (b)(6) days prior to their 4<sup>th</sup> birthday.*

*Additionally, I note that 5 patients in study CAC19-10-10 survived for more than 1 year but died during their second year of life. Two additional patients died during their third year of life. These patients may have had classical Zellwegers disease but had prolonged survival secondary to cholic acid treatment. The Poll-The paper reported only 3 patients that survived beyond 1 year but died before the 3<sup>rd</sup> year of life.*

*Therefore it is my opinion that the differences in survival beyond 4 years in these two groups are not comparable and cannot be taken as clinically meaningful, especially in light of the small numbers of patients that are being evaluated.*

Conclusion:

*Therefore, I do not believe that the historical control data from the applicant proves increased survival, nor do I think that the data from the Poll-The paper shows decreased survival with treatment with cholic acid. The historical data review is inconclusive for the PD population. However, the historical control data for the SED population (see MO review by Dr. Gao) appears to support an increased survival in the SED population with cholic acid treatment.*

*While improvement in survival was not definitely demonstrated for the PD population, improvement in survival is not a necessary requirement for drug approval. Improvement in symptoms or one only aspect of a disease has been acceptable for many other drugs approved by the Agency.*

**Table 8: Survival in PD patients in study CAC19-10-10 (from Dr. Gao’s review)**

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	(b) (6)			14
#11	ZS	Unknown				
#12*	NALD	Alive				18
#13	Type unk	Expired				1.6 (1 yr 7 mo)
#17	ZS	Expired				1.4 (1 yr 5 mo)
#19	ZS	Expired				0.7 (8 mo)
#20*	Refsums	Alive				14
#21*	Refsums	Alive				14
#29	NALD	Expired				1.1 (1 yr 1 mo)
#30*	NALD	Alive				23
#32	ZS	Unknown				
#35	NALD	Unknown				
#36	ZS	Expired				2.1 (2 yr 1 mo)
#37	NALD	Expired				1
#46*	ZS	Alive				18
#51*	Type unk	Alive				28
#59	ZS	Expired				1
#64*	NALD	Alive				21
#69	NALD	Expired				1.5 (1 yr 6 mo)
#72	Refsums	Expired				2.4 (2 yr 5 mo)
#80	ZS	Expired				0.6 (7 mo)
#87	Type unk	Expired				1.3 (1 yr 3 mo)
#91	Type unk	Expired				6
#92*	GPD	Alive				16
#123	ZS	Expired				
#128	Refsums	Expired				9
#130	Type unk	Expired				3
#132	ZS	Expired				5
#173	ZS	Unknown				
Total 29 PD patients grouped into 3 categories				N/A: 5 patients	Classic ZS: 4 patients	MPD: 20 patients

## **f. Literature Review**

This literature review is copied from the draft review of Dr. Julie Beitz, Director Office of New Drugs 3 (ODE3).

“In the published literature, beneficial effects of exogenous cholic acid therapy have been described in patients with single enzyme defects of bile acid synthesis including patients with AMACR defects, and to a lesser extent, in patients with Zellweger spectrum disorders. These effects are summarized below.

- a. From the Gonzales et al. paper that studied 15 patients with SED.<sup>11</sup> Administration of exogenous cholic acid **restores the physiologic feedback inhibition on bile acid synthesis** thereby reducing the formation of potentially hepatotoxic atypical bile acid intermediates. As noted above, primary bile acids are more effective than atypical bile acid intermediates in down-regulating their own biosynthesis via activation of the nuclear receptor farnesoid X receptor (FXR).

In 15 patients with either HSD3B7 or AKR1D1 deficiency on chronic cholic acid therapy (median 12.4 years), excretion of total urinary bile acid, and specific intermediates was reduced; excretion was predominantly cholic acid and its metabolite, deoxycholic acid. All 9 patients with pre-existing jaundice experienced resolution, and 14 of 15 patients experienced resolution of hepatosplenomegaly. Liver biochemistries normalized in all patients. In 14 patients, liver histology showed resolution of cholestasis and inflammation and a decrease or reversal of the extent of liver fibrosis and cirrhosis (Gonzales et al. 2009).<sup>11</sup>

A patient with a defect in AKR1D1 who initiated cholic acid therapy at 8 months of age (at a dose of 10 mg/kg/day) was reported alive and well (Clayton 2011, Table 1).<sup>19</sup> The authors noted that AKR1D1 patients with an INR greater than 1.4 did not respond to bile acid treatment and died or were transplanted. The authors also noted that cholic acid has been used successfully in the treatment of cholestatic liver disease in patients with CTX but no details were provided; they noted that there is no information on the effectiveness of cholic acid in treating neurologic manifestations of the disease.

The case report of a child with AMACR deficiency (Setchell et al. 2003)<sup>12</sup> treated with cholic acid for 7 years noted reduction of C<sub>27</sub> bile acid intermediates in urine, and normalization of liver function and fat-soluble vitamin status, without the need for supplementation.

The first report of cholic acid therapy (and concomitant chenodeoxycholic acid) in a 6 month old patient with ZS noted improvement in liver function and liver histology, and reduction in serum and urinary C<sub>27</sub>-bile acid intermediates (Setchell et al.

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<sup>19</sup> Clayton PT. Disorders of bile acid synthesis. J Inherit Metab Dis 2011; 34:593-604.  
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1992).<sup>20</sup> Despite these improvements, the patient died at one year of age. The multiple metabolic derangements in patients with ZS were believed to be too severe for cholic acid therapy to overcome.

In two Japanese patients with ZS, treatment with bile acids decreased THCA levels and serum transaminases (Maeda et al. 2002).<sup>21</sup>

In an animal model of ZS (*Pex2* knockout mouse), cholic acid combined with ursodeoxycholic acid treatment alleviated intrahepatic cholestasis, however, the degree of hepatic steatosis worsened (Keane et al. 2007).<sup>15</sup> This finding suggests that peroxisome-deficient hepatocytes may be more sensitive to bile acid toxicity, and that cholic acid therapy should be reserved for patients with less severe peroxisomal disorders (i.e., NALD or infantile Refsum disease).

*CDTL Comment:*

*See discussion of the Keane study in Section 5, on page 22.*

- b. Administration of exogenous cholic acid **restores bile acid-dependent bile flow by replenishing the decreased levels of C<sub>24</sub> primary bile acids**. Treatment with exogenous primary bile acids leads to their transport from the intestine to the liver where they can be conjugated and fuel bile flow. Patients with single enzyme defects and those with peroxisomal disorders have low concentrations of the primary bile acid substrates for BSEP, including the glycine and taurine conjugates of cholic acid, and hence, impaired bile flow. In one patient with a defect in HSD37 function, biliary bile acid analysis was performed while on cholic acid therapy; biliary bile acid composition showed enrichment with cholic acid (Gonzales et al. 2009).<sup>11</sup> Restoration of bile flow ameliorates cholestasis, and results in improvement of liver function.
- c. Administration of exogenous cholic acid increases the amount of intraluminal cholic acid, and thereby, **enhances micellar solubilization of dietary fats and absorption of fat-soluble vitamins**. In thirteen patients diagnosed with either HSD3B7 or AKR1D1 defects who had pre-existing steatorrhea, all experienced resolution on chronic cholic acid therapy. Resolution of fat malabsorption was associated with improved growth and development in these patients. Vitamin E deficiency resolved in all 14 patients with pre-existing deficiency and levels remained normal after vitamin E supplementation was stopped (Gonzales et al. 2009).<sup>11</sup>

The published report of a child with a defect in AMACR function (Setchell et al. 2003)<sup>12</sup> treated with cholic acid for 7 years noted normalization of fat-soluble vitamin levels without the need for supplementation.

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<sup>20</sup> Setchell KD, Bragetti P, Zimmer-Nechemias L, Daugherty C, Pelli MA, Vaccaro R, Gentili G, Distrutti E, Dozzini G, Morelli A et al. Oral bile acid treatment and the patient with Zellweger syndrome. *Hepatology* 1992; 15(2):198-207.

<sup>21</sup> Maeda K, Kimura A, Yamato Y, Nittono H, Takei H, Sato T, Mitsubuchi H, Murai T, Kurosawa T. Oral bile acid treatment in two Japanese patients with Zellweger syndrome. *J Pediatr Gastroenterol Nutr* 2002; 35(2):227-230.

The first report of cholic acid therapy in a 6 month old patient with ZS noted improvement in steatorrhea and growth, although the patient died at one year of age (Setchell et al. 1992).<sup>20</sup>

- d. In an animal model of ZS (*PEX2* knockout mouse), cholic acid treatment improved balance and spasticity and was associated with increased dendritic arborization of cerebellar Purkinje cells (Keane et al. 2007).<sup>15</sup> There are as yet no reports of improved balance or spasticity in humans treated with cholic acid.”

### **g. Efficacy Summary**

*CDTL Comment:*

*Much of the applicant’s original analyses of efficacy (which were not prespecified) were not acceptable to the team secondary to the assumptions made, such as the (b) (4) analysis of the transaminases and other biomarkers. A summary of these analyses are discuss below and full review is presented by Dr. Gao in his review in Section 6.1.8 - Additional Effectiveness Analyses.*

*The demographic, disposition data and protocol deviations were combined for both populations making analysis difficult. In addition to the protocol deviations there was missing data for many patients, including bilirubin data and clinical data, therefore narratives were requested for all patients in the initial population from the two main efficacy trials, and multiple information requests were sent. The applicant was able to provide some additional data but the data was still incomplete for many patients. The data collection was much better in the extension trial.*

*The applicant’s efficacy analysis was based on a (b) (4)*

(b) (4)

*However, we do not agree (b) (4) and we requested data for medium-to-median values for all the biomarkers that were assessed in the trial. We also did not agree (b) (4)*

(b) (4)

*The applicant also performed efficacy analyses on transaminases (b) (4)*

(b) (4)

*Again we disagree that this is a valid way to assess the data and our analyses are based on median to median values.*

(b) (4)

*As discussed in Section 7d on page 32, the team elected to use an alternative method to assess efficacy that used a responder analysis of each individual patient with a combination endpoint. The combination endpoint included improvements in transaminases, bilirubin and prothrombin time, and resolution of cholestasis on histology, and the clinical outcomes of survival and weight gain. This method was applied post-hoc and while it was not statistically valid, it appeared to be clinically meaningful, and the team adjudicated that this was the best method to evaluate efficacy in this situation.*

*Dr. Gao found evidence of efficacy for the SED population but not the PD population in his application of the method we had devised to the data from the first two trials. However, when the data was submitted for the extension trial (CAC-002-01) (for which there was better data collection), and analyses of the additional data from this trial shows efficacy, by the criteria as outlined above, in 11 of 24 patients with PDs (See discussion of efficacy in the PD population below). This determination of efficacy is based on the combined data from all three trials, including the extension trial data, and shows efficacy with improved transaminase and/or bilirubin in PD patients with baseline cholestasis, or improvements in steatorrhea or coagulopathy. Dr. Gao did agree that there was evidence of efficacy in the SED population. In team discussions, the other members of the clinical team disagreed with Dr. Gao's assessment of individual patient's efficacy data as he was using a different definition of cholestasis that relied on pathology and the rest of the team defined cholestasis as an elevation on serum bilirubin.*

*There was enough data for us to make a determination of efficacy; however there was not enough data to assess dose adjustments that were made during the trial by the investigators' based on FAB-MS of urinary bile acids (see discussion in Section 5b on page 24). The FAB-MS is not a quantitate test*

*The applicant has committed to developing a quantitate test such as liquid or gas chromatography to accurately determine levels of bile acids in samples as a post-marketing commitment (PMC). We will request comparison of quantitate data from bile acids with dose and dose adjustments in the registry trial the applicant will perform as part of the post-marketing safety requirement.*

#### *Discussion of Efficacy in the PD Population*

*During review of this application the team agreed that evidence for efficacy was clear in the SED population; however the evidence was much less clear in the PD population. There was extensive discussion about the data and multiple information requests were sent to the applicant to clarify the issue of efficacy in the PD population. Because PD is rarer than SED there was less data to evaluate and while we knew that many patients with PD were alive from the initial trials we did not have the data on growth in the initial data sets on these patients.*

*It is clear from the data that cholestasis is not as prominent a feature of PD patients as it is with SED patients. Dr. Kim noted in her review that “Compared to the SED, the elevation of peaks from atypical bile acids was generally not as prominent or as consistent in the PD patients. Among subtypes of PD the mass peaks that are characteristics of patients with Zellwegers subtype were relatively prominent and showed a decreasing trend during cholic acid treatment. However, for generalized, neonatal adrenoleukodystrophy and unknown subtypes, the peaks were detectable only in some urine samples before cholic acid treatment.”*

*It is clear that from the mechanism of action of cholic acid that it would be expected to be effective treatment for patients with SEDs and also for patients with PD who had evidence of liver injury, cholestasis, steatorrhea, or fat soluble vitamin malabsorption. However, cholic acid would not be expected to treat the extra- hepatic manifestations of patients with PDs. Therefore, patients who present with severe forms of PD, like severe Zellweger’s syndrome, that have predominately neurologic manifestations, and do not have evidence of cholestasis or hepatic dysfunction, are unlikely to have a clinically meaningful effects from cholic acid. The investigators have* (b) (4)

*Clinical judgment will need to be utilized in treatment decisions and in discussion with patients and caregivers about the expected benefits from cholic acid in patients with PDs.*

*Peroxisomal Disorders have a heterogeneous phenotype and several of the patients in the trial and in literature reports did have prominent hepatic dysfunction/cholestasis, steatorrhea and/or coagulopathy. These patients would be expected to benefit from cholic acid treatment. In addition, some patients with milder phenotypic presentations of PD with longer life expectancy and milder hepatic disease would be expected to benefit from prevention of progression of liver disease.*

*Therefore, it is my opinion that there is evidence of efficacy from the combined trial data, the mechanism of action and literature to support that cholic acid is effective in the SED population and also in PD patients who have evidence of hepatic injury, cholestasis, malabsorption with steatorrhea, or fat soluble vitamin deficiency.*

## **8. Safety**

As noted previously there were significant deficiencies in the safety database for the trial. Adverse events were not collected systematically, and data collection was incomplete. Narrative were requested for the two main trials, however the data in the narrative were also incomplete. At the beginning of the trial the safety evaluation is confounded by the concomitant administration of other bile acids, ursodeoxycholic acid and chenodeoxycholic acid. In addition, there were multiple protocol deviations and rates of “lost-to-follow-up” were high at approximately 22%.

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

Ursodeoxycholic acid (URSO® & URSO Forte®), a secondary bile acid, was approved for the treatment of primary biliary cirrhosis (PBC) in December 1997 (NDA 20-675).

The FDA issued Warnings and Precautions of ursodiol in December 2012, because:

- Animal studies of bile duct obstruction, UDCA induced bile duct infarcts and bile leakage into the surrounding liver tissues.
- A safety database search by the applicant identified 215 case reports: There was a strong temporal relationship between UDCA administration and sharp increases of ALT and AST in patients with biliary obstruction. Withdrawal of UDCA improved the abnormal LFTs. Maintenance of the bile flow also improved the clinical signs.

Labeling:

- 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.

*CDTL Comment:*

*Because of the fact that these two compounds are both bile acids the*

(b) (4)

### Drug Exposure

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 applicant 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.

*CDTL Comment:*

*Drug exposure was adequate to evaluate safety.*

### Deaths

In trial CAC-91-10-10 there were 6 deaths in the SED population (6/50, 12%) and 14 in the PD population (14/29, 48%) with missing narratives in 7 of the 14 deaths.

IN the combined data, among the 62 patients with single enzyme defects, 7 patients died. Six patients were aged 1 year or less, including four patients diagnosed with AKR1D1 deficiency, one with 3 $\beta$ -HSD deficiency and one with CYP7A1 deficiency. In all but 2 patients, the cause of these deaths was attributed to progression of underlying liver disease.

Of the 31 patients with Zellweger spectrum disorders, 16 patients between the ages of 7 months and 8 years died. In the majority of these patients (10/16), the cause of death was attributed to progression of underlying liver disease or to a worsening of their primary illness.

Two additional patients died who had been off study medication for more than one year with the cause of death most likely being a progression of their underlying liver disease. Of the patients who died with hepatic disease progression, laboratory testing showed abnormal serum transaminases, bilirubin, or cholestasis on liver biopsy suggesting worsening of their underlying cholestasis.

#### Adverse Events

Though adverse events were not systematically collected, in the SED population there were 6 patients with evidence of liver disease progression (2/50, 12%) and 4/5 patients (8%) with diarrhea and 3/50 patients (6%) with jaundice/cholestasis. In the PD population the most frequent treatment-emergent adverse events 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%).

“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 underlying diseases and cholic acid overexposure could present with similar biochemical and histological changes as be attributed to “disease progression”.

#### Hepatic Injury

Evidence of liver dysfunction was present before treatment with Cholbam in 66% (41/62) of patients with bile acid synthesis disorders due to single enzyme defects and in 68% (21/31) of patients with Zellweger spectrum disorders. Nine patients with liver dysfunction at baseline experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy following treatment. A single patient who did not have baseline liver dysfunction experienced an exacerbation of their liver disease while on treatment. Exacerbation of liver dysfunction by Cholbam in these patients cannot be ruled out.

#### *CDTL Comment:*

*While disease progression and overdose of cholic acid may be difficult to differentiate, the labeling that instructs that treatment is stopped for evidence of worsening transaminase levels should protect patients from overdosage. In addition, comparison of serum bile acids levels and GGT should help with differentiating the two etiologies.*

*Additionally a post-marking registry study will be required to obtain additional data on this potential safety issue.*

#### Other adverse reactions

The most common adverse reaction on Cholbam was diarrhea, reported in approximately 2% of patients. All other events were reported in 1% of patients: reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp, urinary tract infection, and peripheral neuropathy. Only one of these reactions, peripheral neuropathy, resulted in discontinuation of study medication.

#### Post-Marketing Experience

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.

#### Literature

In the literature, symptomatic overdose was reported in four pediatric patients with bile acid synthesis disorders due to single enzyme defects, including one instance of accidental overdose involving ingestion of 56 mg/kg as a single dose. One patient experienced pruritus, diarrhea and elevations of serum GGT and ALT. Three patients experienced transient elevations of serum GGT and ALT. Reduction of the cholic acid dose led to resolution of the clinical signs and correction of abnormal laboratory parameters.

### **a. Safety Summary**

#### *CDTL Comment:*

*Cholic acid is a normal component of bile and therefore is a relatively safe drug. However, in cases of bile obstruction or reduced bile flow bile acids can have a deleterious detergent effect and should be stopped. Complete bile duct obstruction would be relatively rare in this patient population and not a part of the underlying disease process, such as is seen in diseases like primary biliary cirrhosis. In addition, over dose of bile acids can occur and their use must be monitored by a physician experienced with liver diseases. In addition, a post-marking safety registry study will be conducted as a PMR to assess further signals of hepatic toxicity.*

To mitigate the risk of use the Dosage and Administration section, Treatment Monitoring subsection of product labeling will note that:

- Treatment with Cholbam should be initiated and monitored by an experienced hepatologist or pediatric gastroenterologist;
- Serum transaminases, gamma glutamyltransferase (GGT), alkaline phosphatase, bilirubin and INR should be monitored every month for the first 3 months, every 3 months for the next 9 months, every 6 months during the subsequent three years and annually thereafter. Monitoring should occur more frequently during periods of rapid growth, concomitant disease, and pregnancy. The lowest dose that effectively maintains hepatic function should be used.

- Treatment with Cholbam should be discontinued if hepatic function (i.e., transaminases, bilirubin and clinical picture) does not improve within 3 months of the start of treatment; and
- Treatment with Cholbam should be discontinued at any time if there are clinical or laboratory indicators of worsening hepatic function or cholestasis.

## 9. Advisory Committee Meeting

*No Advisory Committee Meeting was held for this Application.*

## 10. Pediatrics

Bile acid synthesis disorders are rare diseases diagnosed primarily in neonates, infants and young children. The majority of patients in this trial were less than 5 years of age at diagnosis; however some grew into adulthood during the trial. Because this indication has been granted an Orphan Designation, it is exempt from PREA.

The Use in Specific Populations section, Pediatric Use subsection, of the product label will state that the safety and effectiveness of CHOLBAM has been established in pediatric patients 3 weeks of age and older for the treatment of bile acid synthesis disorders due to single enzyme defects and as an adjunct to standard of care in patients with peroxisomal disorders including Zellweger spectrum disorders who exhibit manifestations of liver disease, steatorrhea, fat soluble vitamin deficiency, or a neuropathic process related to a vitamin deficiency.

## 11. Other Relevant Regulatory Issues

The applicant's proposed tradename "Cholbam" is acceptable from both a promotional and safety perspective. The applicant was informed of this determination on February 20, 2014.

Pediatric Rare Disease Voucher

### ***a. Pediatric Rare Disease Voucher***

Section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA) modified the Rare Pediatric Disease Priority Review Voucher Incentive Program to allow the issuance of a "priority review voucher" to the applicant of a rare pediatric disease product application. The holder of such voucher is entitled to priority review of a single human drug application submitted under section 505(b)(1) after the date of approval of the rare pediatric disease product application. Under the statute, 'rare pediatric disease' is defined as:

1. The disease primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.
2. The disease is a rare disease or condition, within the meaning of section 526.

The term “rare pediatric disease product application” means a human drug application that:

1. is for a drug or biological product—
  - a. that is for the prevention or treatment of a rare pediatric disease; and
  - b. that contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of this Act or section 351(a) or 351(k) of the Public Health Service Act;
2. is submitted under section 505(b)(1) of this Act or section 351(a) of the Public Health Service Act;
3. the Secretary deems eligible for priority review;
4. that relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;
5. that does not seek approval for an adult indication in the original rare pediatric disease product application; and
6. is approved after the date of the enactment of the Prescription Drug User Fee Amendments of 2012.

Asklepiion Pharmaceuticals, LLC submitted a Rare Pediatric Disease Voucher Request for Cholbam (cholic acid) capsules on December 9, 2014 (later resubmitted on December 11, 2014) for the (b) (4)

(b) (4)

In a memo dated February 24<sup>th</sup>, 2015, the Office of Orphan Products Development concluded that inborn errors of bile acid metabolism meet the FDASIA definition of a rare pediatric disease. FDA has further determined that the Cholbam NDA submission represents a rare pediatric disease product application as defined above. While Cholbam’s indication encompasses an adult population, it is understood that the indication in the adult population is merely a continuum of the pediatric indication, and does not represent a different adult indication. Therefore, a Priority Review Voucher will be granted at the time of approval, with a tracking number of NDA205750.

## ***b. Facilities Inspections***

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

#### Overall Assessment of Findings and Recommendations per review of Susan Leibenhaut, MD, dated 9/3/2014

“For this application, inspections were conducted at Dr. Heubi’s site, the clinical study site where the study was conducted as an applicant investigator study from 1994 to 2007 and an inspection was conducted at Asklepion Pharmaceuticals, LLC, the applicant / applicant site. The classification of Dr. Hubei’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.”

### OSI Inspection of Study CAC-003-01:

(Sean Kassim, PhD; DARRTS, 10/21/2014)

See discussion above in Section 2 under “Bioequivalence with to-be-marketed formulation”

## **12. Labeling**

There were major edits and changes made to the labeling during the review cycle; however, all major issues have been agreed to by the team and the applicant and the final labeling is under review by the applicant at this date.

The proprietary name is acceptable to the review team and the Carton and container labels are acceptable

## **13. Recommendations/Risk Benefit Assessment**

### ***a. Recommended Regulatory Action***

Regular (full) approval for both populations:

Treatment of Bile Acid Synthesis disorders due to Single Enzyme Defects, and as an adjunct to standard of care for patients with Peroxisomal Disorders including Zellwegers Spectrum Disorders.

### ***b. Risk Benefit Assessment***

The mechanism by which liver injury occurs in this disorder is considered the combined result of inadequate synthesis of primary bile acids needed for the promotion of bile flow, as well as the accumulation of atypical bile acid metabolites. Limited information<sup>2</sup> is available to establish the role of atypical bile acids in clinical manifestation in patients. While the information is limited, the potential contributions of these atypical bile acids to clinical symptoms cannot be ruled out.

Three Center-level briefings were held during the course of this review (September 11, 2014, November 3, 2014 and December 9, 2014) to discuss the applicant's assessment of efficacy and safety of oral cholic acid therapy in patients with disorders of bile acid synthesis, and the approvability of the two indications sought. An FDA advisory committee was not convened as outside expertise was not deemed necessary to address these issues. Action on the application was delayed past the PDUFA goal date of October 21, 2014, so that safety and efficacy information from continuation study CAC-002-01 could be reviewed and described in product labeling.

The Medical Officer Review by Dr. Wen-Yi Gao is in favor of accelerated approval of Cholbam for the SED population but recommends a complete response for the PD population. This reviewer is in favor of full approval for both populations. Please see the summary of the efficacy review in Section 7g on page 54, for a complete discussion of the differences in these recommendations.

The risks of using cholic acid in this population are low, with the risk of worsening of hepatic injury in the PD population being the primary concern. This risk is based mostly on the data from the animal mice model and the paper by Keane et al., It remains theoretical, however there were 2 cases in the trial that could have been consistent with cholic acid induced liver injury, but it is not clear if the deterioration seen in these patients was from underlying severe disease or from cholic acid.

The benefits of cholic acid for the SED population are clear and most patients who were treated early appeared to respond to treatment. The benefits in the PD population appear to be limited to patients who present with evidence of hepatic dysfunction, cholestasis, and steatorrhea from malabsorption of fats and/or fat soluble vitamin malabsorption. Clinical judgment will be necessary in treatment decisions about patients with PDs.

Overall, the risk/benefit evaluation for cholic acid favors regular approval for both populations. A post-marketing registry will be performed as a PMR and will allow collection of more information on dose adjustment and treatment monitoring and will access for safety concerns of increased liver injury.

**c. Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No REMS is required for this product. A post-marketing Registry Study will be performed as part of a PMR

**d. Recommendation for other Postmarketing Requirements and Commitments**

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of worsening cholestasis, steatorrhea leading to poor growth, fat soluble vitamin deficiency, or neuropathic process related to a vitamin deficiency, reduced survival, and adverse effects on pregnancy, pregnancy outcomes, and infant status.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

Postmarketing Requirement:

2882-1

A prospective, long-term, observational study in a routine clinical setting of patients aged 3 weeks or older with bile acid synthesis disorders due to single enzyme defects and patients with peroxisomal disorders, including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, fat soluble vitamin deficiency, or a neuropathic process related to a vitamin deficiency. The purpose of the study is to assess primarily the long term safety of treatment with Cholbam (cholic acid) capsules with respect to incidence rates of worsening cholestasis, steatorrhea leading to poor growth, fat soluble vitamin deficiency, or neuropathic process related to a vitamin deficiency, and the incidence of death and adverse effects on pregnancy, pregnancy outcomes and infant status. Additional evaluations will include dosing regimens and reasons for any dose modifications, weight gain, length/height and developmental outcomes. Specify concise case definitions and validation algorithms for all outcomes. Enroll at least 55 patients (25 receiving cholic acid and 30 not receiving cholic acid) including at least 20 peroxisomal disorder patients, with liver dysfunction, steatorrhea, fat soluble vitamin deficiency or a neuropathic process related to the latter. Enroll over an initial 3-year period and follow for a minimum of 10 years from the time of enrollment or until death, whichever comes first.

Final Protocol Submission: September 2015  
Study Completion: September 2028  
Final Report Submission: March 2029

Cross Discipline Team Leader Review  
NDA 205-750 – Cholic Acid  
Lara Dimick-Santos, MD

Post-Marketing Commitment:

2882-2 Develop a quantitative urinary bile acid analysis assay method along with standards for bile acid synthesis disorders.

Final Report Submission: March 2017

***e. Recommended Comments to Applicant***

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LARA DIMICK-SANTOS  
03/17/2015