CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205750Orig1s000

STATISTICAL REVIEW(S)

Statistical Review Memorandum

Submission: NDA 205750

Product: CHOLBAM™ (cholic acid) 10-15 mg/kg/day to be administered orally, preferably with food, as 250 mg or 50 mg capsules

Sponsor: Asklepion Pharmaceuticals, LLC

Indication: [redacted]

Medical Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

1 INTRODUCTION

The purpose of this memorandum is to document the statistical reviewer's support to the Division of Gastroenterology and Inborn Errors Products (DGIEP) during the review cycle of NDA 205-750. The clinical efficacy and safety of cholic acid has been primarily evaluated under a single-center, open-label and non-randomized study in treatment naïve patients with inborn errors of bile acid metabolism, and, consequently, no formal statistical review was warranted. However, the reviewer did provide important contributions to the division review team, and these activities are described below.

2 BACKGROUND

On November 21, 2013, Asklepion Pharmaceuticals, LLC submitted this New Drug Application (NDA) for cholic acid in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Title 21 of the Code of Federal Regulations, Part 314. This NDA was later identified by the Division of Gastroenterology and Inborn Errors Products (DGIEP) as a 505(b)(2) submission. Cholic acid is indicated for the treatment of patients with [redacted] a rare, serious, and life threatening condition with an unmet medical need. Cholic acid is to be administered 10-15 mg/kg/day orally, preferably with food, as 250 mg or 50 mg capsules. The capsules are typically sprinkled into food for younger patients who cannot swallow capsules. The active pharmaceutical ingredient (API) of cholic acid is 3α, 7α, 12α-trihydroxy-5ß-cholanic acid which is a white or cream-colored odorless [redacted] powder.

The cholic acid research program began in 1992 as an academic project initiated by James E. Heubi, MD, and Kenneth D. R. Setchell, PhD, at the Cincinnati Children's Hospital Medical Center (CCHMC) located in Cincinnati, Ohio, USA, for the diagnosis and treatment of inborn errors of bile acid synthesis and peroxisomal disorders affecting bile acid metabolism. This was essentially a compassionate use program, and there was no expectation at that time of developing cholic acid as a commercially available drug. Drs. Heubi and Setchell submitted an investigator Investigational New Drug application (under IND 45,470) in June 1994, and evaluated the benefits of cholic acid in their pediatric patients at CCHMC under treatment protocols with Institutional Review Board (IRB) approval. Investigator IND 45,470 was initially managed by R&R Registrations (the agent for Dr. Heubi), but was later transferred to Asklepion Pharmaceuticals, LLC in May 2007. Drs. Heubi and Setchell continued to treat patients under this IND after the transfer to Asklepion. At present, there is no medical product specifically approved in the US for the treatment of inborn errors causing primary defects in bile acid synthesis. The applicant obtained Orphan Designation for cholic acid treatment of patients with inborn errors of cholesterol and bile acid synthesis and metabolism from the Office of Orphan Products Development (OOPD) in 2007. This rare condition has an estimated prevalence of less than 100 total patients in the US.

Patients with inborn errors of bile acid synthesis lack the enzymes needed to produce the primary bile acids, i.e., cholic acid and chenodeoxycholic acids (CDCA). This investigational treatment's aim is to supplement the body directly with cholic acid in order to prevent downstream physiological issues caused by its absence due to the enzyme deficiency. The absence of cholic acid in the body results in the diminished production of primary bile, which is essential for promoting bile flow, and the concomitant production of high concentrations of atypical bile acids and bile acid intermediates. Several of these unusual bile acids have been theorized to be hepatotoxic, and one has been shown to be hepatotoxic in an animal model. The liver disease associated with these inborn errors in bile acid synthesis is progressive in some patients and, if untreated, may lead to death from cirrhosis and liver failure.

There were a series of communications and meetings between the applicant and the Division of Gastroenterology and Inborn Errors Products (DGIEP) prior to the submission of this NDA. The most pertinent industry meetings are as follows: A Type C advice meeting was held on December 6, 2007 for issues pertaining to the lack of a control group in the applicant's main clinical safety and efficacy study, CAC-91-10-10. A Pre-NDA meeting was held on January 25, 2010 where the division stated that the applicant must provide more convincing data to support the effectiveness of cholic acid while reiterating the need for a control group. DGIEP specifically communicated to Asklepion that their uncontrolled study could not be considered adequate and well-controlled. DGIEP suggested that Asklepion utilize an adequate historical control group for comparison to the patients treated by Drs. Heubi and Setchell. Almost two and a half years later on July 25, 2012, a final Type C advice meeting was held in which the applicant finally committed to acquiring a historical control group for their study. On November 21, 2013, Asklepion submitted the NDA under the PDUFA V Program. This is a priority review; however, the review cycle was extended primarily due to clinical issues, and has continued beyond the original PDUFA goal date of October 21, 2014. The new PDUFA goal date is March 17, 2015.

Due to the rare nature of this orphan indication and the difficulty in identifying patients, this application includes data from one main clinical safety and efficacy study, CAC-91-10-10, which corresponds to the treatment protocol under Drs. Heubi and Setchell at CCHMC. The clinical efficacy and safety of cholic acid has been primarily evaluated under this protocol which was a single-center, open-label and non-randomized study in treatment naïve patients with inborn errors of bile acid metabolism. Asklepion did submit historical control group information, based on a retrospective literature review, within this NDA. Ultimately, this submitted historical control group was deemed inadequate by the review team during the NDA review cycle due to the fact that these subjects were discovered to not match the treated patients in regards to disease diagnosis along with relevant demographics and baseline characteristics. Data from currently ongoing extension study CAC-002-01, in which roll over patients from the CAC-91-10-10 trial continued receiving cholic acid therapy, was also submitted for supportive purposes. Table 1 below presents information on the CAC-91-10-10 and CAC-002-01 studies.

This NDA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Drug Evaluation and Research (CDER) electronic document room (EDR) at the following locations: \\CDSESUB1\evsprod\NDA205750\0000 and \\CDSESUB1\evsprod\NDA205750\0002. Sequences 0000, 0002, 0012, 0013, 0014, 0016, 0018, 0020, 0021, 0024, 0026, 0028, 0030, 0034, 0035, 0037, 0045, 0050 and 0054 contain all the contents examined by the primary reviewer.

The clinical study report (CSR), clinical/tabulation datasets and analysis datasets were reviewed for the CAC-91-10-10 and CAC-002-01 studies. The clinical/tabulation datasets and analysis datasets for each study were not compliant to CDISC standards. Sufficient data definition files (in define.xml and define.pdf formats) were also submitted for these studies.

Table 1
Summary Information for Relevant Clinical Trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Status/ Type of Report
Treatment Protocol	CAC-91-10-10	To treat patients with inborn errors of bile acid metabolism using Cholic Acid. Later changed to evaluate the therapeutic efficacy, safety and tolerability of Cholic Acid for treating patients with inborn errors of bile acid metabolism.	Single-center, Open-label, Non-randomized, Historical control (from a retrospective literature review)	Cholic Acid; 10-15 mg/kg/day; 250 mg or 50 mg capsules administered orally, preferably with food	Total: 85	Patients with inborn errors of bile acid metabolism	Up to 10.5 years	Complete/ Full
Treatment Protocol	CAC-002-01	To evaluate the therapeutic efficacy and safety of cholic acid in patients with identified inborn errors of bile acid metabolism.	Single-center, Open-label, Non-randomized	Cholic Acid; 10-15 mg/kg/day; 250 mg or 50 mg capsules administered orally, preferably with food	Total: 41 Roll Over: 31 De Novo: 10	Patients with inborn errors of bile acid metabolism	Open-ended	Ongoing/ Interim

Source: Reviewer's Table.

3 STATISTICAL REVIEW SUPPORT PROVIDED

As stated previously, the cholic acid research program under study CAC-91-10-10 began in 1992 as an Investigator IND. However, this study was originally a treatment protocol, which would have been conducted under an expanded access IND if compassionate use regulatory pathways existed during that time period. The previously described study design was a consequence of the initial objective of the investigators, and, hence, this individual clinical study was identified as not being the proper basis for traditional confirmatory efficacy review and subsequent labeling purposes. The submitted study results, including those from extension study CAC-002-01, were considered descriptive or observational only as they did not rely on appropriate inferential statistics or trial designs that would be considered adequate and well-controlled to support specific endpoint testing. It should be noted that the rarity of this disease would have made a randomized controlled trial impractical even if that was to be the original objective of the study.

At the time of filing, we considered this application as 'No Action Indicated'. The primary statistical reviewer was available to the clinical review team for support as needed to address specific questions or concerns that would require response. The primary statistical reviewer helped the clinical review team appropriately formulate their information requests (IRs) so that they could obtain useful descriptive statistics for the efficacy parameters of interest (i.e., acquiring median pre-treatment to median post-treatment data along with last pre-treatment to last post-treatment data on urinary bile acids, ALT/AST, bilirubin, and height/weight). The primary statistical reviewer also helped the clinical team obtain mortality data for comparisons between the study patients from CAC-91-10-10 and the historical control group produced by the applicant from a retrospective literature review, as previously described. This work included participation in teleconferences (TCs) between the applicant and the clinical review team. Table 2 below presents the specific IRs and TCs that involved the primary statistical reviewer's participation and contribution. The most important contribution by the primary statistical reviewer was in regard to helping the clinical review team identify a subpopulation of patients that best responds to cholic acid therapy and confirming the responder status, as defined by the responder criteria listed in the CDTL review, by Dr. Lara Dimick-Santos, in those patients. This was done by helping the clinical review team interpret results from the IRs presented in Table 2. Further support was given to identify additional issues pertaining to the historical control group along with overall study execution. The primary statistical reviewer continued to assist the clinical review team as needed during the review cycle.

It should be noted that the primary statistical reviewer also helped the overall review team identify and subsequently contend with major data quality issues (i.e., large amounts of missing/unavailable data) inherent within this marketing application. All available CAC-91-10-10 data was captured on patient charts with no quality control/quality assurance mechanisms in place such as 21 CFR 11 compliant data management practices and institutional study monitoring along with other aspects of Good Clinical Practice (GCP). And due to the fact that study CAC-91-10-10 was not a traditional protocol with a formal visit schedule, most of the available data were sparse in nature.

In May 2007 when the IND was transferred to Asklepion, proper auditing and monitoring of the study immediately began. A Paper Care Report Form (CRF) was retrospectively created by the applicant to represent data fields which were originally planned to be captured by the Investigator study. Available data from participating patient charts were then transcribed onto the CRF and subsequently entered into the applicant's 21 CFR 11 compliant clinical data management system (CDMS) where data cleaning ensued. The applicant could not resolve the unavailable data issue due to the inherent nature of the study itself as described above. In addition, patient chart data mismanaged by the CCHMC site staff during the 15 years between 1992 and 2007 were also lost and hence could not be entered into the clinical database. Note that the Office of Scientific Investigation (OSI) confirmed the preponderance of these data quality issues during their field inspections of the CCHMC site during the review cycle.

The database hard-lock for study CAC-91-10-10 was on January 24, 2012. The applicant has stated in the CAC-91-10-10 CSR that these data quality issues were significant, and that they attempted to reconcile those issues that could be resolved. However, they also state that many of these data issues were ultimately unresolvable. Data quality, availability, and reliability were major review issues, which negatively affected study data interpretability. It should be emphasized that all reported CAC-91-10-10 trial results by the applicant should be interpreted with caution due to the nature of the data quality issues.

Table 2
Primary Statistical Reviewer's Participation and Contribution

IR / TC	IR Send Date / Receipt Date (eCTD sequence) Or Date of TC	Contribution
IR: • Comparative analyses between study patients and the historical control group in regard to efficacy parameters (i.e., urinary bile acids, ALT/AST, bilirubin, height/weight). • Analysis of urinary bile acids and ALT/AST as continuous data. • Analysis of (b) (4) median-to-median, mean-to-mean, and last pre-treatment to last post-treatment for all continuous efficacy parameters.	March 5, 2014 / April 4, 2014 (0014)	Wrote the language for the IR with the help of the statistical team leader.
TC to discuss IR made on March 5, 2014.	March 14, 2014	Participated in the TC in order to gain consensus that it would not be feasible to conduct a comparative analysis of the efficacy parameters of interest between the study patients and those from the historical control group due to the lack of available data from the historical control group.
IR for analysis of median-to-median and last pre-treatment to last post-treatment for direct bilirubin, indirect bilirubin, and total bilirubin.	April 10, 2014 / April 25, 2014 (0016)	Helped the clinical review team write the language for the IR.
IR for additional analyses of bilirubin.	April 25, 2014 / May 2, 2014 (0018)	Helped the clinical review team write the language for the IR.

Source: Reviewer's Table.

Table 2 continued:

IR / TC	IR Send Date / Receipt Date (eCTD sequence) Or Date of TC	Contribution
TC to discuss IR made on April 25, 2014.	May 2, 2014	Participated in the TC in order to request that the applicant present the bilirubin results (delivered on May 2, 2014) in the same way as those presented for ALT/AST and height/weight. Note that the resubmission of the subsequent bilirubin results was made on May 6, 2014.
IR for mortality and time-to-death analyses between the study patients and those from the historical control group, specifically the single enzyme defect (SED) patients.	May 15, 2014 / May 23, 2014; June 6, 2014 (0021; 0024)	Helped the clinical review team write the language for the IR.
IR for mortality and time-to-death analyses between the study patients and those from the historical control group, specifically the peroxisomal disease (PD) patients.	June 6, 2014 / June 20, 2014 (0026)	Helped the clinical review team write the language for the IR.
IR for mortality and time-to-death analyses between the study patients and those from the historical control group, specifically subsets of the SED and PD patients. Additional analysis requests made for these study patients in regard to ALT/AST, bilirubin, and height/weight.	June 24, 2014 / July 7, 2014 (0028)	Helped the clinical review team write the language for the IR.
IR for ALT/AST, bilirubin, and height/weight analyses of additional subsets of the SED and PD study patients.	June 30, 2014 / August 8, 2014 (0030)	Helped the clinical review team write the language for the IR.
IR for graphical patient profiles.	August 18, 2014 / September 10 and 12, 2014; October 22, 2014 (0034; 0035; 0037)	Helped the clinical review team write the language for the IR.

Source: Reviewer's Table.

Table 2 continued:

IR / TC	IR Send Date / Receipt Date (eCTD sequence) Or Date of TC	Contribution
IR: (1) Interim CSR for ongoing extension study CAC-002-01. (2) Responder analysis for all patients participating in the CAC-91-10-10 and CAC-002-01 studies. (3) Datasets supporting the aforementioned responder analysis.	(1) December 19 and 23, 2014 / January 7, 2015 (0045) (2) January 21 and 23, 2015/ February 13, 2015 (0050) (3) March 1 and 3, 2015 / March 6, 2015 (0054)	Confirmed the responder analysis results for SED and PD patients presented by the applicant along with results independently assessed by Dr. Julie Beitz (Signatory) and Dr. Lara Dimick-Santos (CDTL).

Source: Reviewer's Table.

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/s/

BEHRANG VALI
03/11/2015

MICHAEL E WELCH
03/12/2015
This is an updated version of the memorandum filed on 2/13/2015.

Statistical Review Memorandum

Submission: NDA 205750

Product: CHOLBAM™ (cholic acid) 10-15 mg/kg/day to be administered orally, preferably with food, as 250 mg or 50 mg capsules

Sponsor: Asklepion Pharmaceuticals, LLC

Indication: [redacted] (b) (4)

Medical Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

1 INTRODUCTION

The purpose of this memorandum is to document the statistical reviewer's support to the Division of Gastroenterology and Inborn Errors Products (DGIEP) during the review cycle of NDA 205-750. The clinical efficacy and safety of cholic acid has been primarily evaluated under a single-center, open-label and non-randomized study in treatment naïve patients with inborn errors of bile acid metabolism, and, consequently, no formal statistical review was warranted. However, the reviewer did provide important contributions to the division review team, and these activities are described below.

2 BACKGROUND

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The cholic acid research program began in 1992 as an academic project initiated by James E. Heubi, MD, and Kenneth D. R. Setchell, PhD, at the Cincinnati Children's Hospital Medical Center (CCHMC) located in Cincinnati, Ohio, USA, for the diagnosis and treatment of inborn errors of bile acid synthesis and peroxisomal disorders affecting bile acid metabolism. This was essentially a compassionate use program, and there was no expectation at that time of developing cholic acid as a commercially available drug. Drs. Heubi and Setchell submitted an investigator Investigational New Drug application (under IND 45,470) in June 1994, and evaluated the benefits of cholic acid in their pediatric patients at CCHMC under treatment protocols with Institutional Review Board (IRB) approval. Investigator IND 45,470 was initially managed by R&R Registrations (the agent for Dr. Heubi), but was later transferred to Asklepion Pharmaceuticals, LLC in May 2007. Drs. Heubi and Setchell continued to treat patients under this IND after the transfer to Asklepion. At present, there is no medical product specifically approved in the US for the treatment of inborn errors causing primary defects in bile acid synthesis. The applicant obtained Orphan Designation for cholic acid treatment of patients with inborn errors of cholesterol and bile acid synthesis and metabolism from the Office of Orphan Products Development (OOPD) in 2007. This rare condition has an estimated prevalence of less than 100 total patients in the US.

Patients with inborn errors of bile acid synthesis lack the enzymes needed to produce the primary bile acids, i.e., cholic acid and chenodeoxycholic acids (CDCA). This investigational treatment's aim is to supplement the body directly with cholic acid in order to prevent downstream physiological issues caused by its absence due to the enzyme deficiency. The absence of cholic acid in the body results in the diminished production of primary bile, which is essential for promoting bile flow, and the concomitant production of high concentrations of atypical bile acids and bile acid intermediates. Several of these unusual bile acids have been shown to be hepatotoxic. The liver disease associated with these inborn errors in bile acid synthesis is progressive and, if untreated, may lead to death from cirrhosis and liver failure.

There were a series of communications and meetings between the applicant and the Division of Gastroenterology and Inborn Errors Products (DGIEP) prior to the submission of this NDA. The most pertinent industry meetings are as follows: A Type C advice meeting was held on December 6, 2007 for issues pertaining to the lack of a control group in the applicant's lone clinical safety and efficacy study, CAC-91-10-10. A Pre-NDA meeting was held on January 25, 2010 where the division stated that the applicant must provide more convincing data to support the effectiveness of cholic acid while reiterating the need for a control group. DGIEP specifically communicated to Asklepion that their uncontrolled study could not be considered adequate and well-controlled. DGIEP suggested that Asklepion utilize an adequate historical control group for comparison to the patients treated by Drs. Heubi and Setchell. Almost two and a half years later on July 25, 2012, a final Type C advice meeting was held in which the applicant finally committed to acquiring a historical control group for their study. On November 21, 2013, Asklepion submitted the NDA under the PDUFA V Program. This is a priority review; however, the review cycle was extended primarily due to clinical issues, and has continued beyond the original PDUFA goal date of October 21, 2014. The new PDUFA goal date is March 5, 2015.

Due to the rare nature of this orphan indication and the difficulty in identifying patients, this application includes data from only one clinical safety and efficacy study, CAC-91-10-10, which corresponds to the primary treatment protocol under Drs. Heubi and Setchell at CCHMC. The clinical efficacy and safety of cholic acid has been primarily evaluated under this protocol which was a single-center, open-label and non-randomized study in treatment naïve patients with inborn errors of bile acid metabolism. Asklepion did submit historical control group information, based on a retrospective literature review, within this NDA. Ultimately, this submitted historical control group was deemed inadequate by the review team during the NDA review cycle due to the fact that these subjects were discovered to not match the treated patients in regards to disease diagnosis along with relevant demographics and baseline characteristics. Table 1 below presents information on the CAC-91-10-10 study.

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The clinical study report (CSR), clinical/tabulation datasets and analysis datasets were reviewed for the CAC-91-10-10 study. The clinical/tabulation datasets and analysis datasets were not compliant to CDISC standards. Sufficient data definition files (in define.xml and define.pdf formats) were also submitted for this study.

Table 1
Summary Information for Relevant Clinical Trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment
Treatment Protocol	CAC-91-10-10	To treat patients with inborn errors of bile acid metabolism using Cholic Acid. Later changed to evaluate the therapeutic efficacy, safety and tolerability of Cholic Acid for treating patients with inborn errors of bile acid metabolism.	Single-center, Open-label, Non-randomized, Historical control (from a retrospective literature review)	Cholic Acid; 10-15 mg/kg/day; 250 mg or 50 mg capsules administered orally, preferably with food	Total: 85	Patients with inborn errors of bile acid metabolism	Up to 10.5 years

Source: Reviewer's Table.

3 STATISTICAL REVIEW SUPPORT PROVIDED

As stated previously, the cholic acid research program under study CAC-91-10-10 began in 1992 as an Investigator IND. However, this study was originally a treatment protocol, which would have been conducted under an expanded access IND if compassionate use regulatory pathways existed during that time period. The previously described study design was a consequence of the initial objective of the investigators, and, hence, this individual clinical study was identified as not being the proper basis for traditional confirmatory efficacy review and subsequent labeling purposes. The submitted study results were considered descriptive or observational only as they did not rely on appropriate inferential statistics or trial designs that would be considered adequate and well-controlled to support specific endpoint testing. It should be noted that the rarity of this disease would have made a randomized controlled trial impractical even if that was to be the original objective of the study.

At the time of filing, we considered this application as 'No Action Indicated'. The primary statistical reviewer was available to the clinical review team for support as needed to address specific questions or concerns that would require response. The primary statistical reviewer helped the clinical review team appropriately formulate their information requests (IRs) so that they could obtain useful descriptive statistics for the efficacy parameters of interest (i.e., acquiring median pre-treatment to median post-treatment data along with last pre-treatment to last post-treatment data on urinary bile acids, ALT/AST, bilirubin, and height/weight). The primary statistical reviewer also helped the clinical team obtain mortality data for comparisons between the study patients from CAC-91-10-10 and the historical control group produced by the applicant from a retrospective literature review, as previously described. This work included participation in teleconferences (TCs) between the applicant and the clinical review team. Table 2 below presents the specific IRs and TCs that involved the primary statistical reviewer's participation and contribution. The most important contribution by the primary statistical reviewer was in regard to helping the clinical review team identify a subpopulation of patients that best responds to cholic acid therapy. This was done by helping the clinical review team interpret results from the IRs presented in Table 2. Further support was given to identify additional issues pertaining to the historical control group along with overall study execution. The primary statistical reviewer continued to assist the clinical review team as needed during the review cycle.

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Table 2
Primary Statistical Reviewer's Participation and Contribution

IR / TC	IR Send Date / Receipt Date (eCTD sequence) Or Date of TC	Contribution
IR: • Comparative analyses between study patients and the historical control group in regard to efficacy parameters (i.e., urinary bile acids, ALT/AST, bilirubin, height/weight). • Analysis of urinary bile acids and ALT/AST as continuous data. • Analysis of (b) (4) median-to-median, mean-to-mean, and last pre-treatment to last post-treatment for all continuous efficacy parameters.	March 5, 2014 / April 4, 2014 (0014)	Wrote the language for the IR with the help of the statistical team leader.
TC to discuss IR made on March 5, 2014.	March 14, 2014	Participated in the TC in order to gain consensus that it would not be feasible to conduct a comparative analysis of the efficacy parameters of interest between the study patients and those from the historical control group due to the lack of available data from the historical control group.
IR for analysis of median-to-median and last pre-treatment to last post-treatment for direct bilirubin, indirect bilirubin, and total bilirubin.	April 10, 2014 / April 25, 2014 (0016)	Helped the clinical review team write the language for the IR.
IR for additional analyses of bilirubin.	April 25, 2014 / May 2, 2014 (0018)	Helped the clinical review team write the language for the IR.

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IR for mortality and time-to-death analyses between the study patients and those from the historical control group, specifically the single enzyme defect (SED) patients.	May 15, 2014 / May 23, 2014; June 6, 2014 (0021; 0024)	Helped the clinical review team write the language for the IR.
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IR for mortality and time-to-death analyses between the study patients and those from the historical control group, specifically subsets of the SED and PD patients. Additional analysis requests made for these study patients in regard to ALT/AST, bilirubin, and height/weight.	June 24, 2014 / July 7, 2014 (0028)	Helped the clinical review team write the language for the IR.
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IR for graphical patient profiles.	August 18, 2014 / September 10 and 12, 2014; October 22, 2014 (0034; 0035; 0037)	Helped the clinical review team write the language for the IR.

Source: Reviewer's Table.

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/s/

BEHRANG VALI
02/13/2015

MICHAEL E WELCH
02/13/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA

NDA Number: 205750	Applicant: Asklepion Pharmaceuticals, LLC	Stamp Date: NOV 21, 2013
Drug Name: Cholic Acid 50 mg and 250 mg	NDA Type: 505(b)(2) New Molecular Entity (NME) Priority	Indication: (b) (4) [redacted]

On **initial** overview of the NDA application for filing:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			This electronic submission was eCTD compliant and of sufficient quality.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			There was an adequate ICH E3 compliant clinical study report (CSR) submitted for study CAC-91-10-10. Separate ISS and ISE reports were also submitted.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).		X		Subgroup analyses for Gender, Race, and Age were not presented for study CAC-91-10-10. All patients were less than 18 years of age while a large proportion of these patients were Caucasian. An information request for separate gender and race subgroup analyses will be issued.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			All data sets provided were of sufficient quality but were not compliant with CDISC data standards (i.e. SDTM and ADaM). Raw bile acid measurements were not included in the data sets, and a subsequent information request for this data will be sent to the applicant by the clinical review team. Sufficient data definition files in Define.XML and Define PDF format were included.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

STATISTICS FILING CHECKLIST FOR A NEW NDA

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The design utilized for study CAC-91-10-10 appeared appropriate given the prevalence of this rare disease.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			For the CAC-91-10-10 study, the endpoints and corresponding methods of analysis were specified in the protocol and Statistical Analysis Plan (SAP).
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	There was no formal interim analysis planned for the CAC-91-10-10 study.
Appropriate references for novel statistical methodology (if present) are included.			X	The statistical methodology in the CAC-91-10-10 study was not novel hence no references were presented.
Safety data organized to permit analyses across clinical trials in the NDA.	X			Safety data sets were submitted for each study individually. In addition, ISS data sets were also submitted.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			The applicant's investigation of the effect of dropouts on the statistical analyses appeared adequate for the CAC-91-10-10 study.

Background

On November 21, 2013, Asklepion Pharmaceuticals, LLC submitted this New Drug Application (NDA) for cholic acid in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Title 21 of the Code of Federal Regulations, Part 314. This NDA was later identified by the Division of Gastroenterology and Inborn Errors Products (DGIEP) as a 505(b)(2) submission. Cholic acid is indicated for the treatment of patients with (b) (4) a rare, serious, and life threatening condition with an unmet medical need. Cholic acid is to be administered 10-15 mg/kg/day orally, preferably with food, as 250 mg or 50 mg capsules. The active pharmaceutical ingredient (API) of cholic acid is 3α, 7α, 12α-trihydroxy-5ß-cholanic acid which is a white or cream-colored odorless (b) (4) powder.

The cholic acid research program began as an academic project initiated by James E. Heubi, MD, and Kenneth D. R. Setchell, PhD, at the Cincinnati Children's Hospital Medical Center

(CCHMC) located in Cincinnati, Ohio, USA, for the diagnosis and treatment of inborn errors of bile acid synthesis and peroxisomal disorders affecting bile acid metabolism. There was no expectation at that time of developing cholic acid as a commercially available drug. Drs. Heubi and Setchell submitted an Investigational New Drug application (under IND 45,470) in June 1994, and evaluated the benefits of cholic acid in their pediatric patients at CCHMC under treatment protocols with Institutional Review Board (IRB) approval. IND 45,470 was subsequently transferred to Asklepion Pharmaceuticals, LLC in May 2007, and Drs. Heubi and Setchell continued to treat patients under this IND. At present, there is no medical product specifically approved in the USA for the treatment of inborn errors causing primary defects in bile acid synthesis. In 2007, FDA granted Orphan Product designation for this rare condition with a prevalence estimated to be less than 100 total patients in the USA.

Patients with inborn errors of bile acid synthesis lack the enzymes needed to produce the primary bile acids, i.e., cholic acid and chenodeoxycholic acids (CDCA). This investigational treatment's aim is to supplement the body directly with cholic acid in order to prevent downstream physiological issues caused by its absence due to the enzyme deficiency. The absence of cholic acid in the body results in the diminished production of primary bile, which is essential for promoting bile flow, and the concomitant production of high concentrations of atypical bile acids and bile acid intermediates. Several of these unusual bile acids have been shown to be hepatotoxic. The liver disease associated with these inborn errors in bile acid synthesis is progressive and, if untreated, may lead to death from cirrhosis and liver failure.

This NDA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Drug Evaluation and Research (CDER) electronic document room (EDR) at the following locations: \\CDSESUB1\evsprod\NDA205750\0000 and \\CDSESUB1\evsprod\NDA205750\0002.

Brief Overview and Summary of Relevant Trials

Due to the rare nature of this orphan indication and the difficulty in identifying patients, this application includes data from only one clinical safety and efficacy study, CAC-91-10-10, which corresponds to the primary treatment protocol under Drs. Heubi and Setchell at CCHMC. The clinical efficacy and safety of cholic acid has been primarily evaluated under this investigational protocol for a phase 3, single-center, open-label and non-randomized study in treatment naïve patients with inborn errors of bile acid metabolism. Note that since this investigational study was originally a treatment protocol, as explained above, the study was not designed with a control group. When Asklepion met with DGIEP at the pre-NDA meeting on January 25, 2010, DGIEP specifically communicated to Asklepion that this uncontrolled study could not be considered adequate and well-controlled. DGIEP suggested that Asklepion utilize an adequate historical control group for comparison to the patients treated by Drs. Heubi and Setchell. Asklepion agreed and has submitted their historical control group information within this NDA.

The submitted clinical/tabulation data sets and analysis data sets were of sufficient quality although not compliant to CDISC data standards. Raw bile acid measurements were not included in the data sets, and a subsequent information request for this data will be sent to the applicant by the clinical review team. Sufficient data definition files (in define.xml and define.pdf formats) were also submitted for this study. The following table presents some information on the CAC-91-10-10 study.

STATISTICS FILING CHECKLIST FOR A NEW NDA

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment
Safety and Efficacy; Phase 3	CAC-91-10-10	To evaluate the therapeutic efficacy of cholic acid to treat patients with identified inborn errors of bile acid metabolism. To assess safety and tolerability of cholic acid in this population.	Single-center, Open-label, Non-randomized, Historical control	Cholic Acid; 10-15 mg/kg/day in divided doses; 250 mg capsules or 15 mg/ml liquid administered orally	Total: 85	Patients with inborn errors of bile acid metabolism	Up to 10.5 years

Review Issues

Additional review issues may be reflected in the final statistical review document and subsequent information requests to the applicant. One initial statistical information request to the Applicant for the 74-day letter is as follows:

For Study CAC-91-10-10, provide separate subgroup efficacy analyses by gender and by race for the primary efficacy variables. For the subgroup efficacy analysis by race, there should be three subgroups analyzed: Whites, Non-Whites, and Unknown.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEHRANG VALI
01/17/2014

FREDA COONER
01/17/2014