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RESEARCH**

APPLICATION NUMBER:

205750Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW ADDENDUM
Office of New Drug Quality Assessment

Application No.:	NDA 205-750	Reviewer: Kareen Riviere, Ph.D.	
Submission Date:	11/21/13; 1/31/14; 2/21/14; 6/6/14		
Division:	DGIEP	Secondary Signature: Tapash Ghosh, Ph.D.	
Applicant:	Askelpion Pharmaceuticals, LLC	Supervisor: Paul Seo, Ph.D.	
Trade Name:	Cholbam	Date Assigned:	11/27/13
Generic Name:	cholic acid	Date of Review:	12/5/14
Indication:	[REDACTED] (b) (4)	Type of Submission: 505(b)(2) NDA	
Formulation/strengths:	IR Capsules/ 50 mg and 250 mg		
Route of Administration:	Oral		

The Applicant conducted a Phase I study (Study CAC-003-01) titled “Comparative Bioavailability of Three Formulations of Cholic Acid in Healthy Male Subjects Using a Multiple Dose Repeated Measures Approach”. The objectives of the study were to evaluate the relative bioavailability/bioequivalence and pharmacokinetics of multiple oral doses of a new cGMP produced cholic acid capsule formulation in comparison to a previously used pharmacy capsule formulation and an oral solution or suspension (250 mg) in 18 healthy male volunteers.

In the Biopharmaceutics review dated June 26, 2014, Dr. Kareen Riviere noted several issues with the design and conduct of Study CAC-003-01 that are concerning [REDACTED] (b) (4)

In the OSI inspection report for Study CAC-003-01 dated September 23, 2014, Drs. Gajendiran Mahadevan and Young Moon Choi stated:

Following the inspections and review of the firm’s responses, the data from study CAC-003-01 were found not to be reliable. Therefore, these DBGLPC reviewers recommend that the data not be accepted for Agency review since the authenticity of the data cannot be assured [REDACTED] (b) (4)

This OSI inspection report validates the concerns expressed in Dr. Riviere’s review regarding Study CAC-003-01. However, as recommended previously in Dr. Riviere’s review dated June 26, 2014 “although BE Study CAC-003-01 study is not acceptable to bridge the pharmacy and to-be marketed formulations, it can be used as evidence of bioavailability of the to-be marketed formulation. Also, phase 3 Study CAC-001-01 can be used for purposes of demonstrating bioavailability or bioequivalence of the proposed drug product. Thus, due to the unmet public health need of this drug product, phase 3 Study CAC-001-01 is deemed adequate to support the bridging of the pharmacy and to-be marketed formulations”.

In summary, even without a valid outcome of Study CAC-003-01, NDA 205750 for Cholbam (cholic acid) 50 mg and 250 mg immediate release capsules is recommended for approval from a Biopharmaceutics perspective based on the data in phase 3 Study CAC-001-01.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Paul Seo

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/s/

KAREEN RIVIERE
12/05/2014

TAPASH K GHOSH
12/05/2014

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	205-750	Reviewer: Kareen Riviere, Ph.D.	
Submission Date:	11/21/13; 1/31/14; 2/21/14; 6/6/14		
Division:	DGIEP	Secondary Signature: Tapash Ghosh, Ph.D.	
Applicant:	Askelpion Pharmaceuticals, LLC	Supervisor: Richard Lostritto, Ph.D.	
Trade Name:	Cholbam	Date Assigned:	11/27/13
Generic Name:	cholic acid	Date of Review:	7/24/14
Indication:	(b) (4)	Type of Submission: 505(b)(2) NDA	
Formulation/strengths:	IR Capsules/ 50 mg and 250 mg		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(2) New Drug Application for 50 mg and 250 mg of Cholbam (cholic acid). The proposed indication is (b) (4).

The Biopharmaceutics information in this submission includes a drug product development section with the proposed dissolution method, the proposed dissolution acceptance criterion, dissolution data supporting the Level 3 drug product manufacturing site change, and the relative bioavailability study comparing the pharmacy and commercial formulation.

A. BE Study Comparing the Pharmacy and Commercial Formulation

The title of the Phase I study (Study CAC-003-01) is "Comparative Bioavailability of Three Formulations of Cholic Acid in Healthy Male Subjects Using a Multiple Dose Repeated Measures Approach". The objectives of the study were to evaluate the relative bioavailability/bioequivalence and pharmacokinetics of multiple oral doses of a new cGMP produced cholic acid capsule formulation in comparison to a previously used pharmacy capsule formulation and an oral solution or suspension (250 mg) in 18 healthy male volunteers.

This reviewer noted several issues with the design and conduct of Study CAC-003-01 that are concerning (b) (4)

Additionally, this study indicates that the 250 mg pharmacy capsule formulation and the 250 mg strength to-be marketed capsule formulation are not bioequivalent. The 90% CI for AUC is (b) (4) while the 90% CI for Cmax is (b) (4)

Although BE Study CAC-003-01 study is not acceptable to bridge the pharmacy and to-be marketed formulations, it can 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). Due to the public health need of this drug product, phase 3 Study CAC-001-01 is deemed adequate to support the bridging of the pharmacy and to-be marketed formulations.

B. Dissolution Method

The proposed dissolution method for both strengths are:

50 mg Capsules

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	500 mL	37 °C	50 mM potassium phosphate buffer, pH 6.8

250 mg Capsules

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	900 mL	37 °C	50 mM potassium phosphate buffer, pH 6.8

The dissolution method is acceptable.

C. Dissolution Acceptance Criterion

The proposed acceptance criterion for both strengths are:

Acceptance Criterion

$Q = \frac{(b)}{(4)}\% \text{ at } \frac{(b)}{(4)} \text{ minutes}$

Based on the mean in-vitro dissolution profile data for all strengths, the following dissolution acceptance criterion was recommended to the Applicant: $Q = \frac{(b)}{(4)}\% \text{ at } 15 \text{ minutes}$. In a submission dated June 6, 2014, the Applicant accepted to revise the acceptance criterion.

D. Data Supporting the Drug Product Manufacturing Site Change

To support the drug product manufacturing site change from Patheon (b)(4) to Patheon France, the Applicant provided *in vitro* comparative dissolution data and f2 similarity values for the drug product manufactured at the old and new site in pH 6.8 buffer. The data demonstrate that the products manufactured at the Patheon (b)(4) and Patheon France sites have f2 similar dissolution profiles. Thus, the manufacturing site change is acceptable.

RECOMMENDATION:

1. Although BE Study CAC-003-01 study is not acceptable to bridge the pharmacy and to-be marketed formulations, it can be used as evidence of bioavailability of the to-be marketed formulation. Also, phase 3 Study CAC-001-01 can be used for purposes of demonstrating bioavailability or bioequivalence of the proposed drug product. Thus, due to the unmet public health need of this drug product, phase 3 Study CAC-001-01 is deemed adequate to support the bridging of the pharmacy and to-be marketed formulations. Considering the totality of evidence presented in this submission, NDA 205750 for Cholbam (cholic acid) 50 mg and 250 mg immediate release capsules is recommended for approval from a Biopharmaceutics perspective.
2. The following dissolution method and acceptance criteria are recommended for both strengths.
 - i. Dissolution Method: Apparatus 2, 100 rpm agitation rate, 500 mL media volume, 37 °C, 50 mM potassium phosphate buffer, pH 6.8.
 - ii. Dissolution acceptance criterion: $\frac{(b)}{(4)}\%$ at 15 minutes.

Kareen Riviere, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.

Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The structure of the drug substance is shown in Figure 1.

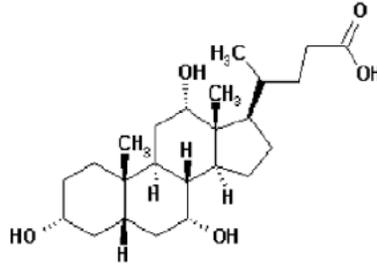


Figure 1. Chemical structure of cholic acid

The solubility profile of cholic acid obtained at 20 °C is shown in Figure 2.

Figure 2. Solubility Profile of cholic acid obtained at 20 °C



Drug Product

The composition of the proposed drug product is shown in Table 1.

Table 1. Composition of Cholic Acid Capsules 50 mg / 250 mg

Each Cholic Acid Capsule Contains the Following	% (w/w)	mg per capsule
Active Ingredient:		
Cholic acid	(b) (4)	50.0/250.0 mg
Other Ingredients:		
Silicified microcrystalline cellulose NF*	(b) (4)	(b) (4)
Magnesium stearate Ph. Eur./NF*		
Total:		
Swedish Orange Capsule Shells Size 2:		
Red iron oxide		
Titanium dioxide		
Gelatin		
Opaque White Capsule Shells Size 0:		
Titanium dioxide		
Gelatin		

Reviewer's Assessment:

(b) (4)

2. Dissolution Method

The proposed dissolution methods for both strengths are listed below.

50 mg Strength

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	500 mL	37 °C	50 mM potassium phosphate buffer, pH 6.8

250 mg Strength

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	900 mL	37 °C	50 mM potassium phosphate buffer, pH 6.8

Selection of Medium and pH

The Applicant explained that they selected the proposed dissolution medium

(b) (4)

Selection of Media Volume

In order to meet sink conditions, solubility in the dissolution medium must be at least = (b) (4) mg/L. The Applicant determined that the solubility of cholic acid in the dissolution medium is approximately (b) (4) mg/L. Therefore, the 900 mL volume is adequate to achieve sink conditions for the 50 and 250 mg strength product. (b) (4)

Selection of Paddle Speed

Dissolution profiles of the proposed product generated with different paddle speeds are shown in Figure 3. The Applicant reports (b) (4)

Figure 3. Effect of Paddle Speed (b) (4) on the Dissolution Profile (b) (4)



Discriminating Ability

The Applicant investigated the discriminating ability of the proposed dissolution method (b) (4)

(b) (4)

Reviewer's Assessment:

The selection of dissolution medium, media volume, and apparatus are acceptable. (b) (4)

(b) (4)

(b) (4)

The Applicant has not shown that the proposed method can discriminate (b) (4) Hence, the proposed method cannot be considered to have discriminating ability.

(b) (4)

As can be seen in the next section, the Applicant has accepted to change the time-point to 15 minutes. Therefore, the proposed dissolution method is adequate.

3. Dissolution Acceptance Criterion

The proposed acceptance criterion for both strengths is shown below.

Acceptance Criterion
$Q = \frac{(b)}{(4)}\% \text{ at } \frac{(b)}{(4)} \text{ minutes}$

Figures 5-7 show dissolution profile data for batches used in Phase 3 study CAC-001-01 which had been stored at 30°C/75% RH for 3 years.

Figure 5. 50 mg Batch PD09174 Dissolution Profile



Figure 6. 250 mg Batch PD09176 Dissolution Profile



Figure 7. 250 mg Batch PD09208 Dissolution Profile



Reviewer's Assessment:

The data in Figures 5-7 show that the Applicant's proposed dissolution acceptance criterion is permissive. Thus, the following IR comments were conveyed to the Applicant on May 15, 2014.

FDA Comment

Based on the mean in-vitro dissolution profile data for all strengths, it appears that the proposed dissolution acceptance criterion (b) (4) $Q = \frac{(b) (4)}{(4)}\%$ at 15 minutes. Provide dissolution data for the stability batches at the 15 minute time-point.

Company Response:

The dissolution acceptance criterion (b) (4) $Q = \frac{(b) (4)}{(4)}\%$ at 15 minutes as requested by the Agency. The drug product specification document, Section 3.2.P.5.1 has been revised accordingly. The batch analysis tables found in Section 3.2.P.5.4 have been revised replacing the (b) (4) minute dissolution data with 15 minutes dissolution data. The stability discussion in Section 3.2.P.8.1 and the stability data tables in Section 3.2.P.8.3 have also been updated with 15 minute dissolution data.

In a submission dated June 6, 2014, the Applicant agreed to revise the acceptance criterion.

4. Manufacturing Site Change

Clinical development lots including the registration stability lots were manufactured at Patheon (b)(4). The Applicant was notified that the Patheon (b)(4) facility (b)(4). Therefore, they transferred the manufacturing process and analytical testing to the proposed commercial manufacturing and testing site, Patheon France.

To support the Level 3 drug product manufacturing site change, the Applicant provided *in vitro* comparative dissolution data and f2 similarity values (n=12) for the drug product manufactured at the old and new site in pH 6.8 buffer. They were not able to provide these data (b)(4). The reference and test lots used for f2 testing are listed in Table 2.

Table 2. Lots of Cholic Acid Capsules Studies for F2 Calculations

Lot Number	Strength	Manufacturing Site	Date of Manufacture
PD09207	50 mg	Patheon (b)(4)	January 2010*
3003	50 mg	Patheon France	July 2013
PD09208	250 mg	Patheon (b)(4)	January 2010*
3103	250 mg	Patheon France	July 2013

* Stored at 5°C until tested.

The comparative dissolution data and f2 results for the 50 mg strength and 250 mg strength product are presented in Table 3 and Table 4 respectively.

Table 3. Dissolution Profile Comparison (50 mg strength) at pH 6.8

Time Point (minutes)	Reference Batch PD09207	Test Batch 3003
5	(b)(4)	
10		
15		
30		
45		
60		
Similarity Factor f2		70
Difference Factor f1		4

Table 4. Dissolution Profile Comparison (250 mg strength) at pH 6.8

Time Point (minutes)	Reference Batch PD09208	Test Batch 3103
5	(b)(4)	
10		
15		
30		
45		
60		
Similarity Factor f2		76
Difference Factor f1		3

Reviewer's Assessment:

The data in Tables 3-4 demonstrate that the products manufactured at the Patheon (b) (4) and Patheon France sites have f2 similar dissolution profiles in the proposed dissolution medium. Thus, the manufacturing site change is acceptable.

5. BE Study Comparing the Pharmacy and Commercial Formulation

The Applicant conducted one Phase 1 study (Study CAC-003-01) and two Phase 3 studies (Study CAC-001-01 and Study CAC-91-10-10). The pharmacy formulation was used in the first Phase 3 study (Study CAC-91-10-10). The 50 mg and 250 mg strengths of the to-be-marketed product were used in the second Phase 3 safety and efficacy study (Study CAC-001-01). The 250 mg pharmacy capsule formulation and the 250 mg strength to-be marketed capsule formulation were used in the Phase 1 study (b) (4) the sponsor used both formulations in Phase 3 studies.

The title of the Phase I study (Study CAC-003-01) is “Comparative Bioavailability of Three Formulations of Cholic Acid in Healthy Male Subjects Using a Multiple Dose Repeated Measures Approach”. The objectives of the study were to evaluate the relative bioavailability/bioequivalence and pharmacokinetics of multiple oral doses of a new cGMP produced cholic acid capsule formulation in comparison to a previously used pharmacy capsule formulation and an oral solution or suspension (250 mg) in 18 healthy male volunteers. In addition, the safety of cholic acid, following multiple dose administration of cholic acid was also assessed.

Treatment Groups

The treatment groups are described below.

1. Treatment A (pharmacy cholic acid capsules) were supplied as:
 - Cholic acid 250.00 mg
 - (b) (4)
 - White, opaque, gelatin (b) (4) capsule
2. Treatment B (cGMP Cholic Acid capsules) were supplied as:
 - Cholic acid 250.00 mg
 - Silicified Microcrystalline Cellulose Ph Eur/USP (b) (4)
 - Magnesium Stearate Ph Eur/USP (b) (4)
 - Hard Gelatin Capsules Ph Eur/USP Size #0.
3. Treatment C (cholic acid oral solution) was supplied as:
 - Cholic acid 250.00 mg in 25 mL (10 mg/mL)
 - (b) (4)
 - (b) (4)

Study Design

The Applicant stated that given the potential for endogenous cholic acid being present, a repeated measures approach without washout was employed (refer to Table 5).

Table 5. Schedule of Study Evaluations

Screen	Baseline Clinic Check-In	In-Patient Observation Treatment Cycle 1				In-Patient Observation Treatment Cycle 2				In-Patient Observation Treatment Cycle 3				Clinic Discharge / ET	F/U
Visit 1 Day-14 to -1	Visit 2 Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Visit 3 Day 22

Eighteen subjects were planned for enrollment, and 18 subjects were randomized and evaluated for safety (refer to Table 6).

Table 6. Randomization Schedule

Subject No.	Treatment 1	Treatment 2	Treatment 3
	Days 1 - 4	Days 5 - 8	Day 9 - 12
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	B	A	C
6	C	B	A
7	A	B	C
8	B	C	A
9	C	A	B
10	A	C	B
11	B	A	C
12	C	B	A
13	A	B	C
14	B	C	A
15	C	A	B
16	A	C	B
17	B	A	C
18	C	B	A

A total of 50 blood samples totaling 300 mL of blood were taken from each subject (refer to Table 7).

Table 7. Description of Plasma (Venous blood) sampling per Treatment Cycle and Dosing Schedule

Cycle	Daily Treatment Dosing			Plasma Sample collection
Cycle 1	Day 1	Dose 1 Day 1: 7 am	Dose 2 Day 1: 7 pm	0 hours (pre dose = dose -1 hr)
	Day 2	Dose 1 Day 2: 7 am	Dose 2 Day 2: 7 pm	N/A
	Day 3	Dose 1 Day 3: 7 am	Dose 2 Day 3: 7 pm	48 (7am), 49, 50, 51, 52, 54, 57, and 60 (7pm) hours after 1 st dose
	Day 4	Dose 1 Day 4: 7 am	Dose 2 Day 4: 7 pm	72 (7am), 73, 74, 75, 76, 78, 81, and 84 (7 pm) hours after 1st dose
Cycle 2	Day 5	Dose 1 Day 1 -7 am	Dose 2 Day 1 -7 pm	N/A
	Day 6	Dose 1 Day 2 -7 am	Dose 2 Day 2 -7 pm	N/A
	Day 7	Dose 1 Day 3 -7 am	Dose 2 Day 3 -7 pm	144 (7am), 145, 146, 147, 148, 150 153 and 156 (7 pm) hours after 1st dose in cycle 1
	Day 8	Dose 1 Day 4 -7 am	Dose 2 Day 4 -7 pm	168 (7am), 169, 170, 171, 172, 174, 177, and 180 (7 pm) hours after 1st dose in cycle 1
Cycle 3	Day 9	Dose 1 Day 1 -7 am	Dose 2 Day 1 -7 pm	192 hours after 1 st dose in cycle 1
	Day 10	Dose 1 Day 2 -7 am	Dose 2 Day 2 -7 pm	N/A
	Day 11	Dose 1 Day 3 -7 am	Dose 2 Day 3 -7 pm	240 (7am), 241, 242, 243, 244, 246, 249 and 252 (7 pm) hours after 1st dose in cycle 1
	Day 12	Dose 1 Day 4 -7 am	Dose 2 Day 4 -7 pm	264 (7am), 265, 266, 267, 268, 270, 273 and 276 (7 pm) hours after 1st dose in cycle 1

Study Results

The cholic acid and total cholic acid plasma concentration data expressed as the means derived from dose administration during the three treatment cycles are presented in Figure 8 and Figure 9, respectively.

Figure 8. Mean Concentrations of Cholic Acid in Healthy Subjects Following Oral Administration of 250 mg of 3 Different Dosage Forms

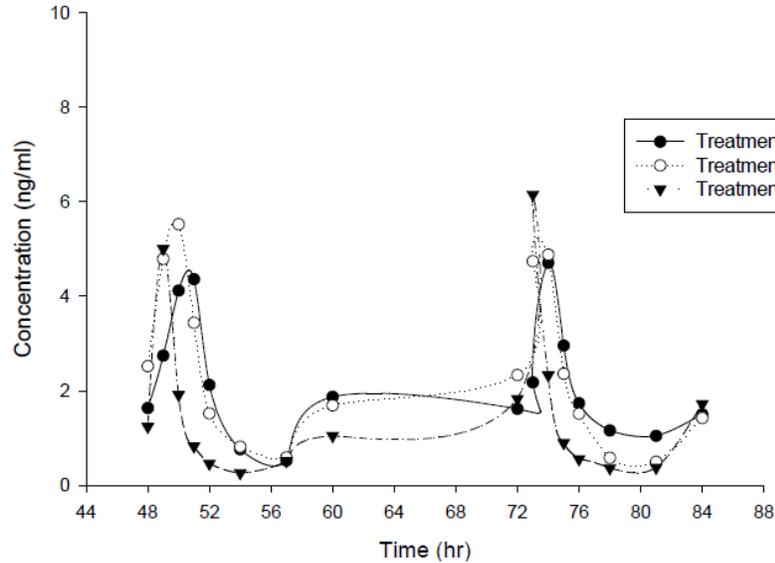
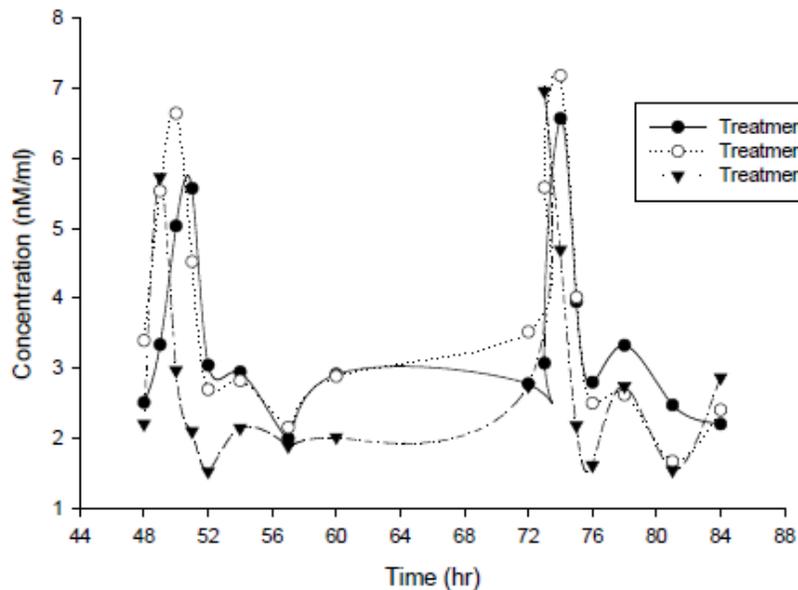


Figure 9. Mean Concentrations of Total Cholic Acid in Healthy Subjects Following Oral Administration of 3 Different Dosage Forms



Mean pharmacokinetic parameters calculated from the individual plasma concentrations of cholic acid and total cholic acid data are reported in Table 8 and Table 9. The Applicant stated that the PK parameters for both Total cholic acid were derived from plasma concentrations of Total cholic acid corrected for pre-dose circulating endogenous concentrations.

Table 8. Pharmacokinetic Parameters of Cholic Acid Following Administration of Multiple Oral Doses of Cholic Acid

Day 3	Treatment A (N = 17)		Treatment B (N = 18)		Treatment C (N = 17)		p-values*
	Mean	SD	Mean	SD	Mean	SD	
PK Parameter							
T _{max} (hr)	2.3	0.77	1.7	0.669	1.0	0.0	< 0.0001
C _{max} (ng/mL)	6.02	3.75	7.13	3.21	5.01	2.01	0.0728
AUC _{tau} (ng•hr/mL)	21.54	14.13	23.66	10.81	12.87	5.36	< 0.0001
C _{min} (ng/mL)	1.76	1.41	2.11	2.40	1.15	0.95	0.5746
K _{el} (hr ⁻¹)	0.410	0.196	0.321	0.172	0.298	0.132	0.4407
Elim. t _{1/2} (hr)	2.13	1.08	2.96	1.77	3.22	2.73	0.4407
Cl/F (L/hr)	15.01	6.486	12.86	5.806	22.77	9.142	< 0.0001
Vd _{ss} /F (L)	48.766	30.276	56.87	45.164	106.26	83.211	0.0003
Day 4							
	Mean	SD	Mean	SD	Mean	SD	
PK Parameter							
T _{max} (hr)	3.1	2.50	1.6	0.85	1.6	2.67	< 0.0001
C _{max} (ng/mL)	5.26	2.64	6.26	2.40	6.37	2.60	0.0728
AUC _{tau} (ng•hr/mL)	21.57	12.35	20.52	6.21	15.78	7.34	< 0.0001
C _{min} (nMol/mL)	1.56	1.57	1.88	1.54	1.78	1.44	0.5746
K _{el} (hr ⁻¹)	0.30	0.108	0.333	0.114	0.308	0.119	0.4407
Elim. t _{1/2} (hr)	3.11	2.91	2.39	1.01	2.78	1.675	0.4407
Cl/F (L/hr)	14.56	6.145	13.57	5.31	19.90	10.38	< 0.0001
Vd _{ss} /F (L)	54.87	19.23	48.10	35.385	120.32	116.80	0.0003

Table 9. Pharmacokinetic Parameters of Total Cholic Acid Following Administration of Multiple 250 mg Oral Doses of Cholic Acid

Day 3	Treatment A (N = 17)		Treatment B (N = 18)		Treatment C (N = 17)		p-values*
	Mean	SD	Mean	SD	Mean	SD	
PK Parameter							
T _{max} (hr)	2.4	0.71	2.7	2.59	2.2	3.19	
C _{max} (nMol/mL)	7.26	4.55	8.45	3.95	5.82	2.29	0.0380
AUC _{tau} (nMol•hr/mL)	37.52	16.94	40.30	17.52	28.29	12.97	< 0.0001
C _{min} (nMol/mL)	2.71	1.39	3.14	3.16	2.11	1.19	0.4470
Day 4							
	Mean	SD	Mean	SD	Mean	SD	
PK Parameter							
T _{max} (hr)	2.8	2.43	2.0	0.91	1.77	2.66	
C _{max} (nMol/mL)	7.06	3.33	8.31	4.48	7.46	3.23	0.0380
AUC _{tau} (nMol•hr/mL)	38.24	18.11	37.48	18.14	33.45	14.81	< 0.0001
C _{min} (nMol/mL)	2.49	1.61	2.96	1.63	2.81	1.62	0.4470

*Note: p-values based upon combined Day 3 & Day 4 LS-Means

Comparison of log transformed PK parameters of cholic acid and Total cholic acid across the three treatments are displayed in Table 10 and Table 11, respectively. It is not clear whether Day 3 or Day 4 PK data was used to generate the BE data.

Table 10. Bioequivalence Determination of Cholic Acid PK Parameters AUC and Cmax for Three Cholic Acid Formulations - Model: Log(var) = treatment sequence day(Cycle) Uncorrected Parameters

Parameter	Pair (Test:Ref)	Reference	Test	Difference Test-Reference	Ratio Test/Reference	(90% Conf Interval)
AUC _{tau}	B:A					(b) (4)
	A:C					
	B:C					
C _{max}	B:A					
	A:C					
	B:C					

Data source: [Appendix 16.2.2.6A](#)
 Where A = cholic acid 250 mg Capsule (Pharmacy)
 Where B = cholic acid 250 mg Capsule (cGMP)
 Where C = cholic acid 250 mg Oral Solution

Table 11. Bioequivalence Determination of Total Cholic Acid PK Parameter for Three Cholic Acid Formulations - Model: Log(var) = treatment sequence day(Cycle) - Uncorrected Parameters

Parameter	Pair (Test:Ref)	Reference	Test	Difference Test-Reference	Ratio Test/Reference	(90% Conf Interval)
AUC _(Tau)	B:A					(b) (4)
	A:C					
	B:C					
C _{max}	B:A					
	A:C					
	B:C					

Data source: [Appendix 16.2.2.6B](#)
 Where A = cholic acid 250 mg Capsule (Pharmacy)
 Where B = cholic acid 250 mg Capsule (cGMP)
 Where C = cholic acid 250 mg Oral Solution

Reviewer's Assessment:

This reviewer has the following concerns about the design and results of BE Study CAC-003-01:

1. *The provided justification for using (b) (4) is not adequate.* (b) (4)
 (b) (4)
 (b) (4)
2. *Also, the Applicant did not provided data or information to support your claim* (b) (4)
 (b) (4)

3.

(b) (4)

(b) (4)

(b) (4) *is not acceptable.*
4.

(b) (4)
5.

(b) (4)

Therefore, the (b) (4) are not consistent.
6.

The (b) (4) are not justified.
7.

This study indicates that the 250 mg pharmacy capsule formulation and the 250 mg strength to-be marketed capsule formulation are not bioequivalent. The 90% CI for AUC is (b) (4) while the 90% CI for Cmax is (b) (4)

The following IR comments were conveyed to the Applicant on May 15, 2014.

We note several issues with the design and conduct of Study CAC-003-01 that are concerning (b) (4). To continue with our review, provide evidence either with your own data or literature data to justify why the proposed study design should be considered adequate for review. Your response should also explain the clinical relevance of the (b) (4) observed for the pharmacy capsule formulation and to-be marketed capsule formulation.

The Applicant submitted a response on June 6, 2014. Thier response was mostly a reiteration of what was presented in the original application. One new justification presented by the Applicant (b) (4)

(b) (4)

(b) (4)

(b) (4)

The Applicant did not design the BE study as described above. Furthermore, they did not request or receive an agreement from FDA

Thus, ^{(b) (4)} BE Study CAC-003-01 study is deemed not acceptable to bridge the pharmacy and to-be marketed formulations.

Although BE Study CAC-003-01 study is not acceptable to bridge the pharmacy and to-be marketed formulations, it can 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), the following is acceptable for determining the bioavailability or bioequivalence of a drug product:

Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the approaches outlined in paragraphs (b)(1)(i) and (b)(2) of this section, when the approaches described in paragraphs (b)(1)(ii), (b)(1)(iii), and (b)(3) of this section are not available.

Also, according to 21CFR320.24 (b)(6):

Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.

Due to the unmet public health need of this drug product, phase 3 Study CAC-001-01 is deemed adequate to support the bridging of the pharmacy and to-be marketed formulations. For detailed review of this phase 3 study, please see the clinical review by Dr. Wen-Yi Gao.

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/s/

KAREEN RIVIERE
07/24/2014

TAPASH K GHOSH
07/24/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

<i>NDA</i>	205-750	<i>Submission Date(s)</i>	11/21/2013, 1/24/14, 1/31/14, 2/21/14, 2/24/14, 3/5/14, 4/4/14, 5/2/14, 6/30/14, 7/7/14
<i>Brand Name</i>	Cholbam®		
<i>Generic Name</i>	Cholic Acid		
<i>Reviewer</i>	Insook Kim, Ph.D.		
<i>Team Leader</i>	Sue-Chih Lee, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology 3		
<i>OND Division</i>	Division of Gastroenterology and Inborn Errors Products		
<i>Sponsor</i>	Asklepion		
<i>Relevant IND(s)</i>	45,470		
<i>Submission Type; Code</i>	Original	NME	
<i>Formulation; Strengths; Regimen</i>	Gelatin capsule for oral administration 50 mg or 250 mg 10-15 mg/kg once daily with food		
<i>Indication</i>	[REDACTED] (b) (4)		

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1 Executive Summary

In this submission the use of cholic acid is proposed [REDACTED] (b) (4). The NDA was submitted via a 505(b)(2) pathway relying on the literature data for the labeling of clinical pharmacology and non-clinical pharmacology and toxicology information. Cholic acid is the second bile acid species proposed as a therapeutics following Ursodeoxycholic acid for Primary Biliary Cirrhosis (Urso®) and for dissolution and prevention of gallstone (Actigall®).

1.1 Recommendations

The Division of Clinical Pharmacology 3 reviewed this application and has following comments.

- The labeling for clinical pharmacology section based on published literatures would be acceptable provided that a mutual agreement on labeling languages can be reached. See Section 3 for more comments.
- The urinary bile acid, which is proposed as an efficacy endpoint is considered a reasonable pharmacodynamic biomarker to evaluate the early response to cholic acid in patients with an enzyme defect in bile acid synthesis pathway if a robust bioanalytical assay method is used. It is based on the mechanism of disease and the expected negative feedback mechanism of bile acid synthesis by cholic acid.
- However, the bioanalytical assay method used to detect the atypical bile acids in this submission was not adequately validated to the regulatory standard to support quantitative assessment of urinary bile acids. (b) (4)
Therefore we do not recommend the urinary bile acid results be used as an efficacy endpoint for the proposed product.
- On the other hand, we do not object to the monitoring of early response to cholic acid treatment using urinary bile acids as a part of clinical management of patients.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

To support this NDA, the sponsor provided the following information:

- (1) The safety and efficacy data of the product collected from 85 patients under a treatment IND over a period of 19 years. Under the treatment IND, patients with single enzyme defect (SED) in bile acid synthesis pathway were mainly enrolled. Later patients with peroxisomal disorder (PD) were also included. The sponsor measured the clinical efficacy by changes in following:
 - liver enzymes
 - atypical urinary bile acid
 - height/weight
 - liver histologyPrimary efficacy endpoint was not pre-specified since the clinical data was collected under a treatment IND.
- (2) A switch-over study from a pharmacy formulation to the to-be-marketed formulation in patients who have been treated with cholic acid. There were no PK data in this study.

- (3) A BE study comparing the pharmacy compounding formulations with the to-be-marketed capsule formulation in healthy subjects. The BE study is primarily reviewed by the biopharmaceutics reviewer in ONDQA.
- (4) Publications to support labeling, including the clinical pharmacology information. No additional in-vivo and in-vitro clinical pharmacology related studies were conducted in support of the proposed product.

This review is focused on the clinical pharmacology labeling based on published literatures and the urinary bile acid data.

Rationale for the proposed dose

The proposed dose of cholic acid is 10-15 mg/kg body weight/day with food. The proposed dose was determined empirically under the treatment IND without an evaluation of dose-response relationship. In 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. While the sponsor states the dose was adjusted based on changes in serum LFT results as well as on the extent of reduction of atypical bile acids in urine, the documentation on the dosage adjustment with relevant clinical observations and biomarkers at the time of dosage adjustment is not adequate for our review. (b) (4)

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 a BE study between TBM capsule and pharmacy prepared capsule or oral liquid formulation, the systemic exposure following multiple doses after TBM and pharmacy prepared capsule was similar. The C_{max} was similar between TBM and oral liquid while AUC of TBM was ~58% higher than that of oral liquid. In a switch-over study CAC-001-01, 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. The detailed review of safety profile is deferred to the clinical reviewer.

Dosage Administration

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 ¹. 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). On the other hand, the BE study was conducted after administration of cholic acid twice daily for 4

¹ In amendment dated 7/7/14

days. In Study CAC-91-10-10 oral solution was used to patients who could not swallow capsule. In CAC 001-01 patients who were not able to swallow the capsule were instructed to sprinkle the contents of capsule on 1-2 teaspoons of plain applesauce before administration. (b) (4)

Atypical bile acids in urine

The detection of atypical bile acids has been used for the diagnosis of inborn errors of bile acid synthesis. The detection of the presence of mass fragments, which were derived from substrates of defected enzymes in the bile acid synthesis pathway, has been used to diagnose a specific enzyme defect. Under the treatment IND, the principal investigators followed the peaks with characteristic m/z from atypical bile acids in mass spectra to monitor the response to treatment during cholic acid treatment. In addition, a change in urinary excretion of atypical bile acids was used as one of efficacy endpoints by the sponsor. The acceptability of urinary bile acids as a surrogate efficacy endpoint has to be further established.

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 information² is available 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 β , 7 α -dihydroxy-5-cholenoic acid and 7 α -hydroxy-3-oxo-4-cholenoic acid which are detectable in patients with deficiency in HSD3 β 7 and 5 β -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.

On the other hand, 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 acids³ and the negative feedback mechanism mediated by cholic acid for the repression of bile acid synthesis from cholesterol^{4,5}. Nevertheless, the significance of reduction of atypical bile acids to the clinical outcome has to be further established.

Reviewer's comments:

² 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 α -hydroxy-3-oxo-4-cholenoic acid and 3 β ,7 α -dihydroxy-5-cholenoic acid in rat liver plasma membrane vesicles, in Cholestatic liver diseases: 82-87

³ Sundaram et al. (2008) Mechanisms of Disease: inborn errors of bile acid synthesis, Gastroenterology & Hepatology, 5 (8): 456

⁴ Hofmann AL (2007) Biliary secretion and excretion in health and disease: Current concepts, Annals of Hepatology 6(1): January-March: 15-27

⁵ Wang et al. (1999) Endogenous Bile Acids Are Ligands for the Nuclear Receptor FXR/BAR, Molecular Cell, Vol. 3, 543-553

Atypical bile acids in urine were analyzed by a bioanalytical assay method using Fast Atom Bombardment-Mass Spectrometry (FAB-MS). The identification of bile acids of interest, which are specific to defective enzyme, was done by molecular structure prediction based on mass fragmentation pattern. 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)

⁶. As such the urinary atypical bile acid information is considered exploratory in this submission.

Pharmacokinetic Properties

Orally administered cholic acid is expected to undergo the same in vivo disposition as with endogenous cholic acid. 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.

Table 1 Pharmacokinetic Parameters of (A) Cholic Acid and (B) Total Cholic Acid Following Administration of 250 mg Cholic Acid Twice a Day for 4 days in healthy male subjects

(A)

Day 4	Treatment A (N = 17)		Treatment B (N = 18)		Treatment C (N = 17)	
	Mean	SD	Mean	SD	Mean	SD
PK Parameter						
T _{max} (hr)	3.1	2.50	1.6	0.85	1.6	2.67
C _{max} (ng/mL)	5.26	2.64	6.26	2.40	6.37	2.60
AUC _{tau} (ng•hr/mL)	21.57	12.35	20.52	6.21	15.78	7.34
C _{min} (nMol/mL)	1.56	1.57	1.88	1.54	1.78	1.44

(B)

Day 4	Mean	SD	Mean	SD	Mean	SD
PK Parameter						
T _{max} (hr)	2.8	2.43	2.0	0.91	1.77	2.66
C _{max} (nMol/mL)	7.06	3.33	8.31	4.48	7.46	3.23
AUC _{tau} (nMol•hr/mL)	38.24	18.11	37.48	18.14	33.45	14.81
C _{min} (nMol/mL)	2.49	1.61	2.96	1.63	2.81	1.62

Treatment A: Pharmacy prepared capsule; Treatment B: To-be-Marketed capsule; Treatment C: Oral solution

Intrinsic and extrinsic factors that may affect the efficacy and safety of CHOLBAM

No studies were conducted to address the effects of intrinsic factors on PK of cholic acid.

⁶ The sponsor submitted urinary BA assay using a LC/MS/MS with synthetic atypical bile acid standards (bile acid intermediates) for 3β-OH-C27-steroid-oxidoreductase (HSD3β7) deficiency to support the identities of the atypical bile acids observed in mass spectrum in an amendment dated 2/21/14. The comparison to the standards for other atypical bile acids was not submitted.

- Followings are reviewer’s assessments
 - **Biliary obstruction:** Cholic acid and its conjugates are mainly excreted to bile. Therefore in patients with biliary obstruction, bile acids including cholic acid may accumulate in hepatocytes.
 - **Deficiency in bile acid conjugating enzymes:** Once absorbed cholic acids are present mostly in conjugated forms and undergo the enterohepatic circulation under normal physiology. Therefore in patients with deficiency in bile acid conjugating enzymes, the possibility of exacerbation of symptoms by exogenous cholic acids cannot be ruled out in part via an increased formation of a secondary bile acid, deoxycholic acid.
- **Drug interactions**
 - Concomitant administration of bile acid binding resins acids can reduce the absorption of orally administered cholic acid. Current labeling of cholestyramine recommends administration of bile acid binding resins at least 1 hour before and 4 hours after concomitant drug administration.
 - Aluminum-based antacid was shown to adsorb bile acids in vitro.⁷ Optimal time interval between aluminum-based antacids and concomitant drug has not been established. Yet the staggered administration at least two hours before and four hours after administration of concomitant drugs that could interact with aluminum-based antacid was suggested.⁸
 - Potentially drugs that inhibit transporters in the canalicular membrane such as bile-salt efflux pump (BSEP) may exacerbate the cholestasis by reducing the biliary excretion of bile acids including cholic acid. On the other hand, the inhibition of uptake transporters such as Apical Sodium-dependent Bile acid Transporter (ASBT) in the intestine may reduce the efficiency of bile acid recycling.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The development of the proposed product was supported by clinical data collected under a treatment IND (IND # 45,470). The treatment IND was opened in June 1994 and maintained by the principal investigators until transferred to the current NDA sponsor in May 2007. Because the clinical data was collected as a part of patient care over a long period of time rather than to establish the evidence for the safety and efficacy of the product, there are many missing information. In addition the data was not collected by the pre-specified schedule so there is significant inconsistency in terms of availability of data.

⁷ Magnell et al. (1986) The ability of antacid and cholestyramine to bind bile acids: effect of pH, Scand J. Gastroenterol. 21: 789-794

⁸ Ogawa and Echizen (2011) Clinically Significant Drug Interactions with Antacids: An Update, Drugs; 71 (14): 1839-1864

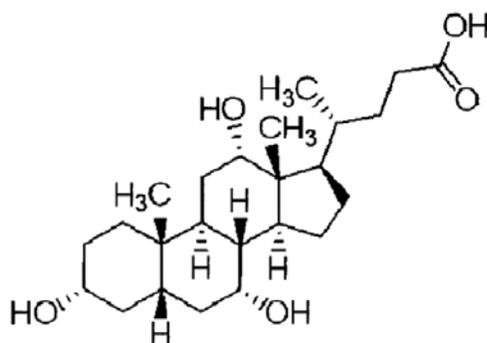
2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Cholic acid is one of the naturally occurring bile acids synthesized from cholesterol and one of two primary bile acids, i.e. cholic acid and chenodeoxycholic acid produced by the human liver.

Prior to the development of the commercial formulation of cholic acid, pharmacy compounded formulations i.e. capsule and oral solution, have been used to treat patients under the treatment IND. The commercial formulation for cholic acid became available in April 2010. A bioequivalence study to bridge the pharmacy compounded formulation to the to-be-marketed formulation was conducted.

Figure 1 Structure of cholic acid

Cholic Acid



2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The proposed indication is [REDACTED] (b) (4)

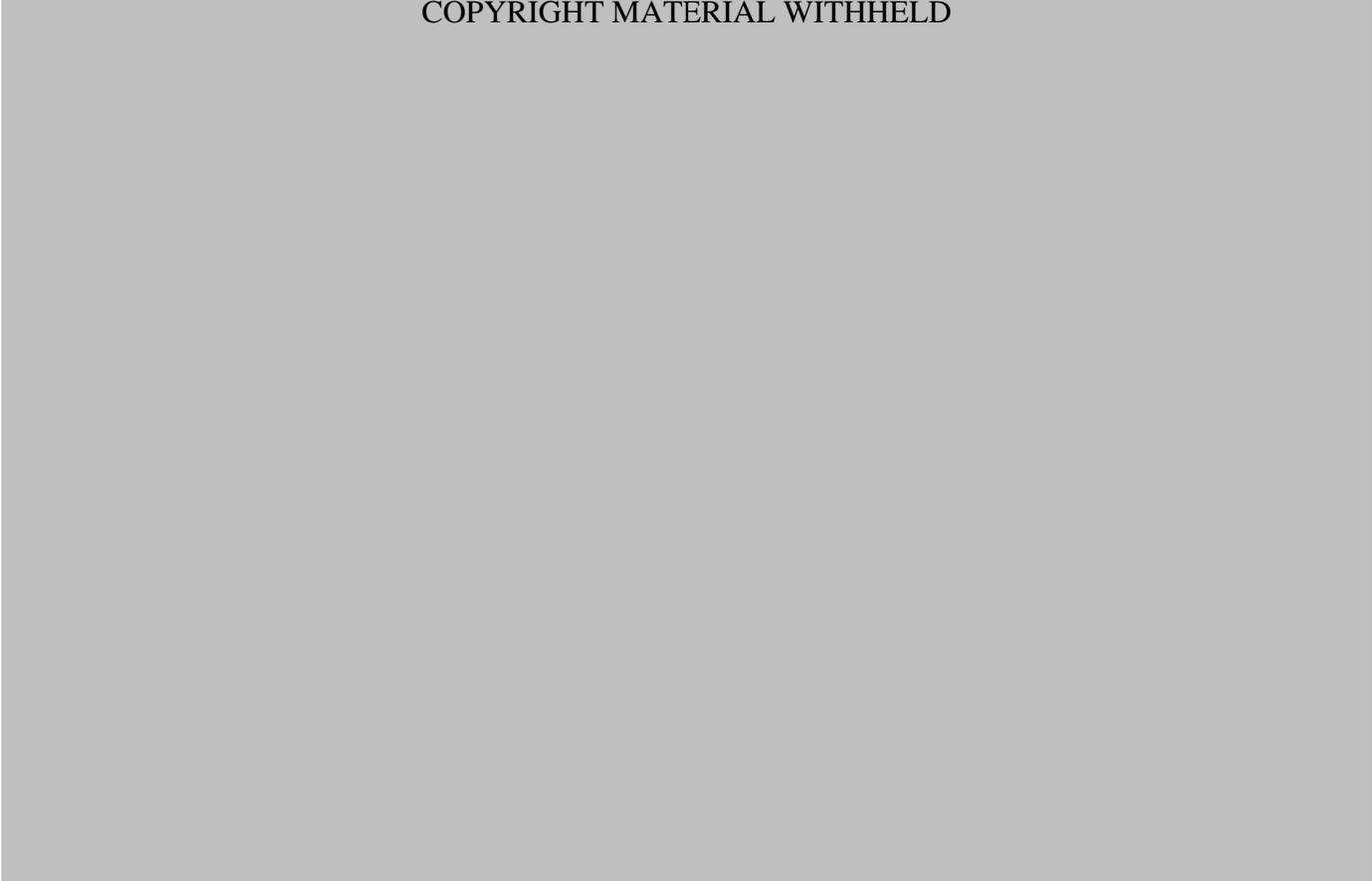
The proposed mechanisms of action [REDACTED] (b) (4) are as follows:

- The feedback mechanism, which regulates endogenous synthesis of bile acids, thus reducing the synthesis of atypical and hepatotoxic bile acids
 - The absence of primary bile acids causes hepatocytes to continuously metabolize cholesterol in an attempt to maintain a normal bile acid pool leading to the continued production of high concentrations of atypical bile acid intermediates and metabolites, which may be hepatotoxic. Once primary bile acids are administered, bile acid synthesis from cholesterol is reduced via negative feedback mechanism.
- The stimulation of bile secretion and improvement of bile flow
- The promotion of micellar solubilization of lipids and fat-soluble vitamins in the intestine

The sponsor proposes to use cholic acid in patients with single enzyme defect in bile acid synthesis and peroxisomal disorder. In peroxisomes, the side-chain modification of bile acids occurs.

Figure 2 Pathways for bile acid synthesis and the number of patients with single enzyme defect in the pathway in Study CAC 90-10-10

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2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage regimen is 10-15 mg/kg once daily by mouth preferably with food. For patients who cannot swallow the capsule, cholic acid is to be mixed with soft food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The study reports of three clinical trials were submitted as below.

Table 2 Summary of clinical trials

Study	Design	Dose	# subject	Treatment Duration	Primary endpoint
CAC-91-10-10 (including sub-study 92-8-19)	Open-label, single arm, non-comparative	Varies (once, twice or three times daily)	85 ITT 79 Safety 70 mITT (M/F: 31/50) Age at diagnosis 2 +/- 4 years	Individual treatment duration: 1 day to 10.5 years	Urinary bile acids, Liver function Liver histology Height/weight
CAC-001-01	Open-label, single arm, Cross-over	10-15 mg/kg/day <u>once daily</u>	N= 16 7.15 yr (0.6-20 year)	30 days after switching to the TBM formulaiton	Urine & serum bile acids, Liver function
CAC-003-01	Randomized, three-way crossover	Cholic acid 250 mg capsule (cGMP formulation) 250 mg capsule (pharmacy formulation) 250 mg oral solution 25 mg cGMP formulation) Twice a day every 12 hours	N=18 Healthy adults	4 day treatment per each formulation	PK endpoints

Clinical efficacy endpoints

The clinical efficacy was evaluated by followings:

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

Reviewer's comments: The primary or secondary efficacy endpoints were not pre-specified while the clinical data was collected under a treatment IND. Similarly the data was analyzed without pre-specified statistical analysis plan. For detailed review of efficacy, please see the clinical review by Dr. Wen-Yi Gao.

Table 3 Primary Diagnosis by Disorder Type CAC-91-10-10

Type of Disorder Primary Diagnosis	ITT (N = 85) N (%)	Safety (N = 79) N (%)	mITT (N = 69) N (%)
Single Enzyme Defect	54 (64)	50 (63)	43 (62)
3 β -hydroxy-5-C27-steroid oxidoreductase (3 β -hydroxy-5-C27-steroid dehydrogenase/isomerase or 3 β -HSD or HSD3 β 7)	35 (41)	35 (44)	32 (46)
Δ 4-3-oxosteroid 5 β -reductase (Δ 4-3-oxo- R or AKR1D1)	10 (12)	9 (11)	6 (9)
Sterol 27-hydroxylase (CTX)	5 (6)	3 (4)	3 (4)
2- (or a-) methylacyl-CoA racemase (AMACR)	1 (1)	1 (1)	1 (1)
Cholesterol 7 α -hydroxylase (CYP7A1)	1 (1)	1 (1)	1 (1)
Smith-Lemli-Opitz	1 (1)	1 (1)	1 (1)
Unknown	1 (1)	1 (1)	0 (0)
Peroxisomal Disorder	31 (36)	29 (37)	26 (38)
Peroxisomal Biogenesis Disorder: Zellwegers	12 (14)	11 (14)	9 (13)
Peroxisomal Biogenesis Disorder: Neonatal adrenoleukodystrophy	8 (9)	8 (10)	7 (10)
Peroxisomal Biogenesis Disorder: Type unknown	6 (7)	5 (6)	5 (7)
Peroxisomal Biogenesis Disorder: Refsum's	4 (5)	4 (5)	4 (6)
Peroxisomal Biogenesis Disorder: Generalized peroxisomal disorder	1 (1)	1 (1)	1 (1)

N = number of patients

Source: CAC-91-10-10 Table 9

*Modified ITT (mITT) set including all patients who received treatment and have at least one pre- and post-treatment outcome assessment for urine bile acid analysis, LFTs, and height/weight.

Of the analyzable modified intent to treat population (mITT), 46% of patients come from 3 β -hydroxy-5-C27-steroid oxidoreductase following by Zellwegers, neonatal adrenoleukodystrophy subtypes and ARK1D1 deficiency.

The detection of atypical bile acids in urine has been used for the diagnosis of a specific enzyme defect.

Reviewer's comments: Whether the cholic acid should be indicated for both SED and PD and all subtypes or to specific subtype of SED or PD is under discussion. Please see the clinical review for more details.

2.2.2 What is the basis for selecting the atypical bile acids in urine as an efficacy endpoint?

Inborn errors of cholesterol and bile acid synthesis and metabolism

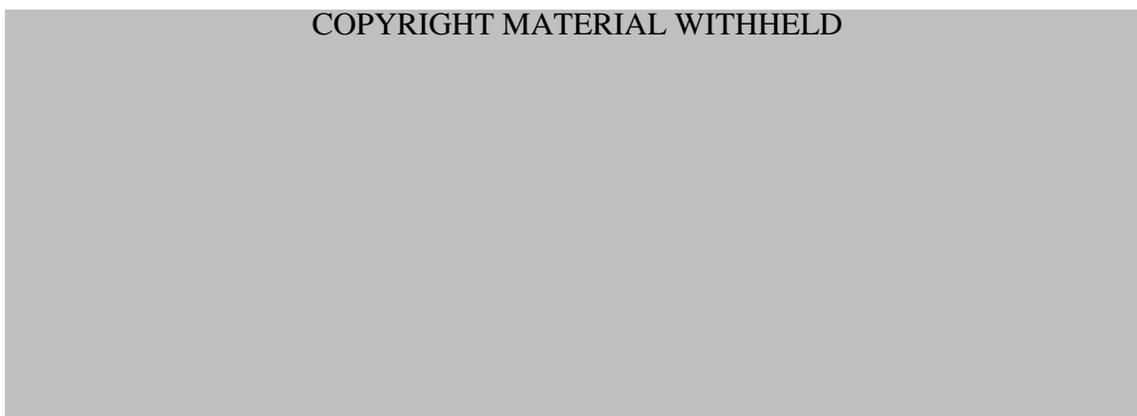
Individuals with inborn errors of bile acid synthesis lack the enzymes needed to synthesize the primary bile acids, cholic acid and chenodeoxycholic acid. This deficiency in activity of specific enzymes involved in bile acid synthesis results in diminished production of primary bile that are essential for promoting bile flow.

The enzyme deficiency allows bile acid intermediates that are the substrates for a particular enzyme, to accumulate and these can be metabolized to an array of unusual bile acids (**Table 4, Figure 3, Figure 4**). The absence of primary bile acids causes hepatocytes to continuously metabolize cholesterol in an attempt to establish a normal bile acid pool. The result is the continued production of high concentrations of these atypical bile acids and a progressive cholestasis.⁹

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. Studies using rat liver canalicular membrane vesicles suggested the cholestatic nature of taurine conjugate of $3\beta,7\alpha$ -dihydroxy-5-cholenoic acid and 7α -OH-3-oxo-4-cholenoyltaurine by inhibiting transport of tauro-cholic acid¹⁰. No additional information is available for atypical bile acids found in other enzyme defects. Nevertheless the significance of atypical bile acids for the clinical symptoms should be further established.

The detection of atypical bile acids in urine has been used to aid the diagnosis of a specific enzyme defect. For example, in patients with 3β -hydroxy-C₂₇-steroid dehydrogenase/isomerase deficiency (HSD3 β 7), the most common of the bile acid synthetic defects, di- or tri-hydroxy cholenoic acids accumulate and atypical peaks in mass spectra of urine sample are from conjugates of di- or tri-hydroxy cholenoic acids (**Figure 5**).

Figure 3 Bile acid intermediates formed during bile acid synthesis¹¹

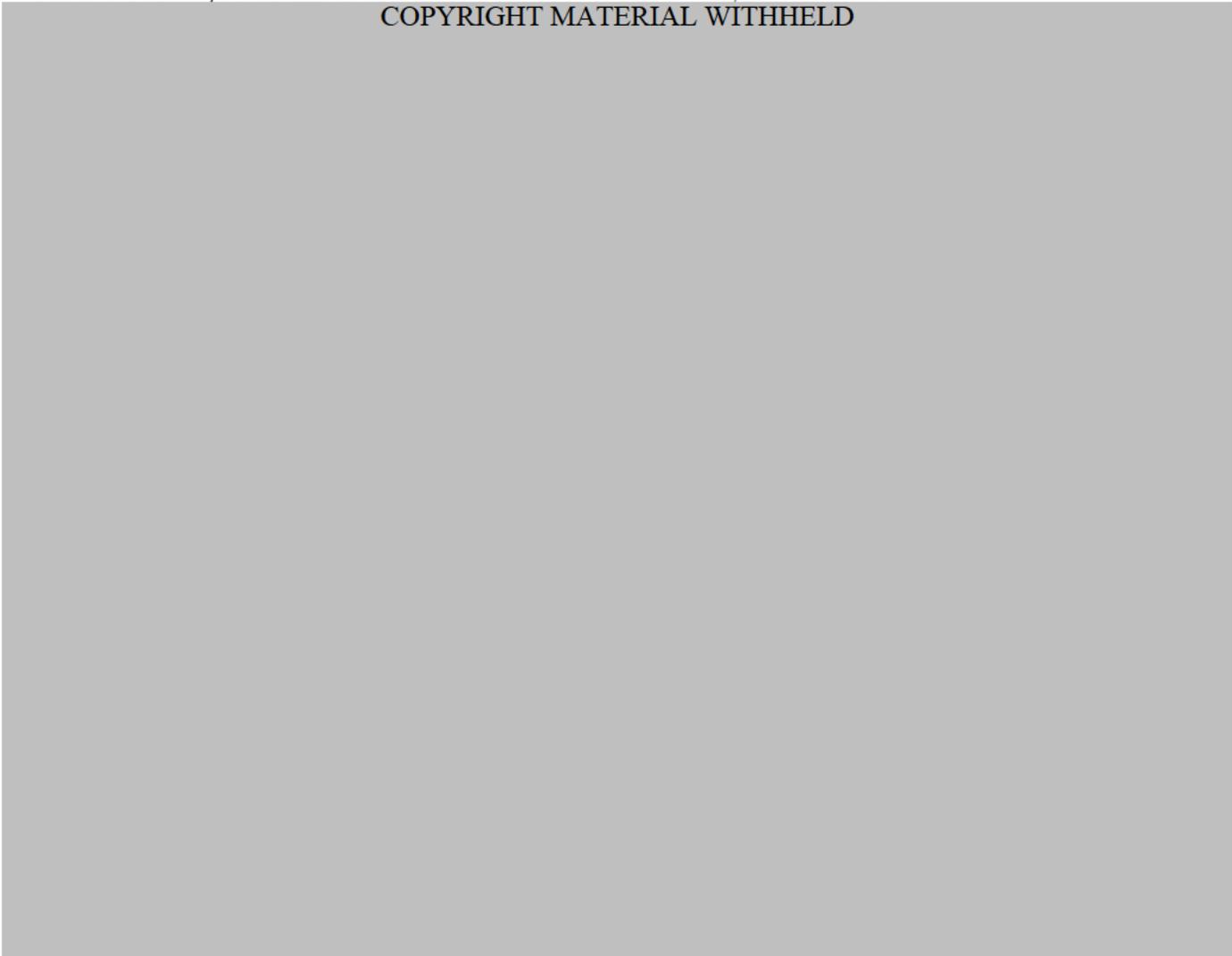


⁹ Setchell and O'Connell, (2007) "Disorders of bile acid synthesis and metabolism: a metabolic basis for liver disease" in *Liver Disease in Children*, Second Edition, Lippincott Williams & Wilkins

¹⁰ 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 and Stieger et al. (1994) Transport of taurine conjugates of 7α -hydroxy-3-oxo-4-cholenoic acid and $3\beta,7\alpha$ -dihydroxy-5-cholenoic acid in rat liver plasma membrane vesicles

¹¹ Mizuochi et al., Molecular Genetic and Bile Acid Profiles in Two Japanese Patients With 3β -Hydroxy- Δ^5 -C₂₇-Steroid Dehydrogenase/Isomerase Deficiency, *Pediatric Research* (2010) 68, 258–263

Table 4 Genetic, biochemical and clinical features of bile acid synthesis defects¹²
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¹² Table 1 from Sundaram et al. (2008) Mechanisms of Disease: inborn errors of bile acid synthesis, Gastroenterology & Hepatology (8); 456

Figure 4 Schematic FAB-MS spectra for various defects in bile acid synthesis (Setchell & Heubi, JPGN 2006)

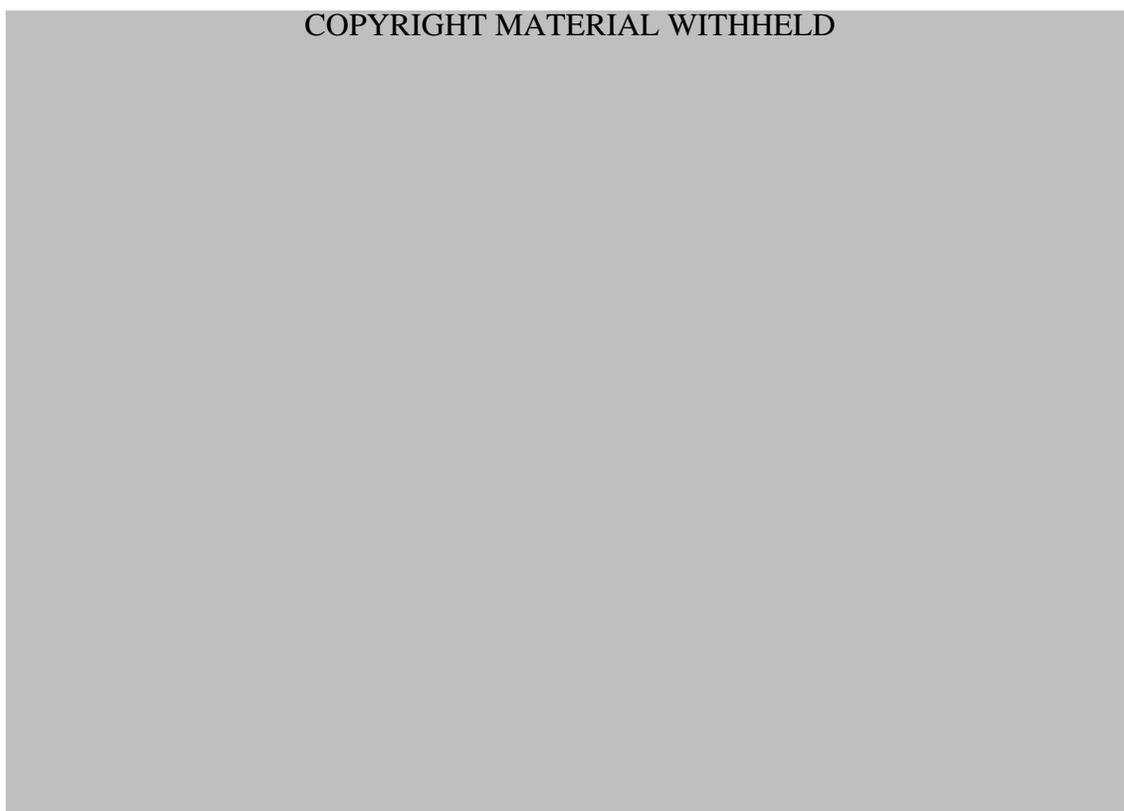
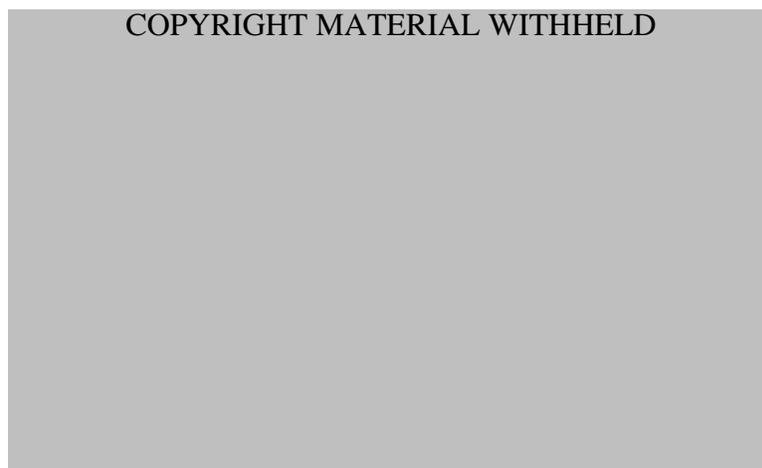


Figure 5 Typical negative ion FAB-MS of the urine from a patient with 3 β -hydroxy-C27-steroid dehydrogenase¹³



It should be noted that analysis of urinary bile acid using GC-MS was not done in studies for this submission.

¹³ Setchell and O'Connell, (2007) "Disorders of bile acid synthesis and metabolism: a metabolic basis for liver disease"

2.2.3 How the proposed dose for cholic acid was determined?

The dosage regimen was empirically determined without an evaluation of dose-response relationship. The sponsor considered the dosage regimens of other bile acid such as UDCA (10 to 15 mg/kg/body weight) and the estimated bile acid pool size; however, did not provide detailed rationale.

Reviewer's comments: The relevancy of doses for other bile acids to the dose for cholic acid is unclear as target patient populations are different in terms of the disease and the age. Ursodeoxycholic acid is a secondary bile acid found in bear not in humans.

In Study CAC-91-10-10, the dose varied significantly (Table 5). The documented first dose on day 1 ranged from 3.3 mg/kg to 26.25 mg/kg¹⁴ and the documented last dose also significantly varied from 3.27 mg/kg to 24.56 mg/kg. The timing of documentation on the last dose also varied from Day 43 to Day 3655. The mean dose on Day 1 was 10.5 mg/kg and 11.4 mg/kg for PD and SED, respectively and similar to the mean from last documented doses.

It was noted that dose has changed over time in some patients. For some patients the dose was documented only for Day 1 and it is unknown if the dose was changed over time or not. Per sponsor, the dose was adjusted on a patient-by-patient basis based on changes in serum LFT results as well as on the extent of reduction of atypical bile acids in urine. However the information on the dosage adjustment with relevant clinical observations including biomarkers at the time of dosage adjustment is not available in this submission. (b) (4)

2.2.4 How cholic acid treatment affected the atypical urinary bile acids?

The analysis and interpretation of data is limited by the bioanalytical assay method which was not validated for quantitative analysis and the insufficient information. (b) (4)

¹⁴ Summary Table for Individual Patient Information Organized by Enzyme Defect (91-10-10) submitted in Amendment dated 4/10/2014

Table 5 Mean observed dose (mg/kg) of cholic acid¹ in Study CAC-91-10-10

Subtype	Subtype	Number of patients	Mean dose on Day 1	Last documented dose
Single enzyme defect		23	10.9 7.8 (median)	11.6 10.95 (median)
	HSD3b7	17	9.21 7.51(median) (n=16)	9.87 10 (median) (n=12)
	AKR1D1	3	18	21 (n=1)
	AMACR	1	8.33	9.26
	Smith-Lemli-Opitz	1	n/a	17.9
	CTX	2	n/a	14.4
	Peroxisomal Disorder		24	10.5 8.3 (median)
Neonatal Adrenoleukodystrophy		14	11 8 (median)	11.6 11.3 (median) (n=8)
Zellwegers		7	9.9 8.2 (median)	7.8 (n=2)
Type unknown		3	9.76	n/a
General		1	7.46	n/a

¹Dosing information is available from a subset of patients based on an amendment dated 4/4/14.

Efficacy analysis based on urinary BA by the sponsor

(b) (4)

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2.2.5. Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Cholic acid, the active moiety of the proposed product and its glycine- and tauro-conjugates were measured in plasma using a validation bioanalytical assay method using LC/MS/MS.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK characteristics of the drug and its major metabolite?

Orally administered cholic acid is subject to the same disposition. The metabolism and enterohepatic circulation of endogenous cholic acid has been summarized in multiple review articles. The sponsor did not conduct any new studies except for a BE study for the PK characterization for cholic acid and its conjugates.

Below is based on literature reviews.

Cholic acid is absorbed by passive diffusion along the length of the gastrointestinal tract. Once absorbed, cholic acids enter into the body's bile acid pool and undergo enterohepatic circulation. Bile acids such as cholic acid are mainly distributed to the enterohepatic circulation, which includes the intestine, portal vein, liver and biliary tract while a small fraction of bile acids is found in the systemic circulation.

Absorbed cholic acids pass to the liver in the portal blood and extracted from portal blood by passive diffusion as well as active transport. In the liver, cholic acid is conjugated with glycine and/or taurine, into a

more hydrophilic form. In humans, glycine-conjugate is the major conjugate form. Conjugated cholic acid is excreted to bile by canalicular transporters such as bile salt efflux pump (BSEP). Conjugated cholic acid is absorbed in the ileum via transporters including apical sodium dependent bile acid transporter (ASBT), passes back to the liver and enters another cycle of enterohepatic circulation.

Any conjugated cholic acid not absorbed in the ileum passes into the colon where deconjugation and 7-dehydroxylation are mediated by bacteria to form deoxycholic acid. Deconjugated cholic acid and deoxycholic acid are passively absorbed in the colon and carried back to the liver in the portal blood, where re-conjugation occurs. Any cholic acid not absorbed will be excreted in the feces, either unchanged or as deoxycholic acid. Under normal physiology, the loss of bile acids via fecal excretion is compensated by the de-novo synthesis of bile acids from cholesterol to maintain the bile acid pool size.

Figure 14 Overview of bile acid transport¹⁸

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¹⁸ Thomas et al. (2008) Targeting bile –acid signaling for metabolic diseases, Nature review Drug Discovery,7: p678-693

2.3 Intrinsic Factors

2.3.1. 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.

2.3.2. 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.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions

No studies were conducted by the sponsor in support of the proposed product.

The sponsor submitted several published literatures to support the proposed labeling about drug interactions. The potential drug interactions with bile acid binding resin, aluminum-based antacids, phenobarbital, cyclosporine, estrogen, oral contraceptive and lipid-lowering agents were proposed in the labeling based on published literatures.

Reviewer's comments: Some publications submitted in support of labeling for drug interactions were either not up-to-date or for studies done in animals. The updated information was requested and the sponsor response was received on 6/30/14. Please see Section 3 for detailed comments on the proposed labeling.

Effects of other drugs on cholic acid

Bile acid binding resin: Typically the bile acid binding resin is used to increase cholesterol catabolism by limiting the reabsorption of bile acids from the intestine which in turn will increase the bile acid formation from cholesterol via negative feedback. Bile acid binding resin reduces the bile acid absorption by forming insoluble complex with bile acids in the intestine. Therefore bile acid binding resins such as cholestyramine, colestipol, or colesevalam can reduce the efficacy of cholic acid by reducing absorption of cholic acid.

When concomitant use of bile acid binding resin and cholic acid in the proposed patient population is necessary, bile acid binding resin should be used at least 1 hour before or 4 hours after cholic acid administration¹⁹.

Inhibitors of BSEP transporter: Drugs that inhibit the biliary excretion of bile salts via inhibition of bile salt export pump (BSEP) can result in accumulation of bile acids including cholic acid in the liver. In in vitro studies, a number of BSEP inhibitors have been suggested including cyclosporine A, rifampicin, and glibenclamide.²⁰

Effects of cholic acid on other drugs

No information was submitted to support the labeling for the potential effects of cholic acid on other drugs. The initiation or discontinuation of cholic acid treatment has a potential to affect PK of other drugs via altering biliary excretion of co-administered drugs in the target patient population.

¹⁹ Package Insert for Cholestyramine

²⁰ Byrne et al. (2002) The human bile salt export pump: Characterization of substrate specificity and identification of inhibitors, *Gastroenterology*, 123 (5); 1649-1658

In addition, cholic acid and its metabolites can alter the activity of CYP enzymes and transporters via activation of nuclear receptors including Farnesoid-X-receptor ^{21, 22, 23}. While cholic acid is expected to be administered life-long from the early life of patients, a caution should be exercised when patients discontinued and resume the cholic acid treatment due to potential effects on concomitant drugs.

2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pharmacy prepared formulation used for patient care under the treatment IND?

The sponsor clarified that the commercial “to-be-marketed” formulation of Cholic Acid (TBM) became available in April 2010 and not administered to any CAC 91-10-10 or 92-8-19 study subject. The TBM formulation was first dispensed to study subjects participating in CAC-001-01. Additionally, those subjects who previously received the liquid preparation of Cholic Acid transitioned to Capsules upon entering the CAC-001-01 study and continued receiving Capsules following study completion.

For treatment with cholic acid prior to the development of commercial drug product, (b) (4) cholic acid was formulated in pharmacy prepared immediate release capsule or in oral liquid formulation. To bridge the clinical data collected using the pharmacy prepared formulation to the to-be-marketed formulation, a BE study was conducted. The BE study was conducted after administration of 250 mg cholic acid twice daily for 4 days in the TBM and the pharmacy compounded formulations. The systemic exposure between the TBM formulation and the pharmacy prepared capsule was generally similar. On the other hand, compared to the oral solution, the TBM formulation resulted in about 56% higher AUC while C_{max} was similar.

Reviewer’s comments: The sponsor proposed a dosage regimen of once a day while the BE study was conducted under twice a day regimen.

While the exposure-response relationship was not studied, the higher systemic exposure after the TBM formulation compared to oral solution raise a question on the safety of the TBM formulation.

In Study CAC-001-01, 16 patients were switched from the Currently Used (CU) cholic acid capsules prepared by the Investigational Pharmacy at CCHMC to the To- Be Marketed (TBM) cholic acid capsules. The primary difference in the 2 investigational drugs was only the source of the API. In this study 6 patients were on liquid formulation prior to switch to the capsule formulation. In this study where cholic acid was administered once a day, no notable safety issues identified during the switch-over. For detailed review of safety profile during the switch-over study, please see the clinical review by Dr. Wen-Yi Gao.

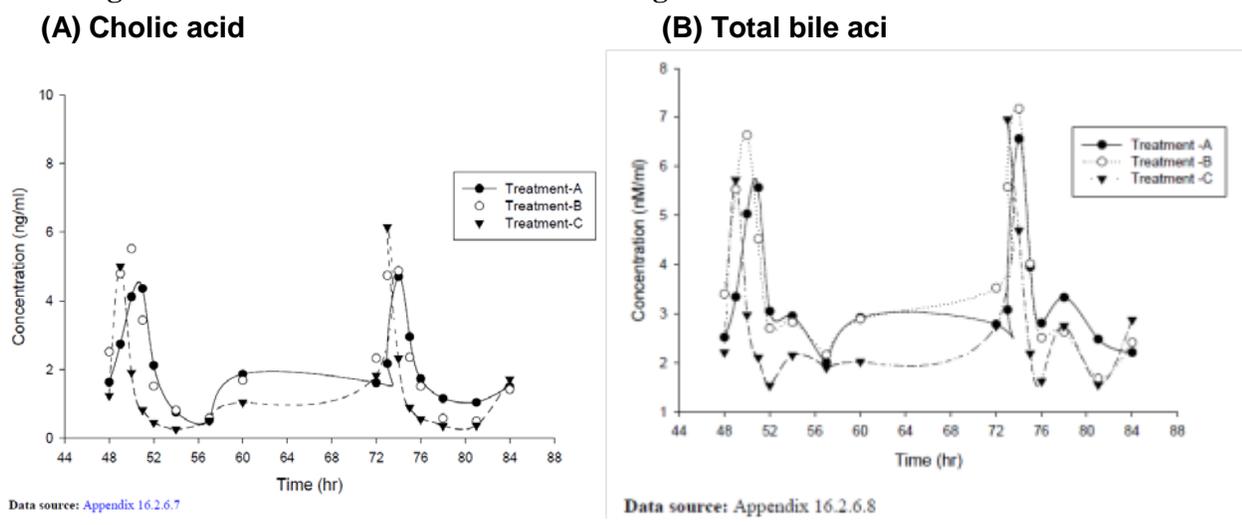
²¹ Jonker et al. (2012) FXR and PXR: Potential therapeutic targets in cholestasis, J. Steroid Biochem. & Mol. Biol. 130: 147-158

²² Matsubara et al. (2013) FXR signaling in the enterohepatic system, Mol. Cell. Endo. 368: 17-29

²³ Zollner et al. (2010) Nuclear receptors as drug targets in cholestasis and drug-induced hepatotoxicity, Pharmacology & Therapeutics 126: 228-243

While the dose is likely to be adjusted based on the patient's response, the dosage adjustment should be based on the response measure rather than the systemic exposure as the exposure-response relationship has not been established.

Figure 15 Mean Concentrations of (A) cholic acid and (B) total cholic acid in Healthy Subjects Following Oral Administration of 3 Different Dosage Forms



Treatment A: Pharmacy prepared capsule
 Treatment B: To-be-marketed capsule
 Treatment C: Oral solution

Table 10 PK parameters of cholic acid following administration of 250 mg twice a day for 4 days

Day 3	Treatment A (N = 17)		Treatment B (N = 18)		Treatment C (N = 17)		p-values*
	Mean	SD	Mean	SD	Mean	SD	
PK Parameter							
T _{max} (hr)	2.3	0.77	1.7	0.669	1.0	0.0	< 0.0001
C _{max} (ng/mL)	6.02	3.75	7.13	3.21	5.01	2.01	0.0728
AUC _{tau} (ng•hr/mL)	21.54	14.13	23.66	10.81	12.87	5.36	< 0.0001
C _{min} (ng/mL)	1.76	1.41	2.11	2.40	1.15	0.95	0.5746
K _{el} (hr ⁻¹)	0.410	0.196	0.321	0.172	0.298	0.132	0.4407
Elim. t _{1/2} (hr)	2.13	1.08	2.96	1.77	3.22	2.73	0.4407
Cl/F (L/hr)	15.01	6.486	12.86	5.806	22.77	9.142	< 0.0001
Vd _{ss} /F (L)	48.766	30.276	56.87	45.164	106.26	83.211	0.0003
Day 4	Mean	SD	Mean	SD	Mean	SD	
PK Parameter							
T _{max} (hr)	3.1	2.50	1.6	0.85	1.6	2.67	< 0.0001
C _{max} (ng/mL)	5.26	2.64	6.26	2.40	6.37	2.60	0.0728
AUC _{tau} (ng•hr/mL)	21.57	12.35	20.52	6.21	15.78	7.34	< 0.0001
C _{min} (nMol/mL)	1.56	1.57	1.88	1.54	1.78	1.44	0.5746
K _{el} (hr ⁻¹)	0.30	0.108	0.333	0.114	0.308	0.119	0.4407
Elim. t _{1/2} (hr)	3.11	2.91	2.39	1.01	2.78	1.675	0.4407
Cl/F (L/hr)	14.56	6.145	13.57	5.31	19.90	10.38	< 0.0001
Vd _{ss} /F (L)	54.87	19.23	48.10	35.385	120.32	116.80	0.0003

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

*Note: p-values based upon combined Day 3 & Day 4 LS-Means

Table 11 Bioequivalence Determination of Cholic Acid PK Parameters AUC and Cmax for Three Cholic Acid Formulations

Parameter	Pair (Test:Ref)	Reference	Test	Difference Test-Reference	Ratio Test/Reference	(90% Conf Interval)
AUC _{tau}	B:A					(b) (4)
	A:C					
	B:C					
C _{max}	B:A					
	A:C					
	B:C					

Data source: [Appendix 16.2.2.6A](#)
 Where A = cholic acid 250 mg Capsule (Pharmacy)
 Where B = cholic acid 250 mg Capsule (cGMP)
 Where C = cholic acid 250 mg Oral Solution

Table 12 PK parameters of total cholic acid following administration of 250 mg twice a day for 4 days

Day 3	Treatment A (N = 17)		Treatment B (N = 18)		Treatment C (N = 17)		p-values*
	Mean	SD	Mean	SD	Mean	SD	
PK Parameter							
T _{max} (hr)	2.4	0.71	2.7	2.59	2.2	3.19	
C _{max} (nMol/mL)	7.26	4.55	8.45	3.95	5.82	2.29	0.0380
AUC _{tau} (nMol•hr/mL)	37.52	16.94	40.30	17.52	28.29	12.97	< 0.0001
C _{min} (nMol/mL)	2.71	1.39	3.14	3.16	2.11	1.19	0.4470
Day 4							
PK Parameter							
T _{max} (hr)	2.8	2.43	2.0	0.91	1.77	2.66	
C _{max} (nMol/mL)	7.06	3.33	8.31	4.48	7.46	3.23	0.0380
AUC _{tau} (nMol•hr/mL)	38.24	18.11	37.48	18.14	33.45	14.81	< 0.0001
C _{min} (nMol/mL)	2.49	1.61	2.96	1.63	2.81	1.62	0.4470

Data source:: [Appendix 16.2.6.2A](#) and [Appendix 16.2.6.2B](#) and [Appendix 16.2.6.6](#)
 *Note: p-values based upon combined Day 3 & Day 4 LS-Means

Table 13 Bioequivalence Determination of Total Cholic Acid PK Parameter for Three Cholic Acid Formulations

Parameter	Pair (Test:Ref)	Reference	Test	Difference Test-Reference	Ratio Test/Reference	(90% Conf Interval)
AUC _(Tau)	B:A					(b) (4)
	A:C					
	B:C					
C _{max}	B:A					
	A:C					
	B:C					

Data source: [Appendix 16.2.2.6B](#)
 Where A = cholic acid 250 mg Capsule (Pharmacy)
 Where B = cholic acid 250 mg Capsule (cGMP)
 Where C = cholic acid 250 mg Oral Solution

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma/urine in the clinical pharmacology and biopharmaceutics studies?

Plasma concentrations of cholic acid, glycocholic acid, and taurocholic acid were measured by a validated method using LC/MS/MS. The validation report titled “Validation report for method BTM-1365-R0: Determination of cholic acid, glycocholic acid, and taurocholic acid in human plasma by LC/MS/MS” was submitted for the analysis in Study CAC-003-01.

The validation report titled “Determination of conjugated and unconjugated bile acids in human serum” was submitted for the analysis in Study CAC-001-01.

2.6.2 How are the abnormal bile acids identified and measured in the urine in the clinical trials?

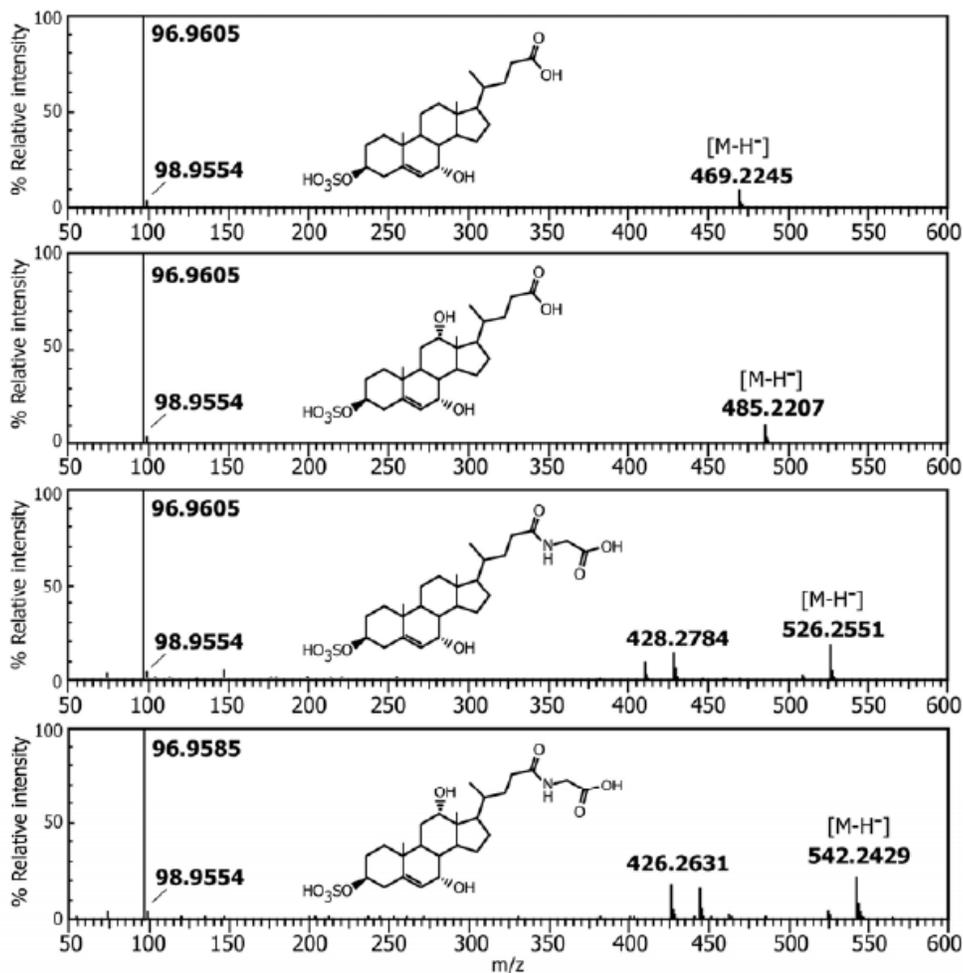
The abnormal bile acids were measured in spot urine samples by a method using Fast-Atom-Bombardment (FAB)-MS. The bioanalytical assay method was qualitatively validated for the detectability of mass peaks of interest (Report titled: Qualitative Fast Atom FAST ATOM BOMBARDMENT BY MASS SPECTROMETRY). Tuning and calibration standard was glycerol. The instrument was tuned before each day of analysis by optimizing all relevant parameters to obtain the best signal strength. Quality control standards were previously confirmed urine samples from studies. Before running a batch of urines for interpretation, glycerol, normal urine, cholestatic urine, and 3 β -HSD urines were ran and evaluated. Before any new samples were run, the quality control samples passed the minimum standards of acceptability.

Reviewer’s comments: The assay has been used by the principal investigators as a diagnostic tool by comparing the pattern of peaks in mass spectra between normal samples and samples from suspected patients. The identification of bile acids of interest was done by molecular structure prediction based on mass fragmentation pattern. (b) (4)

As such the FAB-MS method for urinary atypical bile acids is not adequately validated for the quantitative assessment of atypical bile acids in urine for each bile acid synthesis defect.

The sponsor submitted additional information on the LC-MS assay validation report. Because LC-MS was not used for the analysis of samples from the submitted studies, the report was not reviewed in detail. The LC-MS assay was done with synthesized and supported the identities of mass peaks characteristics of atypical bile acids found in patients with deficiency in HSD3b7.

Figure 16 Mass spectra of atypical bile acids in patients with deficiency in HSD3 β 7



Submitted in an amendment dated 2/27/14

Mass spectra of 3 β ,7 α -dihydroxy-5-cholenoic acid and 3 β ,7 α ,12 α -trihydroxy-5-cholenoic acid 3-sulfate and the corresponding glyco-sulfate conjugates acquired by electrospray ionization and recorded in negative ion mode on Q-TOF mass spectrometer at high resolution to determine accurate mass measurement. Singly charged deprotonated ions at m/z 469.2245, 526.2551, 485.2207, 542.2429 and their common daughter ion m/z 96.9605 are evident.

2.6.3 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

Table 14 Validation Summary Table for the determination of cholic acid, glycocholic acid, and taurocholic acid

Report location	Central Data Room (b) (4)			
Method description	Method BTM-1365-R0 is an LC/MS/MS method for the determination of cholic acid, glycocholic acid, and taurocholic acid in K ₂ EDTA human plasma using cholic acid-d ₄ and glycocholic acid-d ₄ as the internal standards (IS). Cholic acid, glycocholic acid, taurocholic acid and their respective IS were extracted by solid phase extraction from human plasma. Reversed-phase HPLC separation was achieved (b) (4)			
Sample volume	100 µL			
Regression	Linear Regression			
Weighting factor	1/x ²			
Dynamic range	2/2/2-2000/2000/2000 ng/mL for cholic acid\glycocholic acid\taurocholic acid			
QC concentrations	6 ng/mL, 55.982 ng/mL ¹ , 600 ng/mL, and 1500 ng/mL for cholic acid 6 ng/mL, 243.747 ng/mL ¹ , 600 ng/mL, and 1500 ng/mL for glycocholic acid 6 ng/mL, 23.927 ng/mL ¹ , 600 ng/mL, and 1500 ng/mL for taurocholic acid			
Analytes	Cholic Acid	Glycocholic Acid	Taurocholic Acid	
Internal standards	Cholic Acid-d ₄	Glycocholic Acid-d ₄	Glycocholic Acid-d ₄	
Linearity	R ² ≥0.9946	R ² ≥0.9942	R ² ≥0.9943	
Lower limit of quantitation (LLOQ)	2 ng/mL	2 ng/mL	2 ng/mL	
Average recovery of the Analyte (%)	82.7	88.7	88.2	
QC Intra-run precision range (%CV) on an API 5000	Run 1	1.8-3.4	0.7-3.3	0.7-3.0
	Run 2	2.3-4.7	2.0-5.2	2.2-5.8
	Run 3	2.4-4.8	1.1-4.7	1.7-5.0
QC Intra-run accuracy range (%Nominal) on an API 5000	Run 1	92.5-96.3	90.2-97.7	88.6-92.8
	Run 2	91.4-105.8	93.2-107.5	91.8-99.6
	Run 3	94.9-100.4	92.7-106.6	88.1-99.1
QC Inter-run precision range (%CV) on an API 5000	3.9-5.7	2.9-4.6	2.8-5.0	
QC Inter-run accuracy range (%Nominal) on an API 5000	92.9-100.4	92.1-103.9	90.0-96.6	
QC Intra-run precision range (%CV) on an API 4000	3.6-6.9	2.0-11.5	2.4-6.3	
QC Intra-run accuracy range (%Nominal) on an API 4000	97.5-104.9	94.7-102.2	96.7-107.0	
QC sample bench-top stability	At least 6 hours at room temperature in human plasma			

3 Labeling Recommendations

Reviewer's general comments

The sponsor proposes the labeling of Sections 7 and 12 are exclusively based on the published literatures. In general the submitted supporting publications are not most up-to-date and some studies were done in animal models. Labeling based on the study in animal model only is not acceptable for Clinical Pharmacology Section unless the relevancy of such information to humans is further supported.

In addition the clinical implications for drug interactions in the target population are complex. Concomitant drugs that may alter the PK of cholic acid can also influence the bile acid homeostasis in the target population. And the PD effects of cholic acid via alteration of excretion of bile acids can also affect the disposition of concomitant drugs.

Detailed labeling languages will be communicated to the sponsor during the labeling negotiation.

The proposed labeling languages and reviewer's comments are as followings:

Section 7

Proposed labeling language and supporting reference

(b) (4)

(b) (4)

Drug interactions with [TRADENAME[®]] mainly relate to agents capable of interrupting the enterohepatic circulation of bile acids (b) (4)
(Gallaher and Schneeman, 1986).

(b) (4)

(b) (4) Aluminum-based antacids have been shown to adsorb bile acids in vitro and (b) (4)
(b) (4) reduce the bioavailability of [TRADENAME[®]]

Review of the literature and reviewer's comments

- "Intestinal interaction of bile acids, phospholipids, dietary fibers, and cholestyramine" [Am J Physiol](#). 1986 Apr; 250(4 Pt 1):G420-6.
 - In this publication, binding of bile acids to a number of dietary fibers and cholestyramine within the small intestine was determined in rats after feeding cholic acid diet for 14 days and a number of dietary fibers and cholestyramine on day 14. In this study cholestyramine administration reduce the solubilized bile acids in aqueous phase of the intestinal contents.

While this study was not done in humans, cholestyramine, colestipol and colesevalam are known bile acid sequestrants which bind bile acids in humans.

(b) (4)

Reviewer's comments: Acceptable to include in the labeling after a revision to be consistent with the current labeling for cholestyramine.

Current labeling for cholestyramine recommends following:

Since cholestyramine resin may bind other drugs given concurrently, it is recommended that patients take other drugs at least 1 hour before or 4 to 6 hours after cholestyramine resin (or at as great an interval as possible) to avoid impeding their absorption.

Proposed labeling language and supporting reference

(b) (4)

Review of the literature and reviewer's comments

(b) (4)

Reviewer's comments:

(b) (4)

We recommend deletion of this statement because the relevance of this observation to the target patient population is unclear and not supported.

(b) (4)

Proposed labeling language and supporting reference

(b) (4)

Review of the literature and reviewer's comments

(b) (4)

Reviewer's comments:

(b) (4)

The relevance (b) (4) for cholic acid when co-administered with (b) (4) is not supported.

Proposed labeling language and supporting reference

(b) (4)

Review of the literature and reviewer's comments

- (b) (4)

- [Redacted] (b) (4)

Reviewer's comments:

We recommend deletion of this statement because the relevance [Redacted] (b) (4) were not supported by the sponsor's submission.

The sponsor's proposal is similar to the labeling for [Redacted] (b) (4) product [Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

Proposed labeling language and supporting reference

[Redacted] (b) (4)

Reviewer's comments: It is acceptable to include a statement about potential drug interactions with

²⁴ <http://livertox.nlm.nih.gov/Clofibrate.htm>

drugs that inhibit transporters especially BSEP. However the labeling about the (b) (4) is not supported.

Proposed labeling language and supporting reference

(b) (4)

Reviewer's comments:

(b) (4)

(b) (4) the statement should be deleted.

4 Appendices

4.1 OCP Filing Form

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	205-750	Brand Name	To-be-determined	
OCP Division (I, II, III, IV, V)	DCP 3	Generic Name	Cholic acid	
Medical Division	DGIEP	Drug Class	Bile acid	
OCP Reviewer	Insook Kim, Ph.D.	Indication(s)	(b) (4)	
OCP Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	50 mg and 250 mg powder filled capsules	
Date of Submission	November 21, 2013	Dosing Regimen	10-15 mg/kg once daily in both pediatric and adult patients	
Estimated Due Date of OCP Review	April 24, 2014	Route of Administration	Oral	
Medical Division Due Date	June 16, 2014	Sponsor	Askelcion Pharmaceuticals, LLC	
PDUFA Due Date	July 21, 2014	Priority Classification	Priority	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods:	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			CAC-003-01
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	x	2		CAC-91-10-10 CAC-001-01
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design: single / multi dose:	x	1		CAC-003-01
replicate design: single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x	5		Drug disposition and drug interaction information in the label
Total Number of Studies				

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			To be reviewed by biopharmaceutics reviewers in the ONDQA
2	Has the applicant provided metabolism and drug-drug interaction information?	x			Based on published literatures
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA	x			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

	organized, indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		x		Mass spectra for urinary bile acids in individual patients were not submitted.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Pediatric patients data are included in this submission
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			Labeling for cholic acid disposition proposed mainly based on published literatures PK data from CAC-003-01 should be also included
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	All in English

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable

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

- We note that the bioanalytical assay validation for urinary bile acids was done in a qualitative assessment not for quantitative assessment. (b) (4)
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. This will be a review issue in assessment of the suppression of the synthesis of atypical bile acids by cholic acid treatment.

Following information requests have been conveyed to the sponsor on 1/15/14

- For studies CAC 001-01 and CAC 91-10-10, please submit the mass spectra for individual patients for urine bile acids before, during and after treatment. For each spectrum, we recommend that atypical bile acids be identified and the signal-to-noise ratio be documented.
- In the report of Study CAC-001-01, the units for tabulated values and footnotes are missing in all Tables. We recommend that Tables updated with units and relevant footnotes be submitted.
- The chromatograms presented in the LC-MS validation report-serum-complete (16.1.10) is not legible e.g. Figures 1 and 2 in pages 19-20. We recommend resubmission of legible chromatograms.
- Please clarify whether urine samples collected for bile acids were analyzed by FAB-MS on the same day or different days.

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- Please submit the normal range of atypical bile acids in healthy subjects if such information is available.

Filing memo

The sponsor proposes to support safety and efficacy of cholic acid in proposed target patient population mainly based on a series of treatment cases collected over 18 years under a treatment IND. Study CAC-91-10-10 entitled an Investigation in the Pathogenesis of Liver Disease in Patients with Inborn Errors of Bile Acid Metabolism, was conducted from 1992-2009 and 85 patients were enrolled to evaluate the therapeutic efficacy and safety of cholic acid to treat patients with identified inborn errors of bile acid metabolism.

The study reports for clinical trials including one bioequivalence study were submitted. No other clinical pharmacology related studies were submitted. The labeling of drug interaction and description of cholic acid disposition was mainly based on the published literatures.

In this application, therapeutic efficacy was evaluated by assessing the effects of the administration of cholic acid on:

(1) suppression of synthesis of atypical bile acids as measured by urine bile acid analysis using mass spectrometry; (2) serum transaminases and bilirubin; (3) height/weight gain; (4) change in liver histology (for patients in whom biopsy was performed).

For the urinary bile acid analysis, only the urinary bile acid excretion elevation categories were reported (not the actual bile acid measurements themselves).

In Study CAC-91-10-10, patients were mostly treated with cholic acid in a pharmacy compounded capsule until the to-be-marketed capsule formulation was developed in 2011. To bridge the safety and efficacy between pharmacy formulation and the to-be-marketed capsule, a bioequivalence study with PK endpoints (Study CAC-003-01) was conducted in healthy subjects.

In addition, a switch-over study was conducted in pediatric patients. In study CAC-001-01, patients already receiving the hospital pharmacy prepared cholic acid capsules were switched to the proposed commercial capsules for 30 days.

The bioequivalence study CAC-003-01 will be reviewed by a biopharmaceutics reviewer in the ONDQA. Clinical pharmacology review will be focused on the assay for urinary bile acids using FAB-MS and the labeling based on published literatures.

List of Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase III	CAC-001-01	5.3.1.1	To evaluate the therapeutic efficacy of TBM cholic acid compared with the effect of the CU formulation of cholic acid to treat patients with identified inborn errors of bile acid metabolism. To assess safety and tolerability of TBM cholic acid capsules in this population.	Open label, single centre, nonrandomised, comparative, cohort study. Patients served as their own controls.	Cholic acid 50 mg and 250mg capsules 10-15 mg/kg/ day in divided doses Route: oral	16	Patients with inborn errors of bile acid metabolism.	1 month	Complete; Full
Phase I	Study CAC-003-01	5.3.3.1	To evaluate the relative bioavailability/ bioequivalence, pharmacokinetics and safety of multiple oral doses of a new cGMP produced cholic acid capsule formulation.	Randomized, three-way crossover study.	Cholic Acid 250 mg capsule (cGMP formulation) Cholic acid 250 mg capsule (Pharmacy formulation) or Cholic acid 250 mg oral solution 25 mL (cGMP formulation) . every 12 hours Route: oral	18	Healthy	4d x 3	Complete; full
Phase III	CAC-91-10-10	5.3.5.1	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.	Open-label single arm, non-comparative study	Cholic acid 250 mg capsules or liquid (15mg/ml) 10-15 mg/kg/ day in divided doses Route: oral	85	Patients with inborn errors of bile acid metabolism.	Overall study duration: up to 18 years Individual treatment duration: 1 day to 10.5 years	Complete; full

TBM = to be marketed; CU = currently used

Insook Kim, Ph.D.

1/17/14

Reviewing Clinical Pharmacologist

Date

Yow-Ming Wang, Ph.D., Acting deputy division director on behalf of Sue-Chih Lee, Ph.D. 1/17/14

Team Leader/Supervisor

Date

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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.

/s/

INSOOK KIM
07/23/2014

SUE CHIH H LEE
07/23/2014

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205-750	Brand Name	To-be-determined
OCP Division (I, II, III, IV, V)	DCP 3	Generic Name	Cholic acid
Medical Division	DGIEP	Drug Class	Bile acid
OCP Reviewer	Insook Kim, Ph.D.	Indication(s)	(b) (4)
OCP Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	50 mg and 250 mg powder filled capsules
Date of Submission	November 21, 2013	Dosing Regimen	10-15 mg/kg once daily in both pediatric and adult patients
Estimated Due Date of OCP Review	April 24, 2014	Route of Administration	Oral
Medical Division Due Date	June 16, 2014	Sponsor	Askelpion Pharmaceuticals, LLC
PDUFA Due Date	July 21, 2014	Priority Classification	Priority

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			CAC-003-01
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

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renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	x	2		CAC-91-10-10 CAC-001-01
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		CAC-003-01
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x	5		Drug disposition and drug interaction information in the label
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			To be reviewed by biopharmaceutics reviewers in the ONDQA
2	Has the applicant provided metabolism and drug-drug interaction information?	x			Based on published literatures
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA	x			

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	organized, indexed and paginated in a manner to allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		x		Mass spectra for urinary bile acids in individual patients were not submitted.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Pediatric patients data are included in this submission
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	

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17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			Labeling for cholic acid disposition proposed mainly based on published literatures PK data from CAC-003-01 should be also included
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	All in English

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable

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Team Leader/Supervisor

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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.

/s/

INSOOK KIM
01/17/2014

YOW-MING C WANG
01/17/2014

I am signing off on behalf of the TL (Dr. Sue Chih Lee) while she is on leave.