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

Summary

EudraCT number	2011-004491-10
Trial protocol	Outside EU/EEA
Global end of trial date	23 August 2010

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	CAC-001-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01115582
WHO universal trial number (UTN)	-
Other trial identifiers	CCHMC Clinical Equivalence Study: CAC-001-01

Notes:

Sponsors

Sponsor organisation name	Retrophin, Inc.
Sponsor organisation address	12255 El Camino Real, Suite 250, San Diego, United States, CA 92130
Public contact	Retrophin Medical Information, Retrophin, Inc., +1 877659 5518, medinfo@retrophin.com
Scientific contact	Retrophin Medical Information, Retrophin, Inc., +1 877659 5518, medinfo@retrophin.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000651-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 August 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 August 2010
Global end of trial reached?	Yes
Global end of trial date	23 August 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the therapeutic efficacy of TBM cholic acid capsules compared with the effect of the CU formulation of cholic acid prepared in the CCHMC Pharmacy.

Protection of trial subjects:

Not specified

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	16
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	1
Children (2-11 years)	13
Adolescents (12-17 years)	1
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 16 patients were enrolled. The first patient was enrolled on 28 Apr 2010 and the last patient was enrolled on 24 May 2010.

Pre-assignment

Screening details:

Patients with inborn defects of bile acid synthesis who were currently receiving cholic acid capsules prepared by the Cincinnati Children's Hospital Medical Center (CCHMC) under IND 45,470.
The study planned to include 25 patients; however, only 16 patients fulfilled the eligibility criteria and were willing to travel to the CCHMC.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Cholic acid

Arm description:

All patients entered and treated

Arm type	Experimental
Investigational medicinal product name	Cholic Acid 50 mg and 250 mg Capsules
Investigational medicinal product code	
Other name	Kolbam®, Cholbam®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Daily dose of 10-15 mg/kg body weight, administered once daily or in divided doses at the discretion of the investigator.
Dose adjustment on a patient-by-patient basis was possible based on changes in serum liver function test parameters and changes atypical bile acid metabolites in urine.

Number of subjects in period 1	Cholic acid
Started	16
Completed	16

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	1	1	
Children (2-11 years)	13	13	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	1	1	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	7.8		
standard deviation	± 4.6	-	
Gender categorical Units: Subjects			
Male	11	11	
Female	5	5	

Subject analysis sets

Subject analysis set title	All patients
Subject analysis set type	Intention-to-treat

Subject analysis set description:
All patients entered and treated

Reporting group values	All patients		
Number of subjects	16		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	1		
Children (2-11 years)	13		
Adolescents (12-17 years)	1		
Adults (18-64 years)	1		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years			
arithmetic mean	7.8		
standard deviation	± 4.6		
Gender categorical Units: Subjects			
Male			
Female			

End points

End points reporting groups

Reporting group title	Cholic acid
Reporting group description:	
All patients entered and treated	
Subject analysis set title	All patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients entered and treated	

Primary: Serum transaminases

End point title	Serum transaminases[1]
End point description:	
Concentration of serum alanine transaminase (ALT) and aspartate transaminase (AST)	
End point type	Primary
End point timeframe:	
At baseline and after 30 days of treatment	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This Primary endpoint was analysed using descriptive statistics only. No inferential testing was applied. A p-value was not defined.

End point values	Cholic acid			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: U/L				
arithmetic mean (standard deviation)				
ALT, baseline	31.4 (± 21.9)			
ALT, Day 30	30.9 (± 24)			
AST, baseline	62.7 (± 27.1)			
AST, Day 30	65 (± 39)			

Statistical analyses

No statistical analyses for this end point

Primary: Serum and urine bile acids

End point title	Serum and urine bile acids[2]
End point description:	
Concentration of bile acids in serum (S) and urine (U) (abbreviations: chol.=cholenoic; monohydro=monohydroxy; dihydro=dihydroxy)	
End point type	Primary
End point timeframe:	
At baseline (BL) and after 30 days of treatment (D30)	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This Primary endpoint was analysed using descriptive statistics only. No inferential testing was applied. A p-value was not defined.

End point values	Cholic acid			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: mmol/L				
arithmetic mean (standard deviation)				
U, BL: 3β,7α-dihydroxy-Δ5 sulfate m/z 469	12.37 (± 35.31)			
U, D30: 3β,7α-dihydroxy-Δ5 sulfate m/z 469	2.762 (± 3.955)			
U, BL: 3β,7α,12α-trihydroxy-Δ5 sulfate m/z 485	14.11 (± 42.78)			
U, D30: 3β,7α,12α-trihydroxy-Δ5 sulfate m/z 485	2.011 (± 2.995)			
U, BL: 3β,7α-dihydroxy-Δ5 gluycosulfate m/z 526	159.85 (± 474.52)			
U, D30: 3β,7α-dihydroxy-Δ5 gluycosulfate m/z 526	19.958 (± 29.341)			
U,BL: 3β,7α,12α-trihydroxy-Δ5 glycosulfate m/z 542	105.43 (± 337.05)			
U,D30:3β,7α,12α-trihydroxy-Δ5 glycosulfate m/z 542	5.421 (± 7.633)			
S, BL: Glyco-3-oxo-7-α,12α-dihydro.-4-chol. m/z460	0.15 (± 0.07)			
S,D30:Glyco-3-oxo-7-α,12α-dihydro.-4-chol. m/z 460	0.055 (± 0.078)			
S,BL: Glyco-3-oxo-7-α,12α-monohydro.-4-chol.m/z444	0.14 (± 0.01)			
S,D30:Glyco-3-oxo-7-α,12α-monohydro.-4-chol.m/z444	0.14 (± 0.184)			
S,BL:Tauro-3-oxo-7-α,12α-dihydroxy-4-chol. m/z 510	0.52 (± 0.23)			
S,D30:Tauro-3-oxo-7-α,12α-dihydroxy-4-chol. m/z510	0.49 (± 0.679)			
S,BL:Tauro-3-oxo-7-α,12α-monohydro.-4-chol. m/z498	0.05 (± 0.04)			
S,D30:Tauro-3-oxo-7-α,12α-monohydro.-4-chol.m/z498	0.02 (± 0.028)			
U, BL: Total 3β-hydroxy-Δ5 bile acids	291.77 (± 889.56)			
U, D30: Total 3β-hydroxy-Δ5 bile acids	30.148 (± 43.582)			
S, BL: Total 3-oxo-Δ4 bile acids	0.84 (± 0.13)			
S, D30: Total 3-oxo-Δ4 bile acids	0.705 (± 0.601)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events

End point description:

Total number of patients with adverse events

End point type	Secondary

End point timeframe:

From start of treatment through to 30 days after the start of treatment

End point values	Cholic acid			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Patients				
Number of patients with adverse events	9			
Number of patients at risk	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Blood pressure

End point title	Blood pressure

End point description:

Systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point type	Secondary

End point timeframe:

At baseline and after 30 days of treatment

End point values	Cholic acid			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: mmHg				
arithmetic mean (standard deviation)				
SBP, baseline	106.9 (± 10.2)			
SBP, Day 30	109.6 (± 6.6)			
DBP, baseline	63.9 (± 6.7)			
DBP, Day 30	65.4 (± 6.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Physical examination

End point title	Physical examination

End point description:

Total number of patients with abnormal findings from general physical examination

End point type	Secondary

End point timeframe:

At baseline and after 30 days of treatment

End point values	Cholic acid			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Patients				
Baseline, patients with abnormal physical finding	0			
Baseline, patients at risk	16			
D30, patients with abnormal physical findings	0			
D30, patients at risk	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Total bilirubin

End point title	Total bilirubin

End point description:

Concentration of total bilirubin in serum

End point type	Secondary

End point timeframe:

At baseline and after 30 days of treatment

End point values	Cholic acid			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline, total bilirubin	0.35 (± 0.37)			
Day 30, total bilirubin	0.32 (± 0.28)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Total of 30 days, i.e. from the time point the patients entered into the study up to the end of treatment	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups	
Reporting group title	Cholic acid
Reporting group description:	
All patients entered and treated	

Serious adverse events	Cholic acid		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cholic acid		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 16 (56.25%)		
Investigations			

ALT increased	Additional description: In the clinical study Report, this event was counted towards the Body System "Hepatobiliary"		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
AST increased	Additional description: In the clinical study Report, this event was counted towards the Body System "Hepatobiliary"		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vascular disorders			
Nosebleed	Additional description: In the clinical study report, this event was counted towards the Body System "Eye, ear, nose, throat"		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
General disorders and administration site conditions			
Decreased/low 250H/vitamin D			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Decreased vitamin D			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Reflux			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle spasm			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2010	Protocol amended to remove the sentence, "For each visit, parents will be compensated $200 to cover lost wages and incidental expenses." This sentence was inadvertently left in the protocol from a previous version.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported