Clinical trial results:
A Pilot, Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of LUM001, an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Primary Sclerosing Cholangitis (PSC)

Summary

EudraCT number	2014-005558-21
Trial protocol	GB
Global end of trial date	12 February 2016

Results information

Result version number	v1 (current)
This version publication date	07 January 2017
First version publication date	07 January 2017

Trial information

Trial identification

Sponsor protocol code	LUM001-401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02061540
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lumena Pharmaceutical LLC
Sponsor organisation address	300 Shire Way, Lexington, MA, United States, 02421
Public contact	Study Physician, Shire, 1 866-842-5335,
Scientific contact	Study Physician, Shire, 1 866-842-5335,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of LUM001 in subjects with Primary Sclerosing Cholangitis (PSC) during 14 weeks of treatment.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization of Good Clinical Practice, with exceptions that have been addressed, as well as all applicable federal, local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	27
EEA total number of subjects	4

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	25
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 8 centers in Great Britain, Canada, and the United States between 22 April 2014 (first subject first visit) and 12 February 2016 (last subject last visit).

Pre-assignment

Screening details:

A total of 37 subjects were screened, of them 27 subjects were enrolled in the study. 5 subjects were down-titrated during the study.

Period 1

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

Arms

Arm title	Maralixibat (LUM001)

Arm description:

Subjects received LUM001 tablet orally once daily at a dose of 0.5 milligram (mg) during Week 1; 1 mg during Week 2; 2.5 mg during Week 3; 5 mg during Week 4; 7.5 mg during Week 5; 10 mg during Week 6 followed by stable dosing of 10 mg for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Maralixibat chloride
Investigational medicinal product code	LUM001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received LUM001 tablet orally at a dose of 0.5 milligram (mg); 1 mg; 2.5 mg; 5 mg; 7.5 mg; 10 mg.

Number of subjects in period 1	Maralixibat (LUM001)
Started	27
Completed	23
Not completed	4
Consent withdrawn by subject	2
Adverse event, non-fatal	2

Baseline characteristics

Reporting groups	
Reporting group title	Maralixibat (LUM001)
Reporting group description:	
Subjects received LUM001 tablet orally once daily at a dose of 0.5 milligram (mg) during Week 1; 1 mg during Week 2; 2.5 mg during Week 3; 5 mg during Week 4; 7.5 mg during Week 5; 10 mg during Week 6 followed by stable dosing of 10 mg for 8 weeks.	

Reporting group values	Maralixibat (LUM001)	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years arithmetic mean standard deviation	 43.7 ± 11.35	 -	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	9	9	
Male	18	18	

End points

End points reporting groups

Reporting group title	Maralixibat (LUM001)
Reporting group description:	
Subjects received LUM001 tablet orally once daily at a dose of 0.5 milligram (mg) during Week 1; 1 mg during Week 2; 2.5 mg during Week 3; 5 mg during Week 4; 7.5 mg during Week 5; 10 mg during Week 6 followed by stable dosing of 10 mg for 8 weeks.	
Subject analysis set title	Maralixibat (LUM001) 1 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received LUM001 tablet orally once daily at a dose of 1 mg during Week 2 of the treatment period.	
Subject analysis set title	Maralixibat (LUM001) 2.5 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received LUM001 tablet orally once daily at a dose of 2.5 mg during Week 3 of the treatment period.	
Subject analysis set title	Maralixibat (LUM001) 5 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received LUM001 tablet orally once daily at a dose of 5 mg during Week 4 of the treatment period.	
Subject analysis set title	Maralixibat (LUM001) 7.5 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received LUM001 tablet orally once daily at a dose of 7.5 mg during Week 5 of the treatment period.	
Subject analysis set title	Maralixibat (LUM001) 10 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received LUM001 tablet orally once daily at a dose of 10 mg during Week 6 of the treatment period followed by stable dosing of 10 mg for 8 weeks.	

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)[1]
End point description:	
An Adverse Event (AE) was defined as any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE was considered to be related to the investigational drug product. TEAEs were AEs with a start date on or after the first dose of investigational product and started prior to the last dose of investigational product plus 14 days. Safety population included all subjects who received at least 1 dose of the investigational product was analysed for this end point.	
End point type	Primary
End point timeframe:	
From start of study drug administration until Week 18	

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: Inferential statistical analysis was not performed since descriptive statistical analysis was planned for this endpoint.

End point values	Maralixibat (LUM001)	Maralixibat (LUM001) 1 mg	Maralixibat (LUM001) 2.5 mg	Maralixibat (LUM001) 5 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	27	1	2	2
Units: subject	25	1	2	2

End point values	Maralixibat (LUM001) 7.5 mg	Maralixibat (LUM001) 10 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	21		
Units: subject	1	19		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Fasting Serum Bile Acid Level at Week 14

End point title	Change From Baseline in Fasting Serum Bile Acid Level at Week 14[2]

End point description:

Serum bile acid levels were evaluated using blood samples collected. Modified intent-to-treat (mITT) population included all subjects who received at least 1 dose of investigational product and had at least 1 post baseline serum bile acid laboratory assessment was analysed for this end point.

End point type	Primary

End point timeframe:

Baseline, Week 14

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: EudraCT database does not allow to report only one treatment group in statistical analyses section. Due to this format constraint, we are not able to present within the group inferential statistical analysis of single arm.

End point values	Maralixibat (LUM001)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: micromoles per liter				
arithmetic mean (standard deviation)				
Baseline	38.941 (± 38.6614)			
Change From Baseline	-14.841 (± 31.3709)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Liver Enzyme Levels in Serum at Week 14

End point title	Change From Baseline in Liver Enzyme Levels in Serum at Week 14

End point description:

Levels of liver enzymes such as Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP) in serum were evaluated. mITT population was analysed for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	Maralixibat (LUM001)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: units per liter (U/L)				
arithmetic mean (standard deviation)				
ALT: Baseline	108.5 (± 78.95)			
ALT: Change From Baseline	10.5 (± 63.07)			
AST: Baseline	88.3 (± 43.7)			
AST: Change From Baseline	11.7 (± 34.14)			
ALP: Baseline	471.6 (± 316.93)			
ALP: Change From Baseline	36.7 (± 170.87)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Bilirubin Levels at Week 14

End point title	Change From Baseline in Bilirubin Levels at Week 14

End point description:

Total Bilirubin and Direct (Conjugated) Bilirubin levels were evaluated. mITT population was analysed for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	Maralixibat (LUM001)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: milligram per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Total Bilirubin Level: Baseline	1.22 (± 0.775)			
Total Bilirubin Level: Change From Baseline	0.24 (± 0.666)			
Conjugated Bilirubin Level: Baseline	0.6 (± 0.51)			
Conjugated Bilirubin Level: Change From Baseline	0.19 (± 0.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pruritus as Measured by Adult Itch Reported Outcome (ItchRO) Weekly Sum Score at Week 14

End point title	Change From Baseline in Pruritus as Measured by Adult Itch Reported Outcome (ItchRO) Weekly Sum Score at Week 14

End point description:

The Adult ItchRO instrument was completed twice daily using an electronic diary (eDiary). Each morning and evening score had a range from 0-10, with the higher score indicating increasing itch severity. The following was used for assessing the Adult ItchRO daily score: The score which represented the most severe itching for the day (morning or evening) was taken for each day as the daily score (maximum daily score of 10); If only 1 of the 2 scores was available for the day, the score that was available was used as the daily score; If both the morning and the evening scores were missing, the score was considered missing for the day. mITT population was analysed for this end point.

End point type	Secondary

End point timeframe:

Baseline, Week 14

End point values	Maralixibat (LUM001)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: units on scale				
arithmetic mean (standard deviation)				
Baseline	15 (± 18.735)			
Change From Baseline	-7.67 (± 16.326)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline for Other Biochemical Markers of

Cholestasis at Week 14: Total Cholesterol, Low Density Lipoprotein Cholesterol

End point title	Change From Baseline for Other Biochemical Markers of Cholestasis at Week 14: Total Cholesterol, Low Density Lipoprotein Cholesterol

End point description:

Total cholesterol (TC) level and low density lipoprotein cholesterol (LDLC) level were considered as biochemical markers of cholestasis. mITT population was analysed for this end point.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 14

End point values	Maralixibat (LUM001)			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: mg/dL				
arithmetic mean (standard deviation)				
TC Level: Baseline	213 (± 50.62)			
TC Level: Change From Baseline	-21.2 (± 25.46)			
LDLC Level: Baseline	121.4 (± 40.52)			
LDLC Level: Change From Baseline	-16.3 (± 17.64)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study drug administration up to follow up (Week 18)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Maralixibat (LUM001)

Reporting group description:

Subjects received LUM001 tablet orally once daily at a dose of 0.5 milligram (mg) during Week 1; 1 mg during Week 2; 2.5 mg during Week 3; 5 mg during Week 4; 7.5 mg during Week 5; 10 mg during Week 6 followed by stable dosing of 10 mg for 8 weeks.

Serious adverse events	Maralixibat (LUM001)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 27 (14.81%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Maralixibat (LUM001)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 27 (92.59%)		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 27 (22.22%)		
occurrences (all)	7		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	4		
Abdominal distension			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		
Abdominal pain			

subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Frequent bowel movements subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	8 / 27 (29.63%) 8 2 / 27 (7.41%) 4 14 / 27 (51.85%) 27 2 / 27 (7.41%) 2 9 / 27 (33.33%) 12		
Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all) Cholangitis subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2		
Musculoskeletal and connective tissue disorders Neck pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2 3 / 27 (11.11%) 9		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2014	- Removed the Mayo risk score from Inclusion Criterion - Added a qualification for inclusion for subjects receiving azathioprine. - Exclusion Criterion removed the restriction for azathioprine
10 February 2015	- Added a Data Monitoring Board for review of serious adverse events (SAEs) and other key safety data. - Provided for dosing halts for instances of 3 or more subjects exhibiting drug-related toxicity of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or greater in the same system organ class (SOC) - Clarified stopping rules for liver chemistry elevations - Safety monitoring guidelines were added for triglycerides elevations relative to investigational product dosing - Clarified stopping rules for suspending investigational product dosing until DMB investigations if 5 subjects discontinue dosing outside the serum biochemistry parameters specified. - A statement requiring study investigators to discuss with the medical monitor removing subjects prior to their withdrawal from a study was deleted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported