Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study To Evaluate The Safety And Efficacy Of Lum001, An Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), In The Treatment Of Cholestatic Liver Disease In Paediatric Patients With Alagille Syndrome

Summary

EudraCT number	2012-005346-38
Trial protocol	GB
Global end of trial date	23 February 2015

Results information

Result version number	v1 (current)
This version publication date	30 March 2016
First version publication date	30 March 2016

Trial information

Trial identification

Sponsor protocol code	LUM001-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01903460
WHO universal trial number (UTN)	-
Other trial identifiers	SHP625-302: Shire Development LLC, IMAGO: Shire Trial Acronym

Notes:

Sponsors

Sponsor organisation name	Shire Development LLC
Sponsor organisation address	725 Chesterbrook Boulevard, Wayne, United States, 19087
Public contact	Study Physician, Shire Development LLC, +1 8668425335,
Scientific contact	Study Physician, Shire Development LLC, +1 8668425335,

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	23 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 February 2015
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 paediatric subjects with Alagille Syndrome (ALGS), to evaluate the effect of LUM001 versus placebo on serum bile acids associated with ALGS, to evaluate the effect of LUM001 versus placebo on liver enzymes associated with ALGS, to evaluate the effect of LUM001 versus placebo on pruritus associated with ALGS, and to explore the effect of LUM001 versus placebo on other biochemical markers associated with ALGS.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and its revisions as well as with the valid national law(s) of the participating country/ies, with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6) issued in July 1996, and with the Commission Directives 1991/507/EEC, 2001/20/EC, 2005/28/EC and 2001/83/EC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2013
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 Kingdom: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	3
Children (2-11 years)	13
Adolescents (12-17 years)	4
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited to participate at three sites in the United Kingdom.

Pre-assignment

Screening details:

Subjects were screened over a period of 28 days.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Matching placebo contains the diluent with no active ingredient.

Arms

Are arms mutually exclusive?	Yes
Arm title	LUM001 140ug/kg/day

Arm description:

Subjects received an escalating dose of LUM001 over 3 to 5 weeks, from 14ug/kg/day to 140ug/kg/day, then received 8 to 10 weeks of treatment at either 140ug/kg/day or the highest tolerated dose below 140ug/kg/day. Subjects were then followed for 4 weeks after treatment.

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

Dosage and administration details:

Dose (14 to 140ug/kg/day) was administered orally as a 1.0mL solution (for subjects who weighed 10kg or more), or as a 0.5mL solution (for subjects who weighed less than 10kg) containing study drug (LUM001) using the syringe provided. Study drug was to be taken at least 30 minutes prior to the first meal of the day (every morning, before food) and should have been administered approximately at the same time each day for the duration of the treatment period.

Arm title	LUM001 280ug/kg/day

Arm description:

Subjects received an escalating dose of LUM001 over 3 to 5 weeks, from 14ug/kg/day to 280ug/kg/day, then received 8 to 10 weeks of treatment at either 280ug/kg/day or the highest tolerated dose below 280ug/kg/day. Subjects were then followed for 4 weeks after treatment.

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

Dosage and administration details:

Dose (14 to 280ug/kg/day) was administered orally as a 1.0mL solution (for subjects who weighed 10kg or more), as a 0.5mL solution (for subjects who weighed less than 10kg) containing study drug (LUM001) using the syringe provided. Study drug was to be taken at least 30 minutes prior to the first meal of the day (every morning, before food) and should have been administered approximately at the same time each day for the duration of the treatment period.

Arm title	Placebo Cohort A

Arm description:

Subjects received LUM001-matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Matching diluent placebo was administered orally using the syringe provided. Placebo was to be taken at least 30 minutes prior to the first meal of the day (every morning, before food) and should have been administered approximately at the same time each day for the duration of the treatment period.

Arm title	Placebo Cohort B

Arm description:

Subjects received LUM001-matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Matching diluent placebo was administered orally using the syringe provided. Placebo was to be taken at least 30 minutes prior to the first meal of the day (every morning, before food) and should have been administered approximately at the same time each day for the duration of the treatment period.

Number of subjects in period 1	LUM001 140ug/kg/day	LUM001 280ug/kg/day	Placebo Cohort A
Started	6	8	3
Completed	6	8	3
Not completed	0	0	0
Adverse event	-	-	-

Number of subjects in period 1	Placebo Cohort B
Started	3
Completed	2
Not completed	1
Adverse event	1

Baseline characteristics

Reporting groups	
Reporting group title	LUM001 140ug/kg/day
Reporting group description:	
Subjects received an escalating dose of LUM001 over 3 to 5 weeks, from 14ug/kg/day to 140ug/kg/day, then received 8 to 10 weeks of treatment at either 140ug/kg/day or the highest tolerated dose below 140ug/kg/day. Subjects were then followed for 4 weeks after treatment.	
Reporting group title	LUM001 280ug/kg/day
Reporting group description:	
Subjects received an escalating dose of LUM001 over 3 to 5 weeks, from 14ug/kg/day to 280ug/kg/day, then received 8 to 10 weeks of treatment at either 280ug/kg/day or the highest tolerated dose below 280ug/kg/day. Subjects were then followed for 4 weeks after treatment.	
Reporting group title	Placebo Cohort A
Reporting group description:	
Subjects received LUM001-matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.	
Reporting group title	Placebo Cohort B
Reporting group description:	
Subjects received LUM001-matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.	

Reporting group values	LUM001 140ug/kg/day	LUM001 280ug/kg/day	Placebo Cohort A
Number of subjects	6	8	3
Age categorical Units: Subjects			
<2 years	0	3	0
2 to 4 years	3	1	1
5 to 8 years	1	1	2
9 to 12 years	2	0	0
13 to 18 years	0	3	0
Age continuous Units: years			
arithmetic mean	5.8	6.8	5
standard deviation	± 4.49	± 6.73	± 2
Gender categorical Units: Subjects			
Female	2	3	3
Male	4	5	0
Region of enrollment Units: Subjects			
United Kingdom	6	8	3

Reporting group values	Placebo Cohort B	Total	
Number of subjects	3	20	
Age categorical Units: Subjects			
<2 years	0	3	
2 to 4 years	2	7	
5 to 8 years	1	5	

9 to 12 years	0	2	
13 to 18 years	0	3	

Age continuous Units: years			
arithmetic mean	4.3		
standard deviation	± 3.21	-	
Gender categorical Units: Subjects			
Female	2	10	
Male	1	10	
Region of enrollment Units: Subjects			
United Kingdom	3	20	

End points

End points reporting groups

Reporting group title	LUM001 140ug/kg/day

Reporting group description:

Subjects received an escalating dose of LUM001 over 3 to 5 weeks, from 14ug/kg/day to 140ug/kg/day, then received 8 to 10 weeks of treatment at either 140ug/kg/day or the highest tolerated dose below 140ug/kg/day. Subjects were then followed for 4 weeks after treatment.

Reporting group title	LUM001 280ug/kg/day

Reporting group description:

Subjects received an escalating dose of LUM001 over 3 to 5 weeks, from 14ug/kg/day to 280ug/kg/day, then received 8 to 10 weeks of treatment at either 280ug/kg/day or the highest tolerated dose below 280ug/kg/day. Subjects were then followed for 4 weeks after treatment.

Reporting group title	Placebo Cohort A

Reporting group description:

Subjects received LUM001-matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.

Reporting group title	Placebo Cohort B

Reporting group description:

Subjects received LUM001-matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.

Subject analysis set title	LUM001 Overall
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects received either dose of LUM001 for up to 10 or 13 weeks, then were followed for 4 weeks after treatment.

Subject analysis set title	Placebo Overall
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects received LUM001-matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.

Primary: Change From Baseline to Week 13 (End of Treatment) in Fasting Serum Bile Acid Level

End point title	Change From Baseline to Week 13 (End of Treatment) in Fasting Serum Bile Acid Level[1]

End point description:

Subjects were required to fast for at least 4 hours; only water was permitted prior to collection. A negative change from baseline indicates that the level of bile acid decreased.
This endpoint is analyzed for the modified Intent-to-Treat (mITT) population, defined as all subjects in the Safety population who had at least 1 post-baseline efficacy assessment. The Safety population was defined as all subjects randomly assigned to study treatment who received any amount of study drug.

End point type	Primary

End point timeframe:

Baseline to 13 weeks or end of treatment

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Active treatment groups (combined and individual) were tested against the combined placebo group, so data for the individual placebo cohorts are not reported.

End point values	LUM001 140ug/kg/day	LUM001 280ug/kg/day	LUM001 Overall	Placebo Overall
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	8	14	6
Units: umol/L				
least squares mean (standard error)	-82.864 (± 50.1513)	-49.388 (± 43.4732)	-66.126 (± 33.1208)	-42.157 (± 50.0903)

Statistical analyses

Statistical analysis title	Analysis of LUM001 140ug/kg/day
Comparison groups	LUM001 140ug/kg/day v Placebo Overall
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	-40.707
Confidence interval	
level	95 %
sides	2-sided
lower limit	-191.679
upper limit	110.265

Statistical analysis title	Analysis of LUM001 280ug/kg/day
Comparison groups	LUM001 280ug/kg/day v Placebo Overall
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9147
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	-7.231
Confidence interval	
level	95 %
sides	2-sided
lower limit	-148.726
upper limit	134.264

Statistical analysis title	Analysis of all doses of LUM001
Comparison groups	Placebo Overall v LUM001 Overall

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6954
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	-23.969
Confidence interval	
level	95 %
sides	2-sided
lower limit	-151.969
upper limit	104.031

Secondary: Change From Baseline to Week 13 (End of Treatment) in Liver Enzymes

End point title	Change From Baseline to Week 13 (End of Treatment) in Liver Enzymes[2]

End point description:

Analysis of liver enzymes included alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). A negative change from baseline indicates that the level of that enzyme decreased.
This endpoint is analyzed for the mITT population, defined as all subjects in the Safety population who had at least 1 post-baseline efficacy assessment. The Safety population was defined as all subjects randomly assigned to study treatment who received any amount of study drug.

End point type	Secondary

End point timeframe:

Baseline to 13 weeks or end of treatment

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Active treatment groups (combined and individual) were tested against the combined placebo group, so data for the individual placebo cohorts are not reported.

End point values	LUM001 140ug/kg/day	LUM001 280ug/kg/day	LUM001 Overall	Placebo Overall
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	8	14	6
Units: U/L				
least squares mean (standard error)				
ALT	59.3 (± 20.99)	10.5 (± 18.06)	34.9 (± 13.86)	2.7 (± 21.06)
AST	37.2 (± 13.64)	-2.7 (± 11.7)	17.3 (± 8.98)	13.2 (± 13.63)
ALP	71.4 (± 53.35)	31.6 (± 43.59)	51.5 (± 36.13)	19.7 (± 60.76)

Statistical analyses

Statistical analysis title	Analysis of LUM001 140ug/kg/day for ALT
Comparison groups	LUM001 140ug/kg/day v Placebo Overall

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0783
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	56.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	120.6

Statistical analysis title	Analysis of LUM001 280ug/kg/day for ALT
Comparison groups	LUM001 280ug/kg/day v Placebo Overall
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7827
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.4
upper limit	67

Statistical analysis title	Analysis of all doses of LUM001 for ALT
Comparison groups	Placebo Overall v LUM001 Overall
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2235
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	32.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.9
upper limit	86.3

Statistical analysis title	Analysis of LUM001 140ug/kg/day for AST

Comparison groups	LUM001 140ug/kg/day v Placebo Overall
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2372
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	65.5

Statistical analysis title	Analysis of LUM001 280ug/kg/day for AST
Comparison groups	LUM001 280ug/kg/day v Placebo Overall
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3914
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	-15.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.1
upper limit	22.4

Statistical analysis title	Analysis of all doses of LUM001 for AST
Comparison groups	Placebo Overall v LUM001 Overall
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8081
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31
upper limit	39.1

Statistical analysis title	Analysis of LUM001 140ug/kg/day for ALP
Comparison groups	LUM001 140ug/kg/day v Placebo Overall
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5748
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	51.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-140.3
upper limit	243.7

Statistical analysis title	Analysis of LUM001 280ug/kg/day for ALP
Comparison groups	LUM001 280ug/kg/day v Placebo Overall
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8835
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-158.4
upper limit	182.2

Statistical analysis title	Analysis of all doses of LUM001 for ALP
Comparison groups	Placebo Overall v LUM001 Overall
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6917
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	31.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-135.8
upper limit	199.4

Secondary: Change From Baseline to Week 13 (End of Treatment) in Pruritus as Measured by The Patient And Observer Itch Reported Outcome (ItchRO) Average Daily Scores

End point title	Change From Baseline to Week 13 (End of Treatment) in Pruritus as Measured by The Patient And Observer Itch Reported Outcome (ItchRO) Average Daily Scores[3]

End point description:

The ItchRO was administered as a twice daily electronic diary (eDiary). Children ≥9 years of age completed the patient ItchRO; those between 5 and 8 years completed the patient ItchRO with a caregiver's assistance. There was no patient report for subjects under the age of 5. ItchRO scores range from 0 to 4, with higher scores indicating increasing itch severity. ItchRO average daily scores were calculated as the sum of daily scores (ie, the maximum of morning and evening scores) divided by the number of days. The average daily score was calculated by using the 7 days pre-treatment for baseline, and the last 7 days of treatment for Week 13. A negative change from Baseline indicates that itch severity decreased.
This endpoint is analyzed for the mITT population, defined as all subjects in the Safety population who had at least 1 post-baseline efficacy assessment. The Safety population was defined as all subjects randomly assigned to study treatment who received any amount of study drug

End point type	Secondary

End point timeframe:

Baseline to 13 weeks or end of treatment

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Active treatment groups (combined and individual) were tested against the combined placebo group, so data for the individual placebo cohorts are not reported.

End point values	LUM001 140ug/kg/day	LUM001 280ug/kg/day	LUM001 Overall	Placebo Overall
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	6	8	14	6
Units: scores on a scale				
least squares mean (standard error)				
Patient ItchRO	-1.159 (± 0.5396)	-0.608 (± 0.4399)	-0.883 (± 0.3484)	-0.811 (± 0.5684)
Observer ItchRO	-0.802 (± 0.2732)	-0.419 (± 0.2318)	-0.61 (± 0.1776)	-0.592 (± 0.269)

Statistical analyses

Statistical analysis title	Analysis of LUM001 140ug/kg/day Patient ItchRO
Comparison groups	LUM001 140ug/kg/day v Placebo Overall
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6907
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	-0.348

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.468
upper limit	1.772

Statistical analysis title	Analysis of LUM001 280ug/kg/day Patient ItchRO
Comparison groups	LUM001 280ug/kg/day v Placebo Overall
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7897
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.647
upper limit	2.052

Statistical analysis title	Analysis of all doses LUM001 Patient ItchRO
Comparison groups	Placebo Overall v LUM001 Overall
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9203
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	-0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	1.705

Statistical analysis title	Analysis of LUM001 140ug/kg/day Observer ItchRO
Comparison groups	LUM001 140ug/kg/day v Placebo Overall

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5966
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.038
upper limit	0.618

Statistical analysis title	Analysis of LUM001 280ug/kg/day Observer ItchRO
Comparison groups	LUM001 280ug/kg/day v Placebo Overall
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.632
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	0.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.926

Statistical analysis title	Analysis of all doses of LUM001 Observer ItchRO
Comparison groups	Placebo Overall v LUM001 Overall
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9547
Method	ANCOVA
Parameter estimate	LS mean difference from placebo
Point estimate	-0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.673

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 19 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	LUM001 140ug/kg/day

Reporting group description:

Subjects received an escalating dose of LUM001 over 3 to 5 weeks, from 14ug/kg/day to 140ug/kg/day, then received 8 to 10 weeks of treatment at either 140ug/kg/day or the highest tolerated dose below 140ug/kg/day. Subjects were then followed for 4 weeks after treatment.

Reporting group title	LUM001 280ug/kg/day

Reporting group description:

Subjects received an escalating dose of LUM001 over 3 to 5 weeks, from 14ug/kg/day to 280ug/kg/day, then received 8 to 10 weeks of treatment at either 280ug/kg/day or the highest tolerated dose below 280ug/kg/day. Subjects were then followed for 4 weeks after treatment.

Reporting group title	Placebo Overall

Reporting group description:

Subjects received LUM001- matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.

Serious adverse events	LUM001 140ug/kg/day	LUM001 280ug/kg/day	Placebo Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	LUM001 140ug/kg/day	LUM001 280ug/kg/day	Placebo Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	7 / 8 (87.50%)	4 / 6 (66.67%)
General disorders and administration site conditions			
Crying			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Feeling abnormal			

subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Anal injury			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	0 / 6 (0.00%)
occurrences (all)	0	3	0

Contusion			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Excoriation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Hypoaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Middle ear inflammation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Abdominal pain lower			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0

Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	4	0	1
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)	5 / 8 (62.50%)	2 / 6 (33.33%)
occurrences (all)	5	9	3
Frequent bowel movements			
subjects affected / exposed	0 / 6 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Proctalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	2 / 8 (25.00%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	5 / 8 (62.50%)	1 / 6 (16.67%)
occurrences (all)	1	8	5
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Rash generalised			

subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 6 (33.33%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Upper respiratory tract infection			
subjects affected / exposed	3 / 6 (50.00%)	1 / 8 (12.50%)	3 / 6 (50.00%)
occurrences (all)	5	2	6
Viral rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Vitamin E deficiency			
subjects affected / exposed	0 / 6 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2013	Substantive changes to the protocol: 1. Clarified Inclusion Criterion 8B to define effective barrier method of contraception as condom and diaphragm plus a spermicide. 2. Provided instructions in Section 6.4 for unblinding treatment assignment.
03 July 2013	Substantive changes to the protocol: 1. Clarified the following: ItchRO (observer [obs]) and ItchRO (patient [pt]) were analyzed separately; subjects 5 to 8 years of age completed the eDiary with caretaker assistance; no ItchRO (pt) was to be completed for subjects less than 5 years. 2. Removed the following exploratory endpoints: Change from baseline in pruritus as measured by the average daily ItchRO (Observer ItchRO/patient ItchRO) (patient ItchRO/Observer ItchRO) at Weeks 5, 9, and 13. 3. Change from baseline in pruritus as measured by the weekly sum and the average daily and the weekly sum ItchRO for the observer and patient and observer scores separately at Weeks 5, 9, and 13. 4. Updates made to missing data strategy for ItchRO on how compliance was measured. 5. Clarifications made to subject screening and randomization number assignment process. 6. Clarification made regarding the replacement of randomized subjects who were not dosed due to their no longer meeting eligibility criteria. 7. Modification to provide further details regarding eDiary completion and subject/caregiver expectations. 8. Modifications made to the Schedule of Events concerning the visit window for Study Week 7, total serum bile acid during screening if none serum bile acid test was available within the past 3 months, and clarification regarding dose escalation. 9. Patient Global Therapeutic Benefit (PGTB) removed.
25 September 2013	Substantive changes to the protocol: 1. Clarified subject eligibility for the open label study based on completion of the present study. 2. Corrected statement in section discussing previous clinical experience concerning the occurrence of a related SAE.
25 February 2014	Substantive changes to the protocol: 1. Lowered eligibility age from 2 years of age to 12 months of age 2. Subjects who weigh 10 kg or more at screening received a 10 mL solution of LUM001 or placebo; subjects who weigh less than 10 kg at screening received a 0.5 mL solution of LUM001 or placebo. 3. Tabular summaries of the composition of the LUM001 0.5 mL solution and the 0.5 mL placebo solution have been included; a correction was made to the maximum LUM001 dose. 4. Clarified that dosing errors are documented in the eCRF and in paper-dosing diaries. 5. Added PedQL for infants 6. Visit window for Study Week 17 has a ± 5-day window rather than the 7 day window previously noted

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported