



## 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                 |
| <b>Arm title</b>             | 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.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | 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.

|   |                  |
|---|------------------|
| <b>Arm title</b>  | Placebo Cohort A |
| Arm description:<br>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.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | 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.

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

| <b>Number of subjects in period 1</b> | 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:<br>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:<br>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:<br>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:<br>Subjects received LUM001-matching placebo for up to 13 weeks, then were followed for 4 weeks after treatment.  |                     |

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

| Reporting group values             | Placebo Cohort B | Total |  |
|------------------------------------|------------------|-------|--|
| Number of subjects                 | 3                | 20    |  |
| Age categorical<br>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<br>Units: years<br>arithmetic mean<br>standard deviation | 4.3<br>± 3.21 | -  |  |
| Gender categorical<br>Units: Subjects                                   |               |    |  |
| Female  | 2             | 10 |  |
| Male  | 1             | 10 |  |
| Region of enrollment<br>Units: Subjects                                 |               |    |  |
| United Kingdom  | 3             | 20 |  |

## End points

### End points reporting groups

|  |                             |
|--|-----------------------------|
| Reporting group title  | LUM001 140ug/kg/day         |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 <sup>[1]</sup> |
| End point description:<br>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.<br>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:<br>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.



| <b>End point values</b>             | LUM001<br>140ug/kg/day      | LUM001<br>280ug/kg/day      | LUM001<br>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 ( $\pm$<br>50.1513) | -49.388 ( $\pm$<br>43.4732) | -66.126 ( $\pm$<br>33.1208) | -42.157 ( $\pm$<br>50.0903) |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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                               |

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | 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                               |

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[2]</sup> |
|-----------------|--|

### 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<br>140ug/kg/day | LUM001<br>280ug/kg/day | LUM001<br>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                           |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                      |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                    |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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                                  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                    |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                    |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[3]</sup> |
|-----------------|---|

### End point description:

The ItchRO was administered as a twice daily electronic diary (eDiary). Children  $\geq 9$  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<br>140ug/kg/day    | LUM001<br>280ug/kg/day    | LUM001<br>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 ( $\pm$<br>0.5396) | -0.608 ( $\pm$<br>0.4399) | -0.883 ( $\pm$<br>0.3484) | -0.811 ( $\pm$<br>0.5684) |
| Observer ItchRO                     | -0.802 ( $\pm$<br>0.2732) | -0.419 ( $\pm$<br>0.2318) | -0.61 ( $\pm$<br>0.1776)  | -0.592 ( $\pm$<br>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   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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                                       |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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                           |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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<br>140ug/kg/day | LUM001<br>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<br>140ug/kg/day | LUM001<br>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<br>occurrences (all)  | 1 / 6 (16.67%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)      | 1 / 6 (16.67%)<br>1 | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 6 (16.67%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Wheezing<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Psychiatric disorders<br>Abnormal behaviour<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 6 (0.00%)<br>0  | 0 / 8 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 |
| Investigations<br>Body temperature increased<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Injury, poisoning and procedural complications<br>Anal injury<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0  | 2 / 8 (25.00%)<br>3 | 0 / 6 (0.00%)<br>0  |

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

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

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 1 / 6 (16.67%)<br>1 | 0 / 8 (0.00%)<br>0  | 1 / 6 (16.67%)<br>1 |
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)  | 1 / 6 (16.67%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 1 / 6 (16.67%)<br>1 | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Infections and infestations<br>Ear infection<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 6 (16.67%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 2 / 6 (33.33%)<br>2 | 1 / 8 (12.50%)<br>1 | 1 / 6 (16.67%)<br>1 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                                    | 3 / 6 (50.00%)<br>5 | 1 / 8 (12.50%)<br>2 | 3 / 6 (50.00%)<br>6 |
| Viral rash<br>subjects affected / exposed<br>occurrences (all)   | 1 / 6 (16.67%)<br>1 | 0 / 8 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Metabolism and nutrition disorders<br>Vitamin E deficiency<br>subjects affected / exposed<br>occurrences (all)           | 0 / 6 (0.00%)<br>0  | 1 / 8 (12.50%)<br>1 | 0 / 6 (0.00%)<br>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:<br>1. Clarified Inclusion Criterion 8B to define effective barrier method of contraception as condom and diaphragm plus a spermicide.<br>2. Provided instructions in Section 6.4 for unblinding treatment assignment.   |
| 03 July 2013      | Substantive changes to the protocol:<br>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.<br>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.<br>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.<br>4. Updates made to missing data strategy for ItchRO on how compliance was measured.<br>5. Clarifications made to subject screening and randomization number assignment process.<br>6. Clarification made regarding the replacement of randomized subjects who were not dosed due to their no longer meeting eligibility criteria.<br>7. Modification to provide further details regarding eDiary completion and subject/caregiver expectations.<br>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.<br>9. Patient Global Therapeutic Benefit (PGTB) removed. |
| 25 September 2013 | Substantive changes to the protocol:<br>1. Clarified subject eligibility for the open label study based on completion of the present study.<br>2. Corrected statement in section discussing previous clinical experience concerning the occurrence of a related SAE.   |
| 25 February 2014  | Substantive changes to the protocol:<br>1. Lowered eligibility age from 2 years of age to 12 months of age<br>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.<br>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.<br>4. Clarified that dosing errors are documented in the eCRF and in paper-dosing diaries.<br>5. Added PedQL for infants<br>6. Visit window for Study Week 17 has a $\pm$ 5-day window rather than the 7 day window previously noted  |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported