

**Clinical trial results:****OPEN LABEL STUDY OF THE EFFICACY AND LONG TERM SAFETY OF LUM001, AN APICAL SODIUM-DEPENDENT BILE ACID TRANSPORTER INHIBITOR (ASBTi), IN THE TREATMENT OF CHOLESTATIC LIVER DISEASE IN PEDIATRIC PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS****Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-003833-14 |
| Trial protocol           | GB PL FR       |
| Global end of trial date | 20 May 2020    |

**Results information**

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1   |
| This version publication date     | 22 November 2020   |
| First version publication date    | 22 November 2020   |
| Summary attachment (see zip file) | Final Clinical Study Report (lum001-501-report-body.pdf)<br>Final Clinical Study Report Addendum (lum001-501-report-body-addend.pdf) |

**Trial information****Trial identification**

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | LUM001-501 |
|-----------------------|------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02057718 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Mirum Pharmaceuticals, Inc.   |
| Sponsor organisation address | 950 Tower Lane, Suite 1050, Foster City, United States, CA 94404                              |
| Public contact               | Medical Information Mirum, Mirum Pharmaceuticals, Inc., 1 6506674085, medinfo@mirumpharma.com |
| Scientific contact           | Medical Information Mirum, Mirum Pharmaceuticals, Inc., 1 6506674085, medinfo@mirumpharma.com |

Notes:

**Paediatric regulatory details**

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-001475-PIP03-17 |
| 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                       | 20 May 2020 |
| Is this the analysis of the primary completion data? | Yes         |
| Primary completion date                              | 20 May 2020 |
| Global end of trial reached?                         | Yes         |
| Global end of trial date                             | 20 May 2020 |
| Was the trial ended prematurely?                     | No          |

Notes:

## General information about the trial

Main objective of the trial:

Objectives up to/including Week 72:

- To evaluate the long-term safety/tolerability of MRX in pediatric subjects (PS) with PFIC
- To evaluate the effect of LUM001 on serum bile acids in PS with PFIC at 13 wks of treatment
- To evaluate the effect of LUM001 on biochem. markers of cholestasis and liver disease at 13 wks of treatment
- To evaluate the effect of LUM001 on pruritus in PS with PFIC at 13 wks of treatment

Objectives of Optional Follow-up Treatment Period (Post Week 72):

- To offer eligible subjects in the LUM001-501 continued study treatment beyond Week 72 until: (i) the subjects are eligible to enter another LUM001 study or (ii) LUM001 is available commercially
- To obtain safety/efficacy data in subjects treated long-term on LUM001
- To explore a BID and higher daily dosing regimen of LUM001
- To identify genetic indicators of treatment response, incl. exome sequencing
- To assess alpha-fetoprotein levels
- To assess LUM001 formulation palatability

Protection of trial subjects:

All study participants (caregivers as applicable) were required to read and sign an Informed Consent Form.

Background therapy:

none

Evidence for comparator:

none

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 12 February 2014 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 2 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 1          |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | France: 3          |
| Country: Number of subjects enrolled | United States: 15  |

|                                    |    |
|------------------------------------|----|
| Worldwide total number of subjects | 33 |
| EEA total number of subjects       | 18 |

Notes:

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### Subjects enrolled per age group

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 7  |
| Children (2-11 years)                     | 25 |
| Adolescents (12-17 years)                 | 1  |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

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## Subject disposition

### Recruitment

Recruitment details:

A total of 33 participants were enrolled at 11 sites in 4 countries (US, UK, France, Poland). Participants included 19 females and 14 males ranging from 1 to 13 years of age. Screening, treatment and safety follow-up, was approximately 76 weeks after which participants had the option of continuing in the additional follow-up treatment period.

### Pre-assignment

Screening details:

A total of 37 PFIC patients were screened for the study. Four of these patients were screen failures under the original protocol. A total of 33 participants were enrolled and subsequently had genotyping performed. Of the 33 participants, 8 were PFIC1 and 25 were PFIC2. Two pairs of siblings (all with PFIC2) from 2 families were enrolled

### Period 1

|                              |                     |
|------------------------------|---------------------|
| Period 1 title               | Baseline to Week 72 |
| Is this the baseline period? | Yes                 |
| Allocation method            | Not applicable      |
| Blinding used                | Not blinded         |

### Arms

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

Arm description:

All subjects received maralixibat (MRX)

|  |                                      |
|--|--------------------------------------|
| Arm type                               | Experimental                         |
| Investigational medicinal product name | Maralixibat chloride                 |
| Investigational medicinal product code |                                      |
| Other name                             | LUM001                               |
| Pharmaceutical forms                   | Powder and solvent for oral solution |
| Routes of administration               | Oral use                             |

Dosage and administration details:

All participants received MRX, up to 280 µg/kg QD (once daily) until Protocol Amendment 4, when participants continued treatment either on QD dosing, if they met pre-defined responder criteria, or were dose escalated up to a maximum daily dose of 280 µg/kg BID (twice daily) if they did not meet the responder criteria.

Dosing Periods:

- 4-week dose escalation [Dose Level 1-4]
- 4-week stable dosing at 140 µg/kg QD
- 5-week stable dosing at 280 µg/kg QD (participants who tolerated Dose Level 4)
- 59-week long-term exposure (up to maximum 280 µg/kg BID)

| Number of subjects in period 1 | Maralixibat |
|--------------------------------|-------------|
| Started                        | 33          |
| Week 72                        | 22          |
| Completed                      | 22          |
| Not completed                  | 11          |
| Physician decision             | 1           |

|                                |   |
|--------------------------------|---|
| Consent withdrawn by subject   | 1 |
| Adverse event, non-fatal       | 3 |
| Liver Transplant               | 1 |
| Non-compliance with study drug | 1 |
| Consent withdrawn by caregiver | 2 |
| Progressive disease            | 2 |

## Period 2

|                              |                                     |
|------------------------------|-------------------------------------|
| Period 2 title               | Optional follow-up treatment period |
| Is this the baseline period? | No                                  |
| Allocation method            | Not applicable                      |
| Blinding used                | Not blinded                         |

## Arms

|   |  |
|---|--|
| <b>Arm title</b>  | Maralixibat                            |
| Arm description:<br>All subjects received maralixibat (MRX) |  |
| Arm type  | Experimental                           |
| Investigational medicinal product name                      | Maralixibat chloride                   |
| Investigational medicinal product code                      |  |
| Other name  | LUM001                                 |
| Pharmaceutical forms  | Powder and solvent for oral suspension |
| Routes of administration                                    | Oral use                               |

### Dosage and administration details:

All participants received MRX, up to 280 µg/kg QD until Protocol Amendment 4, when participants continued treatment either on QD dosing, if they met pre-defined responder criteria, or were dose escalated up to a maximum daily dose of 280 µg/kg BID if they did not meet the responder criteria.

Subjects may be eligible for BID dosing based on efficacy as measured by sBA level and ItchRO score.

| <b>Number of subjects in period 2</b> | Maralixibat |
|---------------------------------------|-------------|
| Started                               | 22          |
| Completed                             | 12          |
| Not completed                         | 10          |
| Adverse event, non-fatal              | 3           |
| Liver Transplant                      | 2           |
| Did not consent to protocol amendment | 4           |
| Progressive disease                   | 1           |



## Baseline characteristics

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Baseline to Week 72 |
|-----------------------|---------------------|

Reporting group description:

A total of 37 PFIC patients were screened for the study. Four of these patients were screen failures under the original protocol. A total of 33 participants were enrolled in the study and subsequently had genotyping performed. Of the 33 participants, 8 were PFIC1 and 25 were PFIC2.

| Reporting group values   | Baseline to Week 72 | Total |  |
|--|---------------------|-------|--|
| Number of subjects   | 33                  | 33    |  |
| Age categorical  |                     |       |  |
| The mean (SE) overall age was 4.2 (0.56) years, and participants ranged from 1 to 13 years of age. |                     |       |  |
| Units: Subjects  |                     |       |  |
| <2 years   | 7                   | 7     |  |
| 2 to 4 years   | 15                  | 15    |  |
| 5 to 8 years   | 6                   | 6     |  |
| 9 to 12 years  | 4                   | 4     |  |
| 13 to 18 years   | 1                   | 1     |  |
| Gender categorical   |                     |       |  |
| Overall, there were slightly more females than males (19 females [57.6%] and 14 males [42.4%]).    |                     |       |  |
| Units: Subjects  |                     |       |  |
| Female   | 19                  | 19    |  |
| Male   | 14                  | 14    |  |
| Race   |                     |       |  |
| Units: Subjects  |                     |       |  |
| American Indian or Alaska Native   | 0                   | 0     |  |
| Asian  | 3                   | 3     |  |
| Black or African American  | 0                   | 0     |  |
| Native Hawaiian or Other Pacific Islander  | 0                   | 0     |  |
| White  | 26                  | 26    |  |
| More than 1 race   | 1                   | 1     |  |
| Not reported   | 3                   | 3     |  |
| Ethnicity  |                     |       |  |
| Units: Subjects  |                     |       |  |
| Hispanic or Latino   | 1                   | 1     |  |
| Not Hispanic or Latino   | 29                  | 29    |  |
| Not Reported   | 3                   | 3     |  |
| Country  |                     |       |  |
| Units: Subjects  |                     |       |  |
| France   | 3                   | 3     |  |
| Britain  | 14                  | 14    |  |
| Poland   | 1                   | 1     |  |
| United States  | 15                  | 15    |  |
| Height z-score   |                     |       |  |
| Units: z-score   |                     |       |  |
| median   | -1.653              |       |  |
| full range (min-max)   | -6.06 to 0.77       | -     |  |
| Weight z-score   |                     |       |  |

|                      |               |   |  |
|----------------------|---------------|---|--|
| Units: z-score       |               |   |  |
| median               | -0.844        |   |  |
| full range (min-max) | -9.14 to 0.60 | - |  |

## Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | PFIC1              |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Enrolled subjects with PFIC1 subtype

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | nt-PFIC2           |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Enrolled with PFIC2 phenotype: non-truncating (mild to moderate phenotype with residual BSEP [liver-specific transporter] function)

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | t-PFIC2            |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Enrolled with PFIC2 phenotype: truncating (severe phenotype without residual BSEP function or complete absence of BSEP)

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | PFIC2 (overall)    |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Overall PFIC2 subtype to include PFIC2 phenotype:

- non-truncating (mild to moderate phenotype with residual BSEP [liver-specific transporter] function)
- truncating (severe phenotype without residual BSEP function or complete absence of BSEP)

| Reporting group values   | PFIC1 | nt-PFIC2 | t-PFIC2 |
|--|-------|----------|---------|
| Number of subjects   | 8     | 19       | 6       |
| Age categorical  |       |          |         |
| The mean (SE) overall age was 4.2 (0.56) years, and participants ranged from 1 to 13 years of age. |       |          |         |
| Units: Subjects  |       |          |         |
| <2 years   | 1     | 5        | 1       |
| 2 to 4 years   | 5     | 9        | 1       |
| 5 to 8 years   | 2     | 2        | 2       |
| 9 to 12 years  | 0     | 2        | 2       |
| 13 to 18 years   | 0     | 1        | 0       |
| Gender categorical   |       |          |         |
| Overall, there were slightly more females than males (19 females [57.6%] and 14 males [42.4%]).    |       |          |         |
| Units: Subjects  |       |          |         |
| Female   | 2     | 13       | 4       |
| Male   | 6     | 6        | 2       |
| Race   |       |          |         |
| Units: Subjects  |       |          |         |
| American Indian or Alaska Native   | 0     | 0        | 0       |
| Asian  | 2     | 0        | 1       |
| Black or African American  | 0     | 0        | 0       |
| Native Hawaiian or Other Pacific Islander  | 0     | 0        | 0       |
| White  | 6     | 18       | 2       |
| More than 1 race   | 0     | 1        | 0       |
| Not reported   | 0     | 0        | 3       |



|                        |                |               |                |
|------------------------|----------------|---------------|----------------|
| Ethnicity              |                |               |                |
| Units: Subjects        |                |               |                |
| Hispanic or Latino     | 0              | 1             | 0              |
| Not Hispanic or Latino | 8              | 18            | 3              |
| Not Reported           | 0              | 0             | 3              |
| Country                |                |               |                |
| Units: Subjects        |                |               |                |
| France                 | 0              | 0             | 3              |
| Britain                | 3              | 9             | 2              |
| Poland                 | 0              | 1             | 0              |
| United States          | 5              | 9             | 1              |
| Height z-score         |                |               |                |
| Units: z-score         |                |               |                |
| median                 | -2.500         | -1.356        | -1.901         |
| full range (min-max)   | -6.06 to -1.62 | -2.73 to 0.77 | -2.81 to -1.34 |
| Weight z-score         |                |               |                |
| Units: z-score         |                |               |                |
| median                 | -1.775         | -0.216        | -1.267         |
| full range (min-max)   | -9.14 to -0.29 | -1.83 to 0.60 | -2.73 to -0.20 |

|  |                 |  |  |
|--|-----------------|--|--|
| <b>Reporting group values</b>  | PFIC2 (overall) |  |  |
| Number of subjects   | 25              |  |  |
| Age categorical  |                 |  |  |
| The mean (SE) overall age was 4.2 (0.56) years, and participants ranged from 1 to 13 years of age. |                 |  |  |
| Units: Subjects  |                 |  |  |
| <2 years   | 6               |  |  |
| 2 to 4 years   | 10              |  |  |
| 5 to 8 years   | 4               |  |  |
| 9 to 12 years  | 4               |  |  |
| 13 to 18 years   | 1               |  |  |
| Gender categorical   |                 |  |  |
| Overall, there were slightly more females than males (19 females [57.6%] and 14 males [42.4%]).    |                 |  |  |
| Units: Subjects  |                 |  |  |
| Female   | 17              |  |  |
| Male   | 8               |  |  |
| Race   |                 |  |  |
| Units: Subjects  |                 |  |  |
| American Indian or Alaska Native   | 0               |  |  |
| Asian  | 1               |  |  |
| Black or African American  | 0               |  |  |
| Native Hawaiian or Other Pacific Islander  | 0               |  |  |
| White  | 20              |  |  |
| More than 1 race   | 1               |  |  |
| Not reported   | 3               |  |  |
| Ethnicity  |                 |  |  |
| Units: Subjects  |                 |  |  |
| Hispanic or Latino   | 1               |  |  |
| Not Hispanic or Latino   | 21              |  |  |
| Not Reported   | 3               |  |  |
| Country  |                 |  |  |
| Units: Subjects  |                 |  |  |

|                      |               |  |  |
|----------------------|---------------|--|--|
| France               | 3             |  |  |
| Britain              | 11            |  |  |
| Poland               | 1             |  |  |
| United States        | 10            |  |  |
| Height z-score       |               |  |  |
| Units: z-score       |               |  |  |
| median               | -1.493        |  |  |
| full range (min-max) | -2.81 to 0.77 |  |  |
| Weight z-score       |               |  |  |
| Units: z-score       |               |  |  |
| median               | -0.342        |  |  |
| full range (min-max) | -2.73 to 0.60 |  |  |

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## End points

### End points reporting groups

|  |                    |
|--|--------------------|
| Reporting group title  | Maralixibat        |
| Reporting group description:<br>All subjects received maralixibat (MRX)  |                    |
| Reporting group title  | Maralixibat        |
| Reporting group description:<br>All subjects received maralixibat (MRX)  |                    |
| Subject analysis set title   | PFIC1              |
| Subject analysis set type  | Sub-group analysis |
| Subject analysis set description:<br>Enrolled subjects with PFIC1 subtype  |                    |
| Subject analysis set title   | nt-PFIC2           |
| Subject analysis set type  | Sub-group analysis |
| Subject analysis set description:<br>Enrolled with PFIC2 phenotype: non-truncating (mild to moderate phenotype with residual BSEP [liver-specific transporter] function)   |                    |
| Subject analysis set title   | t-PFIC2            |
| Subject analysis set type  | Sub-group analysis |
| Subject analysis set description:<br>Enrolled with PFIC2 phenotype: truncating (severe phenotype without residual BSEP function or complete absence of BSEP)   |                    |
| Subject analysis set title   | PFIC2 (overall)    |
| Subject analysis set type  | Sub-group analysis |
| Subject analysis set description:<br>Overall PFIC2 subtype to include PFIC2 phenotype:<br>- non-truncating (mild to moderate phenotype with residual BSEP [liver-specific transporter] function)<br>- truncating (severe phenotype without residual BSEP function or complete absence of BSEP) |                    |

### Primary: Change from baseline to endpoint (Week 13) in fasting sBA level

|   |   |
|---|---|
| End point title                                     | Change from baseline to endpoint (Week 13) in fasting sBA level |
| End point description:                              |   |
| End point type                                      | Primary   |
| End point timeframe:<br>Baseline (Day 0) to Week 13 |   |

| End point values                       | Maralixibat       | PFIC1                | PFIC2 (overall)      |  |
|--|-------------------|----------------------|----------------------|--|
| Subject group type                     | Reporting group   | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed            | 31                | 8                    | 23                   |  |
| Units: umol/L                          |                   |                      |                      |  |
| arithmetic mean (full range (min-max)) | -23 (-463 to 279) | 18 (-117 to 149)     | -38 (-463 to 279)    |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Change from baseline to Week 13 in sBA levels |
| Statistical analysis description:<br>This analysis shows the change from baseline to Week 13 in sBA levels for the overall Modified Intent-to-treat Population. Even though a comparison of PFIC1 vs PFIC2 (overall) is noted, the results are the change from baseline for all participants and is not comparative. |   |
| Comparison groups  | PFIC1 v PFIC2 (overall)                       |
| Number of subjects included in analysis  | 31  |
| Analysis specification   | Pre-specified                                 |
| Analysis type  | other <sup>[1]</sup>                          |
| Parameter estimate   | Mean difference (net)                         |
| Point estimate   | -23.304                                       |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided                                       |
| lower limit  | -82.35  |
| upper limit  | 35.742  |
| Variability estimate   | Standard deviation                            |
| Dispersion value   | 160.9748                                      |

Notes:

[1] - Null hypothesis (H0): mean change from baseline to Week 13 is zero. The null hypothesis was tested for each of the 2 PFIC subgroups and overall; the change in the overall population is presented here.

### Secondary: Change from baseline to Week 13/ET in ALT

|                             |   |
|-----------------------------|---|
| End point title             | Change from baseline to Week 13/ET in ALT |
| End point description:      |   |
| End point type              | Secondary                                 |
| End point timeframe:        |   |
| Baseline (Day 0) to Week 13 |   |

| End point values                     | Maralixibat     | PFIC1                | PFIC2 (overall)      |  |
|--------------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type                   | Reporting group | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 31              | 8                    | 23                   |  |
| Units: U/L                           |                 |                      |                      |  |
| arithmetic mean (standard deviation) | -9 (± 61.8)     | -2 (± 29.1)          | -11 (± 70.1)         |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to Week 13/ET in total bilirubin

|                        |   |
|------------------------|---|
| End point title        | Change from baseline to Week 13/ET in total bilirubin |
| End point description: |   |
| End point type         | Secondary   |

End point timeframe:

Baseline (Day 0) to Week 13

| End point values                     | Maralixibat     | PFIC1                | PFIC2 (overall)      |  |
|--------------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type                   | Reporting group | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 31              | 8                    | 23                   |  |
| Units: mg/dL                         |                 |                      |                      |  |
| arithmetic mean (standard deviation) | -0.2 (± 1.65)   | -0.8 (± 2.95)        | -0.0 (± 0.90)        |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to Week 13/ET in direct bilirubin

|                 |  |
|-----------------|--|
| End point title | Change from baseline to Week 13/ET in direct bilirubin |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 0) to Week 13

| End point values                     | Maralixibat     | PFIC1                | PFIC2 (overall)      |  |
|--------------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type                   | Reporting group | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 31              | 8                    | 23                   |  |
| Units: mg/dL                         |                 |                      |                      |  |
| arithmetic mean (standard deviation) | -0.1 (± 1.12)   | -0.3 (± 1.93)        | -0.0 (± 0.72)        |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to Week 13/ET in pruritus as measured by ItchRO(Obs)

|                 |   |
|-----------------|---|
| End point title | Change from baseline to Week 13/ET in pruritus as measured by ItchRO(Obs) |
|-----------------|---|

End point description:

ItchRO(Obs) (4-week average morning scores)

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 0) to Week 13

| End point values                     | Maralixibat     | PFIC1                | PFIC2 (overall)      |  |
|--------------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type                   | Reporting group | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 31              | 8                    | 23                   |  |
| Units: Points (0-4)                  |                 |                      |                      |  |
| arithmetic mean (standard deviation) | -0.7 (± 0.65)   | -0.8 (± 0.83)        | -0.7 (± 0.59)        |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to Week 13/ET in pruritus as measured by ItchRO(Pt)

|  |  |
|--|--|
| End point title                            | Change from baseline to Week 13/ET in pruritus as measured by ItchRO(Pt) |
| End point description:                     |  |
| ItchRO(Pt) (4-week average morning scores) |  |
| End point type                             | Secondary  |
| End point timeframe:                       |  |
| Baseline (Day 0) to Week 13                |  |

| End point values                     | Maralixibat     | PFIC1                | PFIC2 (overall)      |  |
|--------------------------------------|-----------------|----------------------|----------------------|--|
| Subject group type                   | Reporting group | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed          | 9               | 2                    | 7                    |  |
| Units: Points (0-4)                  |                 |                      |                      |  |
| arithmetic mean (standard deviation) | -0.6 (± 0.57)   | -0.4 (± 0.65)        | -0.7 (± 0.57)        |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to EOT

Adverse event reporting additional description:

All treatment-emergent AEs, whether observed by the Investigator, reported by the subject, the subject's caregiver, from laboratory findings, or other means, were recorded on the AE eCRF and medical record. 'Occurrences' relates to the number of events; 'subjects affected' relates to the number of subjects who experienced the AE.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description:

The safety population is defined as all subjects who were assigned and received at least one dose of the study drug.

| Serious adverse events                            | Safety population |  |  |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events |                   |  |  |
| subjects affected / exposed                       | 15 / 33 (45.45%)  |  |  |
| number of deaths (all causes)                     | 0                 |  |  |
| number of deaths resulting from adverse events    | 0                 |  |  |
| Investigations                                    |                   |  |  |
| Blood bilirubin increased                         |                   |  |  |
| subjects affected / exposed                       | 1 / 33 (3.03%)    |  |  |
| occurrences causally related to treatment / all   | 1 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| International normalised ratio increased          |                   |  |  |
| subjects affected / exposed                       | 1 / 33 (3.03%)    |  |  |
| occurrences causally related to treatment / all   | 1 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Injury, poisoning and procedural complications    |                   |  |  |
| Radius fracture                                   |                   |  |  |
| subjects affected / exposed                       | 1 / 33 (3.03%)    |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |

|  |                |  |  |
|--|----------------|--|--|
| Ulna fracture  |                |  |  |
| subjects affected / exposed                          | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Upper limb fracture                                  |                |  |  |
| subjects affected / exposed                          | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Surgical and medical procedures                      |                |  |  |
| Enteral nutrition                                    |                |  |  |
| subjects affected / exposed                          | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal tube insertion                      |                |  |  |
| subjects affected / exposed                          | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Condition aggravated                                 |                |  |  |
| subjects affected / exposed                          | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Gastrointestinal disorders                           |                |  |  |
| Abdominal pain                                       |                |  |  |
| subjects affected / exposed                          | 2 / 33 (6.06%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Diarrhoea  |                |  |  |
| subjects affected / exposed                          | 2 / 33 (6.06%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Abdominal pain upper                                 |                |  |  |



|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 3 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Melaena   |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pancreatitis                                    |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Cholelithiasis                                  |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Dyspnoea  |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Epistaxis                                       |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Pruritus  |                |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                                  |  |  |
|---|----------------------------------|--|--|
| Infections and infestations<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all              | 2 / 33 (6.06%)<br>0 / 2<br>0 / 0 |  |  |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | 1 / 33 (3.03%)<br>0 / 2<br>0 / 0 |  |  |
| Viral infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 33 (3.03%)<br>0 / 1<br>0 / 0 |  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 33 (3.03%)<br>0 / 1<br>0 / 0 |  |  |
| Metabolism and nutrition disorders<br>Electrolyte imbalance<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 33 (3.03%)<br>0 / 1<br>0 / 0 |  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 33 (3.03%)<br>0 / 1<br>0 / 0 |  |  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 33 (3.03%)<br>0 / 1<br>0 / 0 |  |  |

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

| <b>Non-serious adverse events</b>                     | Safety population |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 33 / 33 (100.00%) |  |  |
| Vascular disorders                                    |                   |  |  |
| Hypertension  |                   |  |  |
| subjects affected / exposed                           | 1 / 33 (3.03%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Spider vein   |                   |  |  |
| subjects affected / exposed                           | 1 / 33 (3.03%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Surgical and medical procedures                       |                   |  |  |
| biliary-tract operation                               |                   |  |  |
| subjects affected / exposed                           | 1 / 33 (3.03%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Pyrexia   |                   |  |  |
| subjects affected / exposed                           | 20 / 33 (60.61%)  |  |  |
| occurrences (all)                                     | 83                |  |  |
| Fatigue   |                   |  |  |
| subjects affected / exposed                           | 4 / 33 (12.12%)   |  |  |
| occurrences (all)                                     | 4                 |  |  |
| Influenza like illness                                |                   |  |  |
| subjects affected / exposed                           | 3 / 33 (9.09%)    |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Malaise   |                   |  |  |
| subjects affected / exposed                           | 3 / 33 (9.09%)    |  |  |
| occurrences (all)                                     | 4                 |  |  |
| Chest pain  |                   |  |  |
| subjects affected / exposed                           | 2 / 33 (6.06%)    |  |  |
| occurrences (all)                                     | 4                 |  |  |
| Disease progression                                   |                   |  |  |
| subjects affected / exposed                           | 2 / 33 (6.06%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Pain  |                   |  |  |
| subjects affected / exposed                           | 2 / 33 (6.06%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Calcinosis  |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Feeling hot                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Injection site discomfort                       |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Injection site mass                             |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Injection site pain                             |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 5                |  |  |
| Injection site rash                             |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Peripheral swelling                             |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Immune system disorders                         |                  |  |  |
| Seasonal allergy                                |                  |  |  |
| subjects affected / exposed                     | 3 / 33 (9.09%)   |  |  |
| occurrences (all)                               | 7                |  |  |
| Reproductive system and breast disorders        |                  |  |  |
| Scrotal disorder                                |                  |  |  |
| subjects affected / exposed                     | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Cough   |                  |  |  |
| subjects affected / exposed                     | 18 / 33 (54.55%) |  |  |
| occurrences (all)                               | 39               |  |  |
| Oropharyngeal pain                              |                  |  |  |
| subjects affected / exposed                     | 13 / 33 (39.39%) |  |  |
| occurrences (all)                               | 22               |  |  |
| Epistaxis                                       |                  |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed        | 9 / 33 (27.27%) |  |  |
| occurrences (all)                  | 20              |  |  |
| Rhinorrhoea                        |                 |  |  |
| subjects affected / exposed        | 8 / 33 (24.24%) |  |  |
| occurrences (all)                  | 12              |  |  |
| Nasal congestion                   |                 |  |  |
| subjects affected / exposed        | 4 / 33 (12.12%) |  |  |
| occurrences (all)                  | 7               |  |  |
| Sleep apnoea syndrome              |                 |  |  |
| subjects affected / exposed        | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Sneezing                           |                 |  |  |
| subjects affected / exposed        | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Upper-airway cough syndrome        |                 |  |  |
| subjects affected / exposed        | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                  | 3               |  |  |
| Dry throat                         |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Paranasal sinus discomfort         |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Pharyngeal inflammation            |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Respiratory disorder               |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Rhinitis allergic                  |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Sinus disorder                     |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Upper respiratory tract congestion |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Psychiatric disorders                    |                 |  |  |
| Irritability                             |                 |  |  |
| subjects affected / exposed              | 5 / 33 (15.15%) |  |  |
| occurrences (all)                        | 7               |  |  |
| Anxiety                                  |                 |  |  |
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Attention deficit hyperactivity disorder |                 |  |  |
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Encopresis                               |                 |  |  |
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Executive dysfunction                    |                 |  |  |
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Initial insomnia                         |                 |  |  |
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Mood altered                             |                 |  |  |
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Sleep disorder                           |                 |  |  |
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Sleep terror                             |                 |  |  |
| subjects affected / exposed              | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                        | 1               |  |  |
| Investigations                           |                 |  |  |
| International normalised ratio increased |                 |  |  |
| subjects affected / exposed              | 7 / 33 (21.21%) |  |  |
| occurrences (all)                        | 18              |  |  |
| Blood bilirubin increased                |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed             | 5 / 33 (15.15%) |  |  |
| occurrences (all)                       | 6               |  |  |
| Alanine aminotransferase increased      |                 |  |  |
| subjects affected / exposed             | 3 / 33 (9.09%)  |  |  |
| occurrences (all)                       | 3               |  |  |
| Aspartate aminotransferase increased    |                 |  |  |
| subjects affected / exposed             | 3 / 33 (9.09%)  |  |  |
| occurrences (all)                       | 3               |  |  |
| International normalised ratio abnormal |                 |  |  |
| subjects affected / exposed             | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                       | 4               |  |  |
| Vitamin E decreased                     |                 |  |  |
| subjects affected / exposed             | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                       | 3               |  |  |
| Bilirubin conjugated increased          |                 |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Blood bicarbonate decreased             |                 |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Blood phosphorus decreased              |                 |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Blood urine present                     |                 |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                       | 1               |  |  |
| Haemoglobin decreased                   |                 |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Human rhinovirus test positive          |                 |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                       | 2               |  |  |
| Platelet count decreased                |                 |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                    | 1 / 33 (3.03%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Prothrombin time prolonged                     |                |  |  |
| subjects affected / exposed                    | 1 / 33 (3.03%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Vitamin D decreased                            |                |  |  |
| subjects affected / exposed                    | 1 / 33 (3.03%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Injury, poisoning and procedural complications |                |  |  |
| Procedural pain                                |                |  |  |
| subjects affected / exposed                    | 3 / 33 (9.09%) |  |  |
| occurrences (all)                              | 3              |  |  |
| Traumatic haemorrhage                          |                |  |  |
| subjects affected / exposed                    | 3 / 33 (9.09%) |  |  |
| occurrences (all)                              | 3              |  |  |
| Contusion                                      |                |  |  |
| subjects affected / exposed                    | 2 / 33 (6.06%) |  |  |
| occurrences (all)                              | 2              |  |  |
| Scratch  |                |  |  |
| subjects affected / exposed                    | 2 / 33 (6.06%) |  |  |
| occurrences (all)                              | 2              |  |  |
| Skin laceration                                |                |  |  |
| subjects affected / exposed                    | 2 / 33 (6.06%) |  |  |
| occurrences (all)                              | 3              |  |  |
| Upper limb fracture                            |                |  |  |
| subjects affected / exposed                    | 1 / 33 (3.03%) |  |  |
| occurrences (all)                              | 2              |  |  |
| Arthropod bite                                 |                |  |  |
| subjects affected / exposed                    | 1 / 33 (3.03%) |  |  |
| occurrences (all)                              | 2              |  |  |
| Ear injury                                     |                |  |  |
| subjects affected / exposed                    | 1 / 33 (3.03%) |  |  |
| occurrences (all)                              | 1              |  |  |
| Fall   |                |  |  |



|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Femur fracture                             |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Head injury                                |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Humerus fracture                           |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Ligament injury                            |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Ligament sprain                            |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Limb injury                                |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Skin abrasion                              |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Sunburn                                    |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Vaccination complication                   |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Wound haemorrhage                          |                |  |  |
| subjects affected / exposed                | 1 / 33 (3.03%) |  |  |
| occurrences (all)                          | 1              |  |  |
| Congenital, familial and genetic disorders |                |  |  |
| Protein C deficiency                       |                |  |  |

|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>1  |  |  |
| Cardiac disorders<br>Tachycardia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>1  |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Encephalopathy<br>subjects affected / exposed<br>occurrences (all)<br><br>Lethargy<br>subjects affected / exposed<br>occurrences (all)<br><br>Migraine<br>subjects affected / exposed<br>occurrences (all)<br><br>Paraesthesia<br>subjects affected / exposed<br>occurrences (all)<br><br>Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)<br><br>Poor quality sleep<br>subjects affected / exposed<br>occurrences (all)<br><br>Seizure<br>subjects affected / exposed<br>occurrences (all) | 7 / 33 (21.21%)<br>15<br><br>1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>2<br><br>1 / 33 (3.03%)<br>4<br><br>1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>3<br><br>1 / 33 (3.03%)<br>1 |  |  |
| Blood and lymphatic system disorders<br>Increased tendency to bruise<br>subjects affected / exposed<br>occurrences (all)<br><br>Iron deficiency anaemia  | 1 / 33 (3.03%)<br>1  |  |  |

|                              |                 |  |  |
|------------------------------|-----------------|--|--|
| subjects affected / exposed  | 1 / 33 (3.03%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Lymphadenitis                |                 |  |  |
| subjects affected / exposed  | 1 / 33 (3.03%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Lymphadenopathy              |                 |  |  |
| subjects affected / exposed  | 1 / 33 (3.03%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Thrombocytopenia             |                 |  |  |
| subjects affected / exposed  | 1 / 33 (3.03%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Ear and labyrinth disorders  |                 |  |  |
| Ear pain                     |                 |  |  |
| subjects affected / exposed  | 5 / 33 (15.15%) |  |  |
| occurrences (all)            | 9               |  |  |
| Cerumen impaction            |                 |  |  |
| subjects affected / exposed  | 1 / 33 (3.03%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Ear disorder                 |                 |  |  |
| subjects affected / exposed  | 1 / 33 (3.03%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Ear haemorrhage              |                 |  |  |
| subjects affected / exposed  | 1 / 33 (3.03%)  |  |  |
| occurrences (all)            | 2               |  |  |
| Excessive cerumen production |                 |  |  |
| subjects affected / exposed  | 1 / 33 (3.03%)  |  |  |
| occurrences (all)            | 1               |  |  |
| Eye disorders                |                 |  |  |
| Dry eye                      |                 |  |  |
| subjects affected / exposed  | 2 / 33 (6.06%)  |  |  |
| occurrences (all)            | 2               |  |  |
| Eye pain                     |                 |  |  |
| subjects affected / exposed  | 2 / 33 (6.06%)  |  |  |
| occurrences (all)            | 3               |  |  |
| Gastrointestinal disorders   |                 |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Diarrhoea                   |                  |  |  |
| subjects affected / exposed | 19 / 33 (57.58%) |  |  |
| occurrences (all)           | 70               |  |  |
| Abdominal pain              |                  |  |  |
| subjects affected / exposed | 15 / 33 (45.45%) |  |  |
| occurrences (all)           | 34               |  |  |
| Abdominal pain upper        |                  |  |  |
| subjects affected / exposed | 8 / 33 (24.24%)  |  |  |
| occurrences (all)           | 37               |  |  |
| Faeces pale                 |                  |  |  |
| subjects affected / exposed | 6 / 33 (18.18%)  |  |  |
| occurrences (all)           | 7                |  |  |
| Constipation                |                  |  |  |
| subjects affected / exposed | 5 / 33 (15.15%)  |  |  |
| occurrences (all)           | 6                |  |  |
| Toothache                   |                  |  |  |
| subjects affected / exposed | 4 / 33 (12.12%)  |  |  |
| occurrences (all)           | 7                |  |  |
| Nausea                      |                  |  |  |
| subjects affected / exposed | 3 / 33 (9.09%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Vomiting                    |                  |  |  |
| subjects affected / exposed | 17 / 33 (51.52%) |  |  |
| occurrences (all)           | 38               |  |  |
| Frequent bowel movements    |                  |  |  |
| subjects affected / exposed | 4 / 33 (12.12%)  |  |  |
| occurrences (all)           | 5                |  |  |
| Abdominal discomfort        |                  |  |  |
| subjects affected / exposed | 2 / 33 (6.06%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Dyspepsia                   |                  |  |  |
| subjects affected / exposed | 2 / 33 (6.06%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Gastrointestinal pain       |                  |  |  |
| subjects affected / exposed | 2 / 33 (6.06%)   |  |  |
| occurrences (all)           | 2                |  |  |

|                                  |                |  |  |
|----------------------------------|----------------|--|--|
| Gastrooesophageal reflux disease |                |  |  |
| subjects affected / exposed      | 2 / 33 (6.06%) |  |  |
| occurrences (all)                | 2              |  |  |
| Haematochezia                    |                |  |  |
| subjects affected / exposed      | 2 / 33 (6.06%) |  |  |
| occurrences (all)                | 3              |  |  |
| Teething                         |                |  |  |
| subjects affected / exposed      | 2 / 33 (6.06%) |  |  |
| occurrences (all)                | 3              |  |  |
| Anal haemorrhage                 |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 2              |  |  |
| Defaecation urgency              |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 1              |  |  |
| Diarrhoea haemorrhagic           |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 1              |  |  |
| Faeces discoloured               |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 1              |  |  |
| Flatulence                       |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 1              |  |  |
| Gingival bleeding                |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 1              |  |  |
| Haematemesis                     |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 1              |  |  |
| Oral pain                        |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 1              |  |  |
| Pancreatic failure               |                |  |  |
| subjects affected / exposed      | 1 / 33 (3.03%) |  |  |
| occurrences (all)                | 1              |  |  |

|  |                |  |  |
|--|----------------|--|--|
| Pancreatitis                           |                |  |  |
| subjects affected / exposed            | 1 / 33 (3.03%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Perianal erythema                      |                |  |  |
| subjects affected / exposed            | 1 / 33 (3.03%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Rectal tenesmus                        |                |  |  |
| subjects affected / exposed            | 1 / 33 (3.03%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Varices oesophageal                    |                |  |  |
| subjects affected / exposed            | 1 / 33 (3.03%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Rectal haemorrhage                     |                |  |  |
| subjects affected / exposed            | 1 / 33 (3.03%) |  |  |
| occurrences (all)                      | 2              |  |  |
| Hepatobiliary disorders                |                |  |  |
| Hyperbilirubinaemia                    |                |  |  |
| subjects affected / exposed            | 3 / 33 (9.09%) |  |  |
| occurrences (all)                      | 6              |  |  |
| Jaundice                               |                |  |  |
| subjects affected / exposed            | 3 / 33 (9.09%) |  |  |
| occurrences (all)                      | 4              |  |  |
| hepatic mass                           |                |  |  |
| subjects affected / exposed            | 2 / 33 (6.06%) |  |  |
| occurrences (all)                      | 2              |  |  |
| Cholangitis                            |                |  |  |
| subjects affected / exposed            | 1 / 33 (3.03%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Ocular icterus                         |                |  |  |
| subjects affected / exposed            | 1 / 33 (3.03%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Portal hypertension                    |                |  |  |
| subjects affected / exposed            | 1 / 33 (3.03%) |  |  |
| occurrences (all)                      | 1              |  |  |
| Skin and subcutaneous tissue disorders |                |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Pruritus                    |                  |  |  |
| subjects affected / exposed | 10 / 33 (30.30%) |  |  |
| occurrences (all)           | 19               |  |  |
| Rash                        |                  |  |  |
| subjects affected / exposed | 5 / 33 (15.15%)  |  |  |
| occurrences (all)           | 8                |  |  |
| Alopecia                    |                  |  |  |
| subjects affected / exposed | 2 / 33 (6.06%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Dermatitis diaper           |                  |  |  |
| subjects affected / exposed | 2 / 33 (6.06%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Cold sweat                  |                  |  |  |
| subjects affected / exposed | 1 / 33 (3.03%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Dry skin                    |                  |  |  |
| subjects affected / exposed | 1 / 33 (3.03%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Eczema                      |                  |  |  |
| subjects affected / exposed | 1 / 33 (3.03%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Erythema                    |                  |  |  |
| subjects affected / exposed | 1 / 33 (3.03%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Miliaria                    |                  |  |  |
| subjects affected / exposed | 1 / 33 (3.03%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Petechiae                   |                  |  |  |
| subjects affected / exposed | 1 / 33 (3.03%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Spider naevus               |                  |  |  |
| subjects affected / exposed | 1 / 33 (3.03%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Telangiectasia              |                  |  |  |
| subjects affected / exposed | 1 / 33 (3.03%)   |  |  |
| occurrences (all)           | 1                |  |  |

|   |   |  |  |
|---|---|--|--|
| Urticaria<br>subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>2   |  |  |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all)<br><br>Chromaturia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pollakiuria<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract pain<br>subjects affected / exposed<br>occurrences (all)               | 2 / 33 (6.06%)<br>3<br><br>1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>1  |  |  |
| Endocrine disorders<br>Delayed puberty<br>subjects affected / exposed<br>occurrences (all)<br><br>Growth hormone deficiency<br>subjects affected / exposed<br>occurrences (all)   | 1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>1  |  |  |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all)<br><br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)<br><br>Back pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Clubbing<br>subjects affected / exposed<br>occurrences (all) | 6 / 33 (18.18%)<br>8<br><br>1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>1<br><br>1 / 33 (3.03%)<br>1 |  |  |



|                                   |                  |  |  |
|-----------------------------------|------------------|--|--|
| Muscle spasms                     |                  |  |  |
| subjects affected / exposed       | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Myalgia                           |                  |  |  |
| subjects affected / exposed       | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Neck pain                         |                  |  |  |
| subjects affected / exposed       | 1 / 33 (3.03%)   |  |  |
| occurrences (all)                 | 1                |  |  |
| Infections and infestations       |                  |  |  |
| Nasopharyngitis                   |                  |  |  |
| subjects affected / exposed       | 15 / 33 (45.45%) |  |  |
| occurrences (all)                 | 49               |  |  |
| Upper respiratory tract infection |                  |  |  |
| subjects affected / exposed       | 11 / 33 (33.33%) |  |  |
| occurrences (all)                 | 35               |  |  |
| Gastroenteritis                   |                  |  |  |
| subjects affected / exposed       | 4 / 33 (12.12%)  |  |  |
| occurrences (all)                 | 4                |  |  |
| Varicella                         |                  |  |  |
| subjects affected / exposed       | 5 / 33 (15.15%)  |  |  |
| occurrences (all)                 | 5                |  |  |
| Conjunctivitis                    |                  |  |  |
| subjects affected / exposed       | 4 / 33 (12.12%)  |  |  |
| occurrences (all)                 | 5                |  |  |
| Ear infection                     |                  |  |  |
| subjects affected / exposed       | 4 / 33 (12.12%)  |  |  |
| occurrences (all)                 | 4                |  |  |
| Influenza                         |                  |  |  |
| subjects affected / exposed       | 4 / 33 (12.12%)  |  |  |
| occurrences (all)                 | 4                |  |  |
| Pharyngitis streptococcal         |                  |  |  |
| subjects affected / exposed       | 4 / 33 (12.12%)  |  |  |
| occurrences (all)                 | 7                |  |  |
| Viral infection                   |                  |  |  |

|                                   |                 |  |  |
|-----------------------------------|-----------------|--|--|
| subjects affected / exposed       | 4 / 33 (12.12%) |  |  |
| occurrences (all)                 | 7               |  |  |
| Gastroenteritis viral             |                 |  |  |
| subjects affected / exposed       | 3 / 33 (9.09%)  |  |  |
| occurrences (all)                 | 3               |  |  |
| Rhinitis                          |                 |  |  |
| subjects affected / exposed       | 3 / 33 (9.09%)  |  |  |
| occurrences (all)                 | 4               |  |  |
| Tooth abscess                     |                 |  |  |
| subjects affected / exposed       | 3 / 33 (9.09%)  |  |  |
| occurrences (all)                 | 3               |  |  |
| Urinary tract infection           |                 |  |  |
| subjects affected / exposed       | 3 / 33 (9.09%)  |  |  |
| occurrences (all)                 | 9               |  |  |
| Body tinea                        |                 |  |  |
| subjects affected / exposed       | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                 | 2               |  |  |
| Epstein-Barr virus infection      |                 |  |  |
| subjects affected / exposed       | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                 | 2               |  |  |
| Eye infection                     |                 |  |  |
| subjects affected / exposed       | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                 | 3               |  |  |
| Fungal skin infection             |                 |  |  |
| subjects affected / exposed       | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                 | 3               |  |  |
| Hand-foot-and-mouth disease       |                 |  |  |
| subjects affected / exposed       | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                 | 2               |  |  |
| Lower respiratory tract infection |                 |  |  |
| subjects affected / exposed       | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                 | 2               |  |  |
| Otitis media                      |                 |  |  |
| subjects affected / exposed       | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                 | 3               |  |  |
| Pharyngitis                       |                 |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed             | 2 / 33 (6.06%) |  |  |
| occurrences (all)                       | 2              |  |  |
| Respiratory tract infection             |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Tonsillitis                             |                |  |  |
| subjects affected / exposed             | 2 / 33 (6.06%) |  |  |
| occurrences (all)                       | 2              |  |  |
| Viral upper respiratory tract infection |                |  |  |
| subjects affected / exposed             | 2 / 33 (6.06%) |  |  |
| occurrences (all)                       | 3              |  |  |
| Bronchitis                              |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 8              |  |  |
| Candida infection                       |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 2              |  |  |
| Cellulitis                              |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Conjunctivitis viral                    |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Coxsackie viral infection               |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Gastroenteritis norovirus               |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Genital infection fungal                |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Gingivitis                              |                |  |  |
| subjects affected / exposed             | 1 / 33 (3.03%) |  |  |
| occurrences (all)                       | 1              |  |  |
| Laryngitis                              |                |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Lice infestation                   |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Oropharyngeal candidiasis          |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Otitis externa                     |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Sinusitis                          |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Viral pharyngitis                  |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Ear infection viral                |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Metabolism and nutrition disorders |                 |  |  |
| Vitamin D deficiency               |                 |  |  |
| subjects affected / exposed        | 4 / 33 (12.12%) |  |  |
| occurrences (all)                  | 4               |  |  |
| Decreased appetite                 |                 |  |  |
| subjects affected / exposed        | 3 / 33 (9.09%)  |  |  |
| occurrences (all)                  | 3               |  |  |
| Hypocalcaemia                      |                 |  |  |
| subjects affected / exposed        | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Electrolyte imbalance              |                 |  |  |
| subjects affected / exposed        | 1 / 33 (3.03%)  |  |  |
| occurrences (all)                  | 1               |  |  |
| Hypoglycaemia                      |                 |  |  |
| subjects affected / exposed        | 2 / 33 (6.06%)  |  |  |
| occurrences (all)                  | 2               |  |  |

|                             |                |  |  |
|-----------------------------|----------------|--|--|
| Acidosis                    |                |  |  |
| subjects affected / exposed | 1 / 33 (3.03%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hypertriglyceridaemia       |                |  |  |
| subjects affected / exposed | 1 / 33 (3.03%) |  |  |
| occurrences (all)           | 1              |  |  |
| Hypokalaemia                |                |  |  |
| subjects affected / exposed | 1 / 33 (3.03%) |  |  |
| occurrences (all)           | 1              |  |  |
| Iron deficiency             |                |  |  |
| subjects affected / exposed | 1 / 33 (3.03%) |  |  |
| occurrences (all)           | 1              |  |  |
| Malnutrition                |                |  |  |
| subjects affected / exposed | 1 / 33 (3.03%) |  |  |
| occurrences (all)           | 1              |  |  |
| Vitamin E deficiency        |                |  |  |
| subjects affected / exposed | 1 / 33 (3.03%) |  |  |
| occurrences (all)           | 1              |  |  |
| Vitamin K deficiency        |                |  |  |
| subjects affected / exposed | 1 / 33 (3.03%) |  |  |
| occurrences (all)           | 1              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 07 May 2014      | Protocol amendment 1: (UK and EU) Substantial changes made to the protocol were to: limit propylene glycol exposure to within the recommended limits; modify testing requirements for monitoring the liver chemistry test; and add evaluations in the event of a confirmed elevation in ALT or total bilirubin level.<br>(US) In addition to the changes noted for the UK and EU amendment, substantial changes were made to clarify the frequency for the evaluation of MRX plasma levels.  |
| 05 November 2014 | Protocol amendment 2:<br>Substantial changes made to the protocol were to: modify inclusion and exclusion criteria regarding serum bile acid levels, surgical procedures, and prohibited medications; increase the number of evaluable participants; increase the number of clinic visits and duration of treatment from 48 weeks to 72 weeks. A second interim analysis was added when all enrolled subjects reached the 48-week visit.   |
| 02 November 2015 | Protocol amendment 3:<br>Substantial changes made to the protocol were to: add an Optional Follow-up Treatment Period (After Week 72) that allowed eligible participants treated in the LUM001-501 study to continue on treatment after Week 72 until the first of the following occurred: (i) up to 52 weeks of additional treatment (Week 124), or (ii) in the event that a new study opened to enrollment; and added an objective to obtain safety and efficacy data in participants treated long term on MRX including genotyping characteristics  |
| 20 December 2016 | Protocol amendment 4:<br>Substantial changes made to the protocol were to:<br>- allow continued participation in the Optional Follow-Up Treatment Period<br>- clarify that study treatment in the Optional Follow-up Treatment Period could continue until the first of the following occurred: (i) the participants were eligible to enter another MRX study or (ii) MRX was available commercially<br>- clarify that eligible participants who had previously discontinued from the study could re-enter and receive study treatment in the Optional Follow-up Treatment Period (after Week 72)<br>- describe objectives and assessments of the Optional Follow-up Treatment Period, including the following: exploration of a BID dosing regimen and higher daily dosing of MRX; identification of genetic indicators of treatment response, including use of exome sequencing; assessment of AFP levels; assessment of the palatability of the MRX formulation in all patients; addition of an exploratory objective to allow the possibility of analysis of serum markers of treatment response using metabolomic and proteomic analysis on previously collected serum samples.<br><br>A higher maximum dosing level was selected for the Optional Follow-up Treatment Period because of the findings in healthy volunteers (Study SHP625-101) of higher fecal bile acid (fBA) excretion on higher maralixibat doses and BID dosing regimen up to 100 mg QD and 50 mg BID with a comparable safety profile across the tested dose range.<br><br>During the BID dosing regimen, the dose was to be taken at least 30 minutes prior to the main morning and evening meal in order to cover the luminal bile acid release associated with meals.<br>Participants with sBA levels above the ULN and/or ItchRO score $\geq 1.5$ were eligible to start BID dosing.<br><br>If a participant experienced intolerance at any time during the study, the physician Investigator in consultation with the Medical Monitor may have lowered the dose for the remainder of the study. |

|                  |   |
|------------------|---|
| 08 February 2019 | Protocol amendment 4.1:<br>Substantial changes made to the protocol were to reflect the change of sponsorship from Lumena Pharmaceuticals LLC to Mirum Pharmaceuticals, Inc; document the change in Medical Monitor; and reduce the interval that new medications used to treat pruritus were prohibited to between Baseline until Week 13 (time point for primary analysis). |
|------------------|---|

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported