



## Clinical trial results:

**A multi-part, randomized, double-blind, placebo-controlled study to assess the safety, tolerability and efficacy of tropifexor (LJN452) in patients with Primary Biliary Cholangitis**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-001590-41 |
| Trial protocol           | DE PL          |
| Global end of trial date | 02 August 2018 |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 22 August 2019 |
| First version publication date | 22 August 2019 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CLJN452X2201 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02516605 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Novartis Pharma AG                                                                        |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                                              |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

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                       | 02 August 2018 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 02 August 2018 |
| Was the trial ended prematurely?                     | Yes            |

Notes:

## General information about the trial

Main objective of the trial:

Primary Objectives:

- 1) To determine the effect of tropifexor on cholestatic markers in patients with PBC.
- 2) To determine the safety and tolerability of daily dosing of tropifexor in patients with PBC.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 09 September 2015 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | United States: 13     |
| Country: Number of subjects enrolled | Russian Federation: 3 |
| Country: Number of subjects enrolled | Poland: 5             |
| Country: Number of subjects enrolled | United Kingdom: 16    |
| Country: Number of subjects enrolled | Germany: 17           |
| Country: Number of subjects enrolled | Canada: 7             |
| Worldwide total number of subjects   | 61                    |
| EEA total number of subjects         | 38                    |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |

|                           |    |
|---------------------------|----|
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 49 |
| From 65 to 84 years       | 12 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This study comprised of an escalating multiple dose design in PBC patients with incomplete biochemical response to, but still taking, ursodeoxycholic acid (UDCA).

### 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, Monitor, Carer, Data analyst, Assessor |

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | LJN452 - 0.03 mg qd |

Arm description:

Tropifexor 0.03 mg daily for 28 days

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Tropifexor   |
| Investigational medicinal product code | LJN452       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

0.01 mg or 0.03 mg was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | LJN452 - 0.06 mg qd |
|------------------|---------------------|

Arm description:

Tropifexor 0.06 mg daily for 28 days

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Tropifexor   |
| Investigational medicinal product code | LJN452       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

0.01 mg or 0.03 mg was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | LJN452 - 0.09 mg qd |
|------------------|---------------------|

Arm description:

Tropifexor 0.09 mg daily for 28 days

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Tropifexor   |
| Investigational medicinal product code | LJN452       |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

0.01 mg or 0.03 mg was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

|                                                          |                     |
|----------------------------------------------------------|---------------------|
| <b>Arm title</b>                                         | LJN452 - 0.15 mg qd |
| Arm description:<br>Tropifexor 0.15 mg daily for 28 days |                     |
| Arm type                                                 | Experimental        |
| Investigational medicinal product name                   | Tropifexor          |
| Investigational medicinal product code                   | LJN452              |
| Other name                                               |                     |
| Pharmaceutical forms                                     | Capsule             |
| Routes of administration                                 | Oral use            |

**Dosage and administration details:**

0.01 mg or 0.03 mg was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

|                                                          |            |
|----------------------------------------------------------|------------|
| <b>Arm title</b>                                         | Placebo qd |
| Arm description:<br>Tropifexor placebo daily for 28 days |            |
| Arm type                                                 | Placebo    |
| Investigational medicinal product name                   | Placebo    |
| Investigational medicinal product code                   |            |
| Other name                                               |            |
| Pharmaceutical forms                                     | Capsule    |
| Routes of administration                                 | Oral use   |

**Dosage and administration details:**

0.01 mg or 0.03 mg matching placebo was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

| <b>Number of subjects in period 1</b> | LJN452 - 0.03 mg qd | LJN452 - 0.06 mg qd | LJN452 - 0.09 mg qd |
|---------------------------------------|---------------------|---------------------|---------------------|
| Started                               | 11                  | 9                   | 12                  |
| Completed                             | 11                  | 9                   | 12                  |
| Not completed                         | 0                   | 0                   | 0                   |
| Consent withdrawn by subject          | -                   | -                   | -                   |
| Protocol deviation                    | -                   | -                   | -                   |

| <b>Number of subjects in period 1</b> | LJN452 - 0.15 mg qd | Placebo qd |
|---------------------------------------|---------------------|------------|
| Started                               | 8                   | 21         |
| Completed                             | 7                   | 20         |
| Not completed                         | 1                   | 1          |
| Consent withdrawn by subject          | 1                   | -          |
| Protocol deviation                    | -                   | 1          |



## Baseline characteristics

### Reporting groups

|                                      |                     |
|--------------------------------------|---------------------|
| Reporting group title                | LJN452 - 0.03 mg qd |
| Reporting group description:         |                     |
| Tropifexor 0.03 mg daily for 28 days |                     |
| Reporting group title                | LJN452 - 0.06 mg qd |
| Reporting group description:         |                     |
| Tropifexor 0.06 mg daily for 28 days |                     |
| Reporting group title                | LJN452 - 0.09 mg qd |
| Reporting group description:         |                     |
| Tropifexor 0.09 mg daily for 28 days |                     |
| Reporting group title                | LJN452 - 0.15 mg qd |
| Reporting group description:         |                     |
| Tropifexor 0.15 mg daily for 28 days |                     |
| Reporting group title                | Placebo qd          |
| Reporting group description:         |                     |
| Tropifexor placebo daily for 28 days |                     |

| Reporting group values                             | LJN452 - 0.03 mg qd | LJN452 - 0.06 mg qd | LJN452 - 0.09 mg qd |
|----------------------------------------------------|---------------------|---------------------|---------------------|
| Number of subjects                                 | 11                  | 9                   | 12                  |
| Age categorical                                    |                     |                     |                     |
| Units: Subjects                                    |                     |                     |                     |
| In utero                                           | 0                   | 0                   | 0                   |
| Preterm newborn infants (gestational age < 37 wks) | 0                   | 0                   | 0                   |
| Newborns (0-27 days)                               | 0                   | 0                   | 0                   |
| Infants and toddlers (28 days-23 months)           | 0                   | 0                   | 0                   |
| Children (2-11 years)                              | 0                   | 0                   | 0                   |
| Adolescents (12-17 years)                          | 0                   | 0                   | 0                   |
| Adults (18-64 years)                               | 7                   | 6                   | 11                  |
| From 65-84 years                                   | 4                   | 3                   | 1                   |
| 85 years and over                                  | 0                   | 0                   | 0                   |
| Age Continuous                                     |                     |                     |                     |
| Units: years                                       |                     |                     |                     |
| arithmetic mean                                    | 58.6                | 57.9                | 53.6                |
| standard deviation                                 | ± 12.42             | ± 11.21             | ± 7.42              |
| Sex: Female, Male                                  |                     |                     |                     |
| Units: Subjects                                    |                     |                     |                     |
| Female                                             | 11                  | 7                   | 12                  |
| Male                                               | 0                   | 2                   | 0                   |
| Race/Ethnicity, Customized                         |                     |                     |                     |
| Units: Subjects                                    |                     |                     |                     |
| Caucasian                                          | 10                  | 8                   | 12                  |
| Asian                                              | 0                   | 0                   | 0                   |
| Other                                              | 1                   | 1                   | 0                   |

| Reporting group values | LJN452 - 0.15 mg qd | Placebo qd | Total |
|------------------------|---------------------|------------|-------|
|------------------------|---------------------|------------|-------|

|                                                       |         |         |    |
|-------------------------------------------------------|---------|---------|----|
| Number of subjects                                    | 8       | 21      | 61 |
| Age categorical                                       |         |         |    |
| Units: Subjects                                       |         |         |    |
| In utero                                              | 0       | 0       | 0  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0       | 0       | 0  |
| Newborns (0-27 days)                                  | 0       | 0       | 0  |
| Infants and toddlers (28 days-23<br>months)           | 0       | 0       | 0  |
| Children (2-11 years)                                 | 0       | 0       | 0  |
| Adolescents (12-17 years)                             | 0       | 0       | 0  |
| Adults (18-64 years)                                  | 6       | 19      | 49 |
| From 65-84 years                                      | 2       | 2       | 12 |
| 85 years and over                                     | 0       | 0       | 0  |
| Age Continuous                                        |         |         |    |
| Units: years                                          |         |         |    |
| arithmetic mean                                       | 57.4    | 53.7    |    |
| standard deviation                                    | ± 13.81 | ± 10.19 | -  |
| Sex: Female, Male                                     |         |         |    |
| Units: Subjects                                       |         |         |    |
| Female                                                | 8       | 21      | 59 |
| Male                                                  | 0       | 0       | 2  |
| Race/Ethnicity, Customized                            |         |         |    |
| Units: Subjects                                       |         |         |    |
| Caucasian                                             | 8       | 19      | 57 |
| Asian                                                 | 0       | 1       | 1  |
| Other                                                 | 0       | 1       | 3  |

## End points

### End points reporting groups

|                                                                                                                   |                                    |
|-------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Reporting group title                                                                                             | LJN452 - 0.03 mg qd                |
| Reporting group description:<br>Tropifexor 0.03 mg daily for 28 days                                              |                                    |
| Reporting group title                                                                                             | LJN452 - 0.06 mg qd                |
| Reporting group description:<br>Tropifexor 0.06 mg daily for 28 days                                              |                                    |
| Reporting group title                                                                                             | LJN452 - 0.09 mg qd                |
| Reporting group description:<br>Tropifexor 0.09 mg daily for 28 days                                              |                                    |
| Reporting group title                                                                                             | LJN452 - 0.15 mg qd                |
| Reporting group description:<br>Tropifexor 0.15 mg daily for 28 days                                              |                                    |
| Reporting group title                                                                                             | Placebo qd                         |
| Reporting group description:<br>Tropifexor placebo daily for 28 days                                              |                                    |
| Subject analysis set title                                                                                        | LJN452 - 0.03 mg qd vs Placebo qd  |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.03 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |
| Subject analysis set title                                                                                        | LJN452 - 0.06 mg qd vs. Placebo qd |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.06 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |
| Subject analysis set title                                                                                        | LJN452 - 0.09 mg qd vs. Placebo qd |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.09 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |
| Subject analysis set title                                                                                        | LJN452 - 0.15 mg qd vs. Placebo qd |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.15 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |
| Subject analysis set title                                                                                        | LJN452 - 0.03 mg qd vs Placebo qd  |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.03 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |
| Subject analysis set title                                                                                        | LJN452 - 0.03 mg qd vs Placebo qd  |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.03 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |
| Subject analysis set title                                                                                        | LJN452 - 0.06 mg qd vs. Placebo qd |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.06 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |

|                                                                                                                   |                                    |
|-------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Subject analysis set title                                                                                        | LJN452 - 0.09 mg qd vs. Placebo qd |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.09 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |
| Subject analysis set title                                                                                        | LJN452 - 0.15 mg qd vs. Placebo qd |
| Subject analysis set type                                                                                         | Sub-group analysis                 |
| Subject analysis set description:<br>Tropifexor 0.15 mg daily for 28 days<br>Tropifexor placebo daily for 28 days |                                    |

### Primary: Fold change in serum gamma-glutamyl transferase (GGT)

|                                                                                                         |                                                                         |
|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| End point title                                                                                         | Fold change in serum gamma-glutamyl transferase (GGT) <sup>[1][2]</sup> |
| End point description:<br>Fold change in serum gamma-glutamyl transferase (GGT) from baseline to Day 28 |                                                                         |
| End point type                                                                                          | Primary                                                                 |
| End point timeframe:<br>Baseline to Day 28                                                              |                                                                         |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: p-values were obtained from ANCOVA test but not shown due to system limitation.

[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: p-values were obtained from ANCOVA test but not shown due to system limitation.

| End point values                 | LJN452 - 0.03 mg qd | LJN452 - 0.06 mg qd | LJN452 - 0.09 mg qd | LJN452 - 0.15 mg qd |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type               | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed      | 11 <sup>[3]</sup>   | 9 <sup>[4]</sup>    | 12 <sup>[5]</sup>   | 8 <sup>[6]</sup>    |
| Units: U/L                       |                     |                     |                     |                     |
| number (confidence interval 90%) | 0.86 (0.68 to 1.09) | 0.47 (0.37 to 0.60) | 0.32 (0.26 to 0.40) | 0.36 (0.27 to 0.47) |

Notes:

[3] - Overall Study LJN452 - 0.03 mg qd vs placebo

[4] - Overall Study LJN452 - 0.06 mg qd vs placebo

[5] - Overall Study LJN452 - 0.09 mg qd vs placebo

[6] - Overall Study LJN452 - 0.15 mg qd vs placebo

| End point values                 | LJN452 - 0.03 mg qd vs Placebo qd | LJN452 - 0.06 mg qd vs. Placebo qd | LJN452 - 0.09 mg qd vs. Placebo qd | LJN452 - 0.15 mg qd vs. Placebo qd |
|----------------------------------|-----------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type               | Subject analysis set              | Subject analysis set               | Subject analysis set               | Subject analysis set               |
| Number of subjects analysed      | 11                                | 9                                  | 12                                 | 8                                  |
| Units: U/L                       |                                   |                                    |                                    |                                    |
| number (confidence interval 90%) | 0.86 (0.68 to 1.09)               | 0.47 (0.37 to 0.60)                | 0.32 (0.26 to 0.40)                | 0.36 (0.27 to 0.47)                |

### Statistical analyses

No statistical analyses for this end point

**Primary: Blood pressure**

|                 |                               |
|-----------------|-------------------------------|
| End point title | Blood pressure <sup>[7]</sup> |
|-----------------|-------------------------------|

End point description:

Vital signs - Systolic Blood pressure

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: descriptive analysis

| End point values                     | LJN452 - 0.03<br>mg qd | LJN452 - 0.06<br>mg qd | LJN452 - 0.09<br>mg qd | LJN452 - 0.15<br>mg qd |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed          | 11                     | 9                      | 12                     | 8                      |
| Units: mm Hg                         |                        |                        |                        |                        |
| arithmetic mean (standard deviation) |                        |                        |                        |                        |
| Screening                            | 122.5 (± 12.21)        | 125.8 (± 11.79)        | 129.3 (± 14.42)        | 129.5 (± 17.42)        |
| Baseline                             | 124.7 (± 17.66)        | 128.4 (± 13.83)        | 122.0 (± 18.18)        | 132.3 (± 18.09)        |
| Day 1                                | 129.6 (± 20.48)        | 122.4 (± 20.24)        | 119.9 (± 11.84)        | 129.1 (± 25.12)        |
| Day 7                                | 127.2 (± 20.18)        | 123.7 (± 13.04)        | 125.6 (± 14.22)        | 128.0 (± 26.58)        |
| Day 14                               | 122.4 (± 16.30)        | 124.6 (± 20.67)        | 127.1 (± 16.45)        | 127.3 (± 12.45)        |
| Day 21                               | 121.5 (± 11.25)        | 126.3 (± 27.65)        | 123.9 (± 13.14)        | 124.0 (± 14.23)        |
| Day 28                               | 118.0 (± 11.22)        | 127.1 (± 28.55)        | 121.4 (± 12.82)        | 126.0 (± 7.71)         |
| Day 56                               | 121.4 (± 10.76)        | 125.4 (± 18.48)        | 121.5 (± 11.55)        | 129.1 (± 26.45)        |
| Day 84                               | 131.3 (± 16.04)        | 124.6 (± 15.77)        | 122.3 (± 7.70)         | 130.4 (± 25.51)        |

| End point values                     | Placebo qd      |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 21              |  |  |  |
| Units: mm Hg                         |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Screening                            | 123.0 (± 15.40) |  |  |  |
| Baseline                             | 118.7 (± 12.76) |  |  |  |
| Day 1                                | 123.0 (± 21.84) |  |  |  |
| Day 7                                | 120.9 (± 19.57) |  |  |  |
| Day 14                               | 118.7 (± 12.88) |  |  |  |
| Day 21                               | 124.5 (± 19.8)  |  |  |  |

|        |                 |  |  |  |
|--------|-----------------|--|--|--|
| Day 28 | 120.1 (± 22.38) |  |  |  |
| Day 56 | 123.8 (± 19.74) |  |  |  |
| Day 84 | 123.6 (± 19.09) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Pulse rate

|                                                                           |                           |
|---------------------------------------------------------------------------|---------------------------|
| End point title                                                           | Pulse rate <sup>[8]</sup> |
| End point description:                                                    |                           |
| Vital signs                                                               |                           |
| End point type                                                            | Primary                   |
| End point timeframe:                                                      |                           |
| Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84 |                           |

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: descriptive analysis

| End point values                     | LJN452 - 0.03<br>mg qd | LJN452 - 0.06<br>mg qd | LJN452 - 0.09<br>mg qd | LJN452 - 0.15<br>mg qd |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed          | 11                     | 9                      | 12                     | 8                      |
| Units: bpm                           |                        |                        |                        |                        |
| arithmetic mean (standard deviation) |                        |                        |                        |                        |
| Screening                            | 68.6 (± 10.63)         | 61.2 (± 7.05)          | 75.3 (± 8.22)          | 72.8 (± 8.26)          |
| Baseline                             | 64.3 (± 7.79)          | 64.1 (± 8.70)          | 70.8 (± 8.63)          | 74.4 (± 5.15)          |
| Day 1                                | 67.7 (± 11.93)         | 64.2 (± 8.07)          | 69.7 (± 7.50)          | 74.1 (± 11.62)         |
| Day 7                                | 65.2 (± 9.98)          | 66.8 (± 11.31)         | 70.1 (± 11.64)         | 73.5 (± 8.33)          |
| Day 14                               | 62.9 (± 10.03)         | 64.8 (± 8.09)          | 70.5 (± 14.16)         | 75.1 (± 6.74)          |
| Day 21                               | 65.5 (± 8.26)          | 65.8 (± 11.18)         | 73.2 (± 8.43)          | 72.5 (± 6.75)          |
| Day 28                               | 65.5 (± 10.83)         | 68.9 (± 10.60)         | 68.5 (± 9.01)          | 67.2 (± 3.42)          |
| Day 56                               | 66.8 (± 9.64)          | 67.7 (± 7.53)          | 69.7 (± 8.17)          | 69.7 (± 4.07)          |
| Day 84                               | 65.6 (± 10.24)         | 64.0 (± 9.11)          | 70.2 (± 8.14)          | 72.8 (± 8.12)          |

| End point values                     | Placebo qd      |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 21              |  |  |  |
| Units: bpm                           |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Screening                            | 69.3 (± 10.69)  |  |  |  |
| Baseline                             | 66.3 (± 9.30)   |  |  |  |
| Day 1                                | 67.6 (± 8.35)   |  |  |  |
| Day 7                                | 65.2 (± 8.92)   |  |  |  |

|        |                |  |  |  |
|--------|----------------|--|--|--|
| Day 14 | 66.1 (± 9.61)  |  |  |  |
| Day 21 | 67.7 (± 10.18) |  |  |  |
| Day 28 | 65.8 (± 9.29)  |  |  |  |
| Day 56 | 68.1 (± 10.11) |  |  |  |
| Day 84 | 68.1 (± 9.82)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Body Temperature

|                                                                           |                                 |
|---------------------------------------------------------------------------|---------------------------------|
| End point title                                                           | Body Temperature <sup>[9]</sup> |
| End point description:                                                    |                                 |
| Vital signs                                                               |                                 |
| End point type                                                            | Primary                         |
| End point timeframe:                                                      |                                 |
| Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84 |                                 |

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: descriptive analysis

| End point values                     | LJN452 - 0.03<br>mg qd | LJN452 - 0.06<br>mg qd | LJN452 - 0.09<br>mg qd | LJN452 - 0.15<br>mg qd |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed          | 11                     | 9                      | 12                     | 8                      |
| Units: Celsius                       |                        |                        |                        |                        |
| arithmetic mean (standard deviation) |                        |                        |                        |                        |
| screening                            | 36.605 (± 0.2813)      | 36.567 (± 0.2000)      | 36.424 (± 0.3429)      | 36.650 (± 0.1604)      |
| baseline                             | 36.582 (± 0.2960)      | 36.644 (± 0.2128)      | 36.398 (± 0.3385)      | 36.638 (± 0.1506)      |
| day 1                                | 36.436 (± 0.3139)      | 36.537 (± 0.3076)      | 36.482 (± 0.2636)      | 36.575 (± 0.1982)      |
| day 7                                | 36.582 (± 0.2040)      | 36.533 (± 0.1323)      | 36.258 (± 0.3965)      | 36.600 (± 0.1195)      |
| day 14                               | 36.516 (± 0.1793)      | 36.444 (± 0.2007)      | 36.291 (± 0.4109)      | 36.500 (± 0.1826)      |
| day 21                               | 36.500 (± 0.2490)      | 36.267 (± 0.4637)      | 36.308 (± 0.3288)      | 36.433 (± 0.1966)      |
| day 28                               | 36.382 (± 0.2228)      | 36.444 (± 0.2128)      | 36.308 (± 0.3397)      | 36.520 (± 0.2950)      |
| day 56                               | 36.527 (± 0.2102)      | 36.500 (± 0.2179)      | 36.350 (± 0.4602)      | 36.443 (± 0.3309)      |
| day 84                               | 36.482 (± 0.2483)      | 36.500 (± 0.1500)      | 36.383 (± 0.2980)      | 36.638 (± 0.1506)      |

| End point values            | Placebo qd      |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 21              |  |  |  |

|                                      |                        |  |  |  |
|--------------------------------------|------------------------|--|--|--|
| Units: Celsius                       |                        |  |  |  |
| arithmetic mean (standard deviation) |                        |  |  |  |
| screening                            | 36.460 ( $\pm$ 0.4500) |  |  |  |
| baseline                             | 36.376 ( $\pm$ 0.5118) |  |  |  |
| day 1                                | 36.390 ( $\pm$ 0.4867) |  |  |  |
| day 7                                | 36.345 ( $\pm$ 0.4639) |  |  |  |
| day 14                               | 36.310 ( $\pm$ 0.4576) |  |  |  |
| day 21                               | 36.455 ( $\pm$ 0.4236) |  |  |  |
| day 28                               | 36.380 ( $\pm$ 0.4047) |  |  |  |
| day 56                               | 36.285 ( $\pm$ 0.4246) |  |  |  |
| day 84                               | 36.295 ( $\pm$ 0.4248) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: ECG - Heart Rate

|                        |                                    |
|------------------------|------------------------------------|
| End point title        | ECG - Heart Rate <sup>[10]</sup>   |
| End point description: | Electrocardiogram (ECG)            |
| End point type         | Primary                            |
| End point timeframe:   | Screening, Baseline, day 1, day 28 |

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: descriptive analysis

| End point values                     | LJN452 - 0.03 mg qd | LJN452 - 0.06 mg qd | LJN452 - 0.09 mg qd | LJN452 - 0.15 mg qd |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed          | 11                  | 9                   | 12                  | 8                   |
| Units: bpm                           |                     |                     |                     |                     |
| arithmetic mean (standard deviation) |                     |                     |                     |                     |
| Screening                            | 65.8 ( $\pm$ 11.32) | 61.8 ( $\pm$ 9.97)  | 67.3 ( $\pm$ 5.58)  | 67.8 ( $\pm$ 6.54)  |
| Baseline                             | 60.5 ( $\pm$ 8.99)  | 61.4 ( $\pm$ 8.75)  | 64.6 ( $\pm$ 7.95)  | 67.9 ( $\pm$ 6.45)  |
| Day 1                                | 61.5 ( $\pm$ 11.16) | 63.4 ( $\pm$ 11.17) | 63.9 ( $\pm$ 8.21)  | 66.9 ( $\pm$ 11.97) |
| Day 28                               | 60.5 ( $\pm$ 11.39) | 65.2 ( $\pm$ 11.95) | 63.5 ( $\pm$ 9.95)  | 65.8 ( $\pm$ 4.55)  |

|                  |            |  |  |  |
|------------------|------------|--|--|--|
| End point values | Placebo qd |  |  |  |
|------------------|------------|--|--|--|

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 21              |  |  |  |
| Units: bpm                           |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Screening                            | 63.4 (± 9.35)   |  |  |  |
| Baseline                             | 63.8 (± 9.41)   |  |  |  |
| Day 1                                | 63.5 (± 7.12)   |  |  |  |
| Day 28                               | 60.8 (± 7.03)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: ECG Intervals - PR interval

|                                    |                                             |
|------------------------------------|---------------------------------------------|
| End point title                    | ECG Intervals - PR interval <sup>[11]</sup> |
| End point description:             |                                             |
| Electrocardiogram (ECG)            |                                             |
| End point type                     | Primary                                     |
| End point timeframe:               |                                             |
| Screening, Baseline, day 1, day 28 |                                             |

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: descriptive analysis

| End point values                     | LJN452 - 0.03<br>mg qd | LJN452 - 0.06<br>mg qd | LJN452 - 0.09<br>mg qd | LJN452 - 0.15<br>mg qd |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed          | 11                     | 9                      | 12                     | 8                      |
| Units: msec                          |                        |                        |                        |                        |
| arithmetic mean (standard deviation) |                        |                        |                        |                        |
| Screening                            | 159.2 (± 27.34)        | 158.0 (± 23.71)        | 172.0 (± 24.12)        | 159.9 (± 17.24)        |
| Baseline                             | 165.8 (± 20.81)        | 156.2 (± 18.99)        | 175.0 (± 34.96)        | 152.0 (± 22.21)        |
| Day 1                                | 165.5 (± 21.76)        | 162.9 (± 27.06)        | 175.7 (± 28.29)        | 160.0 (± 20.32)        |
| Day 28                               | 164.9 (± 19.75)        | 157.1 (± 26.70)        | 180.4 (± 31.63)        | 155.4 (± 23.51)        |

| End point values                     | Placebo qd      |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 21              |  |  |  |
| Units: msec                          |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Screening                            | 162.6 (± 19.03) |  |  |  |
| Baseline                             | 160.3 (± 19.77) |  |  |  |

|        |                 |  |  |  |
|--------|-----------------|--|--|--|
| Day 1  | 161.6 (± 20.28) |  |  |  |
| Day 28 | 160.2 (± 28.70) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Haemoglobin

|                        |                                                                           |
|------------------------|---------------------------------------------------------------------------|
| End point title        | Haemoglobin <sup>[12]</sup>                                               |
| End point description: | Hematology panel for safety laboratory assessments.                       |
| End point type         | Primary                                                                   |
| End point timeframe:   | Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84 |

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: descriptive analysis

| End point values                     | LJN452 - 0.03 mg qd | LJN452 - 0.06 mg qd | LJN452 - 0.09 mg qd | LJN452 - 0.15 mg qd |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed          | 11                  | 9                   | 12                  | 8                   |
| Units: g/L                           |                     |                     |                     |                     |
| arithmetic mean (standard deviation) |                     |                     |                     |                     |
| screening                            | 127.9 (± 9.24)      | 125.6 (± 11.70)     | 130.5 (± 9.73)      | 133.9 (± 12.70)     |
| baseline                             | 126.5 (± 8.58)      | 127.4 (± 11.85)     | 130.5 (± 11.90)     | 134.6 (± 13.24)     |
| day 1                                | 124.7 (± 8.21)      | 132.9 (± 10.05)     | 127.0 (± 9.03)      | 133.1 (± 11.37)     |
| day 7                                | 124.0 (± 8.23)      | 128.8 (± 16.97)     | 132.4 (± 10.66)     | 134.0 (± 8.75)      |
| day 14                               | 126.5 (± 9.83)      | 127.3 (± 12.64)     | 128.6 (± 7.82)      | 135.4 (± 13.50)     |
| day 21                               | 127.5 (± 8.32)      | 128.0 (± 13.49)     | 130.5 (± 10.40)     | 134.2 (± 9.91)      |
| day 28                               | 125.3 (± 9.18)      | 127.1 (± 14.67)     | 129.6 (± 10.02)     | 136.4 (± 13.50)     |
| day 56                               | 126.7 (± 6.96)      | 125.8 (± 11.15)     | 128.6 (± 10.63)     | 133.6 (± 12.00)     |
| day 84                               | 126.5 (± 8.78)      | 124.9 (± 9.75)      | 125.9 (± 11.19)     | 131.1 (± 10.91)     |

| End point values                     | Placebo qd      |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 21              |  |  |  |
| Units: g/L                           |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |

|           |                 |  |  |  |
|-----------|-----------------|--|--|--|
| screening | 132.2 (± 8.81)  |  |  |  |
| baseline  | 131.3 (± 8.02)  |  |  |  |
| day 1     | 126.8 (± 7.63)  |  |  |  |
| day 7     | 128.6 (± 9.18)  |  |  |  |
| day 14    | 128.7 (± 10.84) |  |  |  |
| day 21    | 128.8 (± 10.79) |  |  |  |
| day 28    | 125.7 (± 9.71)  |  |  |  |
| day 56    | 129.3 (± 11.39) |  |  |  |
| day 84    | 129.3 (± 9.24)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PK parameter - AUC 0-8h

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Plasma PK parameter - AUC 0-8h <sup>[13]</sup> |
|-----------------|------------------------------------------------|

End point description:

Tropifexor levels were determined in plasma using a validated LC-MS/MS method. AUC0-t=The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]

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

End point timeframe:

Day 1, Day 28

Notes:

[13] - 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: descriptive analysis

| End point values                     | LJN452 - 0.03 mg qd | LJN452 - 0.06 mg qd | LJN452 - 0.09 mg qd | LJN452 - 0.15 mg qd |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed          | 9                   | 7                   | 3                   | 4                   |
| Units: hr*ng/mL                      |                     |                     |                     |                     |
| arithmetic mean (standard deviation) |                     |                     |                     |                     |
| Day 1                                | 4.98 (± 2.87)       | 12.1 (± 2.68)       | 999 (± 999)         | 24.5 (± 15.9)       |
| Day 28                               | 7.95 (± 4.21)       | 17.6 (± 5.30)       | 23.4 (± 8.70)       | 44.2 (± 25.8)       |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma PK parameter - Cmax

|                 |                                            |
|-----------------|--------------------------------------------|
| End point title | Plasma PK parameter - Cmax <sup>[14]</sup> |
|-----------------|--------------------------------------------|

End point description:

Tropifexor levels were determined in plasma using a validated LC-MS/MS method. Cmax=The observed

maximum plasma concentration following drug administration [mass /volume]

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Day 1, Day 28        |           |

Notes:

[14] - 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: descriptive analysis

| End point values                     | LJN452 - 0.03<br>mg qd | LJN452 - 0.06<br>mg qd | LJN452 - 0.09<br>mg qd | LJN452 - 0.15<br>mg qd |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed          | 11                     | 9                      | 12                     | 8                      |
| Units: ng/mL                         |                        |                        |                        |                        |
| arithmetic mean (standard deviation) |                        |                        |                        |                        |
| Day 1                                | 1.04 (± 0.484)         | 1.80 (± 0.585)         | 2.37 (± 1.56)          | 4.84 (± 2.59)          |
| Day 28                               | 1.25 (± 0.559)         | 2.55 (± 0.946)         | 4.30 (± 2.10)          | 6.37 (± 3.40)          |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma PK parameter - Tmax

|                                                                                                                                                                    |                                            |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                                                                                                                    | Plasma PK parameter - Tmax <sup>[15]</sup> |
| End point description:                                                                                                                                             |                                            |
| Tropifexor levels were determined in plasma using a validated LC-MS/MS method. Tmax = The time to reach the maximum concentration after drug administration [time] |                                            |
| End point type                                                                                                                                                     | Secondary                                  |
| End point timeframe:                                                                                                                                               |                                            |
| Day 1, Day 28                                                                                                                                                      |                                            |

Notes:

[15] - 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: descriptive analysis

| End point values                      | LJN452 - 0.03<br>mg qd | LJN452 - 0.06<br>mg qd | LJN452 - 0.09<br>mg qd | LJN452 - 0.15<br>mg qd |
|---------------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type                    | Reporting group        | Reporting group        | Reporting group        | Reporting group        |
| Number of subjects analysed           | 11                     | 9                      | 12                     | 8                      |
| Units: hr                             |                        |                        |                        |                        |
| median (inter-quartile range (Q1-Q3)) |                        |                        |                        |                        |
| Day 1                                 | 4.12 (2.00 to 8.00)    | 4.00 (3.70 to 6.00)    | 4.00 (0 to 7.83)       | 4.00 (4.00 to 4.18)    |
| Day 28                                | 4.08 (2.00 to 8.00)    | 4.00 (3.13 to 7.60)    | 4.00 (0 to 6.00)       | 5.00 (3.03 to 6.00)    |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Changes from baseline in total PBC-40 score

|                 |                                             |
|-----------------|---------------------------------------------|
| End point title | Changes from baseline in total PBC-40 score |
|-----------------|---------------------------------------------|

End point description:

Median difference: LJN452 vs Placebo. Baseline is defined as the latest available predose value. The PBC-40 is a paper-based patient-derived, disease specific quality of life patient reported outcome (PRO) measure which was developed and validated for use in subjects with PBC (Jacoby et al 2005). It consists of 40 questions arranged in 8 domains with between 3 and 11 questions in each domain. Each question is scored from 1 to 5 in increasing order of severity. The difference in total sum score between each treated group and placebo at Day 28 is presented.

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

End point timeframe:

Baseline, Day 28, Day 56, Day 84

| End point values                 | LJN452 - 0.03 mg qd vs Placebo qd | LJN452 - 0.06 mg qd vs. Placebo qd | LJN452 - 0.09 mg qd vs. Placebo qd | LJN452 - 0.15 mg qd vs. Placebo qd |
|----------------------------------|-----------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type               | Subject analysis set              | Subject analysis set               | Subject analysis set               | Subject analysis set               |
| Number of subjects analysed      | 10                                | 9                                  | 12                                 | 8                                  |
| Units: PBC-40 points             |                                   |                                    |                                    |                                    |
| median (confidence interval 90%) |                                   |                                    |                                    |                                    |
| Day 28                           | 1.0 (-7.0 to 6.0)                 | 1.5 (-5.0 to 7.0)                  | 4.0 (-3.0 to 8.0)                  | 2.0 (-2.0 to 9.0)                  |
| Day 56                           | 2.0 (-4.0 to 10.0)                | -2.0 (-12.0 to 4.0)                | -6.0 (-14.0 to 1.0)                | -11.0 (-21.0 to -1.0)              |
| Day 84                           | -3.0 (-11.0 to 4.0)               | -1.0 (-10.0 to 8.0)                | -6.5 (-15.0 to 1.0)                | -3.5 (-11.0 to 3.0)                |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in itch subdomain of PBC-40 score

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Change from baseline in itch subdomain of PBC-40 score |
|-----------------|--------------------------------------------------------|

End point description:

Median difference: LJN452 vs Placebo. Baseline is defined as the latest available predose value. The domain specifically relates to cholestatic itch symptomatology. In addition to the investigation of the total PBC-40 sum score, the sum scores from the 3 question itch sub-domain of the PBC-40 questionnaire was determined and used to test for an effect of tropifexor relative to placebo.

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

End point timeframe:

Baseline, Day 28, Day 56, Day 84

| End point values                 | LJN452 - 0.06 mg qd vs. Placebo qd | LJN452 - 0.09 mg qd vs. Placebo qd | LJN452 - 0.15 mg qd vs. Placebo qd | LJN452 - 0.03 mg qd vs. Placebo qd |
|----------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type               | Subject analysis set               | Subject analysis set               | Subject analysis set               | Subject analysis set               |
| Number of subjects analysed      | 9                                  | 12                                 | 8                                  | 9                                  |
| Units: PBC-40 points             |                                    |                                    |                                    |                                    |
| median (confidence interval 90%) |                                    |                                    |                                    |                                    |
| Day 28                           | 1.0 (0.0 to 2.0)                   | 2.0 (0.0 to 4.0)                   | 2.0 (0.0 to 5.0)                   | 1.0 (-1.0 to 2.0)                  |
| Day 56                           | 1.0 (0.0 to 2.0)                   | 0.0 (-1.0 to 2.0)                  | 0.0 (-1.0 to 1.0)                  | 0.0 (-1.0 to 2.0)                  |
| Day 84                           | 0.0 (-2.0 to 1.0)                  | 0.0 (-2.0 to 1.0)                  | 0.0 (-2.0 to 1.0)                  | -1.0 (-3.0 to 1.0)                 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Global Itch Visual Analogue Scale (VAS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Change from baseline in Global Itch Visual Analogue Scale (VAS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                 |
| The Global Itch Visual Analogue Scale, a 100 mm visual analogue scale (VAS) was used to assess the severity of patients itch (ranging from 0 = none at all to 10 = the worst imaginable itch) and the 100 mm Sleep Disturbance Visual Analogue Scale was used to assess the impact of nocturnal itch on sleep (from 0 = no sleep loss to 10 = cannot sleep at all). The score (distance in mm from left) on the VAS was recorded for both parameters by the patient marking with a line and used to test for an effect of tropifexor over placebo. |                                                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Secondary                                                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                 |
| Day 7, Day 14, Day 21, Day 28, Day 56, and Day 84                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                 |

| End point values                          | LJN452 - 0.03 mg qd vs. Placebo qd | LJN452 - 0.06 mg qd vs. Placebo qd | LJN452 - 0.09 mg qd vs. Placebo qd | LJN452 - 0.15 mg qd vs. Placebo qd |
|-------------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type                        | Subject analysis set               | Subject analysis set               | Subject analysis set               | Subject analysis set               |
| Number of subjects analysed               | 10                                 | 9                                  | 12                                 | 8                                  |
| Units: mm                                 |                                    |                                    |                                    |                                    |
| arithmetic mean (confidence interval 90%) |                                    |                                    |                                    |                                    |
| Day 7                                     | -2.78 (-16.91 to 11.34)            | 11.34 (-2.78 to 25.46)             | 13.92 (0.58 to 27.25)              | 26.70 (11.97 to 41.44)             |
| Day 14                                    | -14.07 (-27.85 to -0.28)           | 7.74 (-6.05 to 21.52)              | 0.48 (-12.57 to 13.53)             | 8.17 (-6.96 to 23.29)              |
| Day 21                                    | 7.78 (-6.81 to 22.38)              | 16.79 (2.20 to 31.38)              | 5.02 (-8.79 to 18.83)              | 5.90 (-10.86 to 22.66)             |
| Day 28                                    | 7.03 (-8.36 to 22.43)              | 14.05 (-1.35 to 29.44)             | 0.19 (-14.38 to 14.77)             | 8.91 (-9.34 to 27.15)              |
| Day 56                                    | -15.25 (-27.30 to -3.19)           | -1.75 (-13.80 to 10.31)            | -13.82 (-25.21 to -2.43)           | -11.08 (-23.95 to 1.80)            |
| Day 84                                    | -16.93 (-31.31 to -2.54)           | -10.90 (-25.29 to 3.48)            | -18.23 (-31.81 to -4.64)           | -16.93 (-31.94 to -1.92)           |

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 56 days post last dose.

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Assessment type                                                      | Systematic          |
| <b>Dictionary used</b>                                               |                     |
| Dictionary name                                                      | MedDRA              |
| Dictionary version                                                   | 21.0                |
| <b>Reporting groups</b>                                              |                     |
| Reporting group title                                                | LJN452 - 0.03 mg qd |
| Reporting group description:<br>Tropifexor 0.03 mg daily for 28 days |                     |
| Reporting group title                                                | Placebo qd          |
| Reporting group description:<br>Tropifexor placebo daily for 28 days |                     |
| Reporting group title                                                | LJN452 - 0.15 mg qd |
| Reporting group description:<br>Tropifexor 0.15 mg daily for 28 days |                     |
| Reporting group title                                                | LJN452 - 0.06 mg qd |
| Reporting group description:<br>Tropifexor 0.06 mg daily for 28 days |                     |
| Reporting group title                                                | LJN452 - 0.09 mg qd |
| Reporting group description:<br>Tropifexor 0.09 mg daily for 28 days |                     |

| <b>Serious adverse events</b>                     | LJN452 - 0.03 mg qd | Placebo qd     | LJN452 - 0.15 mg qd |
|---------------------------------------------------|---------------------|----------------|---------------------|
| Total subjects affected by serious adverse events |                     |                |                     |
| subjects affected / exposed                       | 0 / 11 (0.00%)      | 0 / 21 (0.00%) | 0 / 8 (0.00%)       |
| number of deaths (all causes)                     | 0                   | 0              | 0                   |
| number of deaths resulting from adverse events    | 0                   | 0              | 0                   |

| <b>Serious adverse events</b>                     | LJN452 - 0.06 mg qd | LJN452 - 0.09 mg qd |  |
|---------------------------------------------------|---------------------|---------------------|--|
| Total subjects affected by serious adverse events |                     |                     |  |
| subjects affected / exposed                       | 0 / 9 (0.00%)       | 0 / 12 (0.00%)      |  |
| number of deaths (all causes)                     | 0                   | 0                   |  |
| number of deaths resulting from adverse events    | 0                   | 0                   |  |

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

| <b>Non-serious adverse events</b>                           | <b>LJN452 - 0.03 mg<br/>qd</b> | <b>Placebo qd</b> | <b>LJN452 - 0.15 mg<br/>qd</b> |
|-------------------------------------------------------------|--------------------------------|-------------------|--------------------------------|
| Total subjects affected by non-serious adverse events       |                                |                   |                                |
| subjects affected / exposed                                 | 9 / 11 (81.82%)                | 16 / 21 (76.19%)  | 8 / 8 (100.00%)                |
| <b>Vascular disorders</b>                                   |                                |                   |                                |
| Hypertension                                                |                                |                   |                                |
| subjects affected / exposed                                 | 1 / 11 (9.09%)                 | 0 / 21 (0.00%)    | 0 / 8 (0.00%)                  |
| occurrences (all)                                           | 1                              | 0                 | 0                              |
| <b>General disorders and administration site conditions</b> |                                |                   |                                |
| Fatigue                                                     |                                |                   |                                |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                 | 1 / 21 (4.76%)    | 1 / 8 (12.50%)                 |
| occurrences (all)                                           | 0                              | 1                 | 1                              |
| Non-cardiac chest pain                                      |                                |                   |                                |
| subjects affected / exposed                                 | 1 / 11 (9.09%)                 | 0 / 21 (0.00%)    | 0 / 8 (0.00%)                  |
| occurrences (all)                                           | 1                              | 0                 | 0                              |
| Oedema peripheral                                           |                                |                   |                                |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                 | 2 / 21 (9.52%)    | 0 / 8 (0.00%)                  |
| occurrences (all)                                           | 0                              | 2                 | 0                              |
| <b>Reproductive system and breast disorders</b>             |                                |                   |                                |
| Vulvovaginal discomfort                                     |                                |                   |                                |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                 | 0 / 21 (0.00%)    | 0 / 8 (0.00%)                  |
| occurrences (all)                                           | 0                              | 0                 | 0                              |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                                |                   |                                |
| Cough                                                       |                                |                   |                                |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                 | 1 / 21 (4.76%)    | 0 / 8 (0.00%)                  |
| occurrences (all)                                           | 0                              | 1                 | 0                              |
| Epistaxis                                                   |                                |                   |                                |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                 | 1 / 21 (4.76%)    | 0 / 8 (0.00%)                  |
| occurrences (all)                                           | 0                              | 1                 | 0                              |
| Nasal congestion                                            |                                |                   |                                |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                 | 0 / 21 (0.00%)    | 0 / 8 (0.00%)                  |
| occurrences (all)                                           | 0                              | 0                 | 0                              |
| Oropharyngeal pain                                          |                                |                   |                                |

|                                        |                |                |                |
|----------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0              |
| Productive cough                       |                |                |                |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0              |
| Sinus congestion                       |                |                |                |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                      | 1              | 0              | 0              |
| Psychiatric disorders                  |                |                |                |
| Initial insomnia                       |                |                |                |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 21 (4.76%) | 0 / 8 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0              |
| Insomnia                               |                |                |                |
| subjects affected / exposed            | 1 / 11 (9.09%) | 0 / 21 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)                      | 1              | 0              | 1              |
| Sleep disorder                         |                |                |                |
| subjects affected / exposed            | 1 / 11 (9.09%) | 1 / 21 (4.76%) | 1 / 8 (12.50%) |
| occurrences (all)                      | 1              | 1              | 1              |
| Investigations                         |                |                |                |
| Alanine aminotransferase increased     |                |                |                |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all)                      | 0              | 0              | 2              |
| Aspartate aminotransferase increased   |                |                |                |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Blood creatine phosphokinase increased |                |                |                |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                      | 0              | 0              | 0              |
| Blood creatinine increased             |                |                |                |
| subjects affected / exposed            | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Low density lipoprotein increased      |                |                |                |
| subjects affected / exposed            | 0 / 11 (0.00%) | 1 / 21 (4.76%) | 0 / 8 (0.00%)  |
| occurrences (all)                      | 0              | 1              | 0              |
| Weight increased                       |                |                |                |

|                                                  |                     |                     |                    |
|--------------------------------------------------|---------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 11 (9.09%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0 |
| Injury, poisoning and procedural complications   |                     |                     |                    |
| Arthropod bite                                   |                     |                     |                    |
| subjects affected / exposed                      | 2 / 11 (18.18%)     | 0 / 21 (0.00%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 2                   | 0                   | 0                  |
| Muscle strain                                    |                     |                     |                    |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 1 / 21 (4.76%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                  |
| Cardiac disorders                                |                     |                     |                    |
| Trifascicular block                              |                     |                     |                    |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 0 / 21 (0.00%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                  |
| Nervous system disorders                         |                     |                     |                    |
| Aphasia                                          |                     |                     |                    |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 1 / 21 (4.76%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                  |
| Dizziness                                        |                     |                     |                    |
| subjects affected / exposed                      | 1 / 11 (9.09%)      | 1 / 21 (4.76%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 1                   | 1                   | 0                  |
| Dysgeusia                                        |                     |                     |                    |
| subjects affected / exposed                      | 1 / 11 (9.09%)      | 0 / 21 (0.00%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                  |
| Headache                                         |                     |                     |                    |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 3 / 21 (14.29%)     | 1 / 8 (12.50%)     |
| occurrences (all)                                | 0                   | 3                   | 1                  |
| Hypoaesthesia                                    |                     |                     |                    |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 0 / 21 (0.00%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                  |
| Optic neuritis                                   |                     |                     |                    |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 1 / 21 (4.76%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                  |
| Blood and lymphatic system disorders             |                     |                     |                    |
| Anaemia                                          |                     |                     |                    |
| subjects affected / exposed                      | 0 / 11 (0.00%)      | 0 / 21 (0.00%)      | 0 / 8 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                  |

|                             |                 |                 |               |
|-----------------------------|-----------------|-----------------|---------------|
| Leukopenia                  |                 |                 |               |
| subjects affected / exposed | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Thrombocytopenia            |                 |                 |               |
| subjects affected / exposed | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Eye disorders               |                 |                 |               |
| Dry eye                     |                 |                 |               |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 21 (4.76%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 0               | 1               | 0             |
| Eye pruritus                |                 |                 |               |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 21 (4.76%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 0               | 1               | 0             |
| Gastrointestinal disorders  |                 |                 |               |
| Abdominal discomfort        |                 |                 |               |
| subjects affected / exposed | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Abdominal distension        |                 |                 |               |
| subjects affected / exposed | 1 / 11 (9.09%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 1               | 0               | 0             |
| Abdominal pain lower        |                 |                 |               |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 21 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 2               | 0               | 0             |
| Abdominal pain upper        |                 |                 |               |
| subjects affected / exposed | 1 / 11 (9.09%)  | 3 / 21 (14.29%) | 0 / 8 (0.00%) |
| occurrences (all)           | 1               | 3               | 0             |
| Constipation                |                 |                 |               |
| subjects affected / exposed | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Diarrhoea                   |                 |                 |               |
| subjects affected / exposed | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 0               | 0               | 0             |
| Dry mouth                   |                 |                 |               |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 21 (4.76%)  | 0 / 8 (0.00%) |
| occurrences (all)           | 0               | 1               | 0             |
| Dyspepsia                   |                 |                 |               |

|                                        |                 |                 |                |
|----------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 21 (0.00%)  | 1 / 8 (12.50%) |
| occurrences (all)                      | 1               | 0               | 1              |
| Epigastric discomfort                  |                 |                 |                |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0              |
| Flatulence                             |                 |                 |                |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                      | 2               | 0               | 0              |
| Gastrooesophageal reflux disease       |                 |                 |                |
| subjects affected / exposed            | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 1 / 8 (12.50%) |
| occurrences (all)                      | 0               | 0               | 1              |
| Haemorrhoidal haemorrhage              |                 |                 |                |
| subjects affected / exposed            | 0 / 11 (0.00%)  | 1 / 21 (4.76%)  | 0 / 8 (0.00%)  |
| occurrences (all)                      | 0               | 1               | 0              |
| Nausea                                 |                 |                 |                |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 3 / 21 (14.29%) | 0 / 8 (0.00%)  |
| occurrences (all)                      | 1               | 3               | 0              |
| Varices oesophageal                    |                 |                 |                |
| subjects affected / exposed            | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                      | 0               | 0               | 0              |
| Vomiting                               |                 |                 |                |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 2 / 21 (9.52%)  | 0 / 8 (0.00%)  |
| occurrences (all)                      | 1               | 2               | 0              |
| Skin and subcutaneous tissue disorders |                 |                 |                |
| Pruritus                               |                 |                 |                |
| subjects affected / exposed            | 3 / 11 (27.27%) | 6 / 21 (28.57%) | 7 / 8 (87.50%) |
| occurrences (all)                      | 3               | 7               | 7              |
| Pruritus generalised                   |                 |                 |                |
| subjects affected / exposed            | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                      | 0               | 0               | 0              |
| Psoriasis                              |                 |                 |                |
| subjects affected / exposed            | 0 / 11 (0.00%)  | 0 / 21 (0.00%)  | 0 / 8 (0.00%)  |
| occurrences (all)                      | 0               | 0               | 0              |
| Rash                                   |                 |                 |                |
| subjects affected / exposed            | 1 / 11 (9.09%)  | 1 / 21 (4.76%)  | 1 / 8 (12.50%) |
| occurrences (all)                      | 1               | 1               | 2              |

|                                                                          |                      |                     |                     |
|--------------------------------------------------------------------------|----------------------|---------------------|---------------------|
| Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all)  | 0 / 11 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0  |
| Renal and urinary disorders                                              |                      |                     |                     |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)              | 0 / 11 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)          | 0 / 11 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)          | 1 / 11 (9.09%)<br>1  | 0 / 21 (0.00%)<br>0 | 1 / 8 (12.50%)<br>1 |
| Musculoskeletal and connective tissue disorders                          |                      |                     |                     |
| Costochondritis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 11 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1 | 0 / 8 (0.00%)<br>0  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)        | 2 / 11 (18.18%)<br>2 | 0 / 21 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)    | 1 / 11 (9.09%)<br>1  | 0 / 21 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0  |
| Infections and infestations                                              |                      |                     |                     |
| Fungal infection<br>subjects affected / exposed<br>occurrences (all)     | 1 / 11 (9.09%)<br>1  | 0 / 21 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)      | 2 / 11 (18.18%)<br>2 | 1 / 21 (4.76%)<br>1 | 0 / 8 (0.00%)<br>0  |
| Overgrowth bacterial<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1 | 0 / 8 (0.00%)<br>0  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 11 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0 | 0 / 8 (0.00%)<br>0  |

|                                         |                |                |                |
|-----------------------------------------|----------------|----------------|----------------|
| Rash pustular                           |                |                |                |
| subjects affected / exposed             | 1 / 11 (9.09%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                       | 1              | 0              | 0              |
| Sinusitis                               |                |                |                |
| subjects affected / exposed             | 1 / 11 (9.09%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                       | 1              | 0              | 0              |
| Tooth abscess                           |                |                |                |
| subjects affected / exposed             | 1 / 11 (9.09%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                       | 1              | 0              | 0              |
| Upper respiratory tract infection       |                |                |                |
| subjects affected / exposed             | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                       | 0              | 0              | 0              |
| Urinary tract infection                 |                |                |                |
| subjects affected / exposed             | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                       | 0              | 0              | 0              |
| Viral infection                         |                |                |                |
| subjects affected / exposed             | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Viral upper respiratory tract infection |                |                |                |
| subjects affected / exposed             | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all)                       | 0              | 0              | 1              |
| Metabolism and nutrition disorders      |                |                |                |
| Decreased appetite                      |                |                |                |
| subjects affected / exposed             | 0 / 11 (0.00%) | 2 / 21 (9.52%) | 1 / 8 (12.50%) |
| occurrences (all)                       | 0              | 2              | 1              |
| Hypercholesterolaemia                   |                |                |                |
| subjects affected / exposed             | 0 / 11 (0.00%) | 1 / 21 (4.76%) | 0 / 8 (0.00%)  |
| occurrences (all)                       | 0              | 1              | 0              |
| Hyperlipidaemia                         |                |                |                |
| subjects affected / exposed             | 0 / 11 (0.00%) | 1 / 21 (4.76%) | 0 / 8 (0.00%)  |
| occurrences (all)                       | 0              | 1              | 0              |
| Iron deficiency                         |                |                |                |
| subjects affected / exposed             | 0 / 11 (0.00%) | 0 / 21 (0.00%) | 0 / 8 (0.00%)  |
| occurrences (all)                       | 0              | 0              | 0              |

|                                   |                     |                     |  |
|-----------------------------------|---------------------|---------------------|--|
| <b>Non-serious adverse events</b> | LJN452 - 0.06 mg qd | LJN452 - 0.09 mg qd |  |
|-----------------------------------|---------------------|---------------------|--|

|                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                            |                                                                                                                                 |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                                                                                                                                                                                                                                                                                                                    | 8 / 9 (88.89%)                                                                                                             | 11 / 12 (91.67%)                                                                                                                |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                  | 0 / 9 (0.00%)<br>0                                                                                                         | 0 / 12 (0.00%)<br>0                                                                                                             |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                      | 0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0                                                     | 1 / 12 (8.33%)<br>1<br><br>0 / 12 (0.00%)<br>0<br><br>0 / 12 (0.00%)<br>0                                                       |  |
| Reproductive system and breast disorders<br>Vulvovaginal discomfort<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                 | 0 / 9 (0.00%)<br>0                                                                                                         | 1 / 12 (8.33%)<br>1                                                                                                             |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasal congestion<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Productive cough<br>subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0<br><br>0 / 12 (0.00%)<br>0<br><br>1 / 12 (8.33%)<br>1<br><br>0 / 12 (0.00%)<br>0<br><br>1 / 12 (8.33%)<br>1 |  |

|                                                                                            |                    |                     |  |
|--------------------------------------------------------------------------------------------|--------------------|---------------------|--|
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Psychiatric disorders                                                                      |                    |                     |  |
| Initial insomnia<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 9 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 |  |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Investigations                                                                             |                    |                     |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0 | 1 / 12 (8.33%)<br>2 |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Low density lipoprotein increased<br>subjects affected / exposed<br>occurrences (all)      | 0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 9 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |  |
| Injury, poisoning and procedural complications                                             |                    |                     |  |
| Arthropod bite                                                                             |                    |                     |  |

|                                                                                                     |                     |                      |  |
|-----------------------------------------------------------------------------------------------------|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                    | 0 / 9 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |  |
| Muscle strain<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 9 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |  |
| Cardiac disorders<br>Trifascicular block<br>subjects affected / exposed<br>occurrences (all)        | 1 / 9 (11.11%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Nervous system disorders<br>Aphasia<br>subjects affected / exposed<br>occurrences (all)             | 0 / 9 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 9 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 9 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                        | 0 / 9 (0.00%)<br>0  | 2 / 12 (16.67%)<br>2 |  |
| Hypoaesthesia<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 9 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  |  |
| Optic neuritis<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 9 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 9 (11.11%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Thrombocytopenia                                                                                    |                     |                      |  |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 9 (11.11%)<br>1 | 0 / 12 (0.00%)<br>0 |  |
| Eye disorders                                    |                     |                     |  |
| Dry eye                                          |                     |                     |  |
| subjects affected / exposed                      | 0 / 9 (0.00%)       | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                   |  |
| Eye pruritus                                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 9 (0.00%)       | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                   |  |
| Gastrointestinal disorders                       |                     |                     |  |
| Abdominal discomfort                             |                     |                     |  |
| subjects affected / exposed                      | 1 / 9 (11.11%)      | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Abdominal distension                             |                     |                     |  |
| subjects affected / exposed                      | 0 / 9 (0.00%)       | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                   |  |
| Abdominal pain lower                             |                     |                     |  |
| subjects affected / exposed                      | 0 / 9 (0.00%)       | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                   |  |
| Abdominal pain upper                             |                     |                     |  |
| subjects affected / exposed                      | 0 / 9 (0.00%)       | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Constipation                                     |                     |                     |  |
| subjects affected / exposed                      | 1 / 9 (11.11%)      | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 1                   | 1                   |  |
| Diarrhoea                                        |                     |                     |  |
| subjects affected / exposed                      | 0 / 9 (0.00%)       | 1 / 12 (8.33%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Dry mouth                                        |                     |                     |  |
| subjects affected / exposed                      | 0 / 9 (0.00%)       | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                   |  |
| Dyspepsia                                        |                     |                     |  |
| subjects affected / exposed                      | 2 / 9 (22.22%)      | 0 / 12 (0.00%)      |  |
| occurrences (all)                                | 2                   | 0                   |  |
| Epigastric discomfort                            |                     |                     |  |

|                                        |                |                 |  |
|----------------------------------------|----------------|-----------------|--|
| subjects affected / exposed            | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 0              | 0               |  |
| Flatulence                             |                |                 |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Gastrooesophageal reflux disease       |                |                 |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 0              | 0               |  |
| Haemorrhoidal haemorrhage              |                |                 |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 0              | 0               |  |
| Nausea                                 |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 2 / 12 (16.67%) |  |
| occurrences (all)                      | 1              | 2               |  |
| Varices oesophageal                    |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Vomiting                               |                |                 |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 0              | 0               |  |
| Skin and subcutaneous tissue disorders |                |                 |  |
| Pruritus                               |                |                 |  |
| subjects affected / exposed            | 6 / 9 (66.67%) | 5 / 12 (41.67%) |  |
| occurrences (all)                      | 7              | 5               |  |
| Pruritus generalised                   |                |                 |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                      | 0              | 1               |  |
| Psoriasis                              |                |                 |  |
| subjects affected / exposed            | 1 / 9 (11.11%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 1              | 0               |  |
| Rash                                   |                |                 |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                      | 0              | 0               |  |
| Rash maculo-papular                    |                |                 |  |
| subjects affected / exposed            | 0 / 9 (0.00%)  | 1 / 12 (8.33%)  |  |
| occurrences (all)                      | 0              | 1               |  |

|                                                 |               |                |  |
|-------------------------------------------------|---------------|----------------|--|
| Renal and urinary disorders                     |               |                |  |
| Dysuria                                         |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0             | 1              |  |
| Pollakiuria                                     |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0             | 0              |  |
| Proteinuria                                     |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0             | 0              |  |
| Musculoskeletal and connective tissue disorders |               |                |  |
| Costochondritis                                 |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0             | 0              |  |
| Muscle spasms                                   |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0             | 0              |  |
| Pain in extremity                               |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0             | 0              |  |
| Infections and infestations                     |               |                |  |
| Fungal infection                                |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0             | 0              |  |
| Nasopharyngitis                                 |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0             | 1              |  |
| Overgrowth bacterial                            |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0             | 0              |  |
| Pneumonia                                       |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 1 / 12 (8.33%) |  |
| occurrences (all)                               | 0             | 1              |  |
| Rash pustular                                   |               |                |  |
| subjects affected / exposed                     | 0 / 9 (0.00%) | 0 / 12 (0.00%) |  |
| occurrences (all)                               | 0             | 0              |  |

|                                         |                |                 |  |
|-----------------------------------------|----------------|-----------------|--|
| Sinusitis                               |                |                 |  |
| subjects affected / exposed             | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 0              | 0               |  |
| Tooth abscess                           |                |                 |  |
| subjects affected / exposed             | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 0              | 0               |  |
| Upper respiratory tract infection       |                |                 |  |
| subjects affected / exposed             | 1 / 9 (11.11%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 1              | 0               |  |
| Urinary tract infection                 |                |                 |  |
| subjects affected / exposed             | 0 / 9 (0.00%)  | 2 / 12 (16.67%) |  |
| occurrences (all)                       | 0              | 2               |  |
| Viral infection                         |                |                 |  |
| subjects affected / exposed             | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 0              | 0               |  |
| Viral upper respiratory tract infection |                |                 |  |
| subjects affected / exposed             | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 0              | 0               |  |
| Metabolism and nutrition disorders      |                |                 |  |
| Decreased appetite                      |                |                 |  |
| subjects affected / exposed             | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 0              | 0               |  |
| Hypercholesterolaemia                   |                |                 |  |
| subjects affected / exposed             | 1 / 9 (11.11%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 1              | 0               |  |
| Hyperlipidaemia                         |                |                 |  |
| subjects affected / exposed             | 0 / 9 (0.00%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 0              | 0               |  |
| Iron deficiency                         |                |                 |  |
| subjects affected / exposed             | 1 / 9 (11.11%) | 0 / 12 (0.00%)  |  |
| occurrences (all)                       | 1              | 0               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 08 September 2015 | The purpose of this amendment was to address comments from a health authority.<br>Additional inclusion criterion for Part 2 were updated.                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 06 November 2015  | During the creation of Version No. 01 of the protocol, pregnancy testing was inadvertently removed from the Assessment Schedule. The purpose of this amendment was to re-add pregnancy testing into the protocol.                                                                                                                                                                                                                                                                                                                                                                                    |
| 18 March 2016     | The purpose of this amendment was to add a separate renal function exclusion criteria (criteria no.14). Exclusion criteria 2 and 3 were updated.<br>In addition, other minor changes, such as the inclusion of ALP isozyme analysis, a patient dosing diary to monitor compliance, and typographical corrections were made to the protocol.                                                                                                                                                                                                                                                          |
| 14 July 2016      | The purpose of this amendment was to address feedback from a health authority. Changes have also been made to the protocol to reduce the burden on the patients participating in the study.<br>Additional changes were made including clarification and slight modification of eligibility criteria (BMI range in the inclusion criteria 5 was updated, additional inclusion criteria for Part 1 were updated and exclusion criteria 3 and 4 were updated), addition of updated text describing the statistical analysis, addition of a higher dosage form, and addition of minor editorial updates. |
| 22 June 2017      | To enable higher dose(s) in Part 1 & 2 of the study, supported by new preclinical safety data, and to update the Part 2 study design to allow 12 wks of treatment in patients with PBC, to provide longer-term safety, tolerability and efficacy data.<br>The additional incl criteria for Part 2 were updated to add further details. Exclusion criteria 2 & 10 were updated. Excl criteria 3, 4, 15, 16, 17 & 18 were added in this amendment.                                                                                                                                                     |
| 27 November 2017  | The purpose of this amendment was to address comments received from a health authority in response to protocol amendment 5. In addition, the blood volume was updated to enable the collection of additional samples for Vitamin D, biomarker and PK back-up samples.<br>The inclusion criteria 4 was updated to included additional biochemical criteria at enrollment. The exclusion 4, 14 and 15 were updated to add additional details.                                                                                                                                                          |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Part 2 was not executed and a decision was made to terminate the study early as data revealed that Part 1 fulfilled the strategic purpose of the study.

Notes: