# Clinical trial results:
# A randomized, double-blind, placebo controlled, 3-part, adaptive design, multicenter study to assess safety, tolerability and efficacy of tropifexor (LJN452) in patients with non-alcoholic steatohepatitis (NASH) FLIGHT-FXR

## Summary

| | |
|---|---|
| EudraCT number | 2015-005215-33 |
| Trial protocol | SK IT DE NL BE AT ES |
| Global end of trial date | 06 April 2020 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 28 April 2021 |
| First version publication date | 28 April 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CLJN452A2202 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02855164 |
| 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 | Study Director, Novartis Pharma AG, 1 8627788300, 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 | 06 April 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 06 April 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To determine safety and tolerability of different doses of tropifexor

To determine the dose-response relationship of tropifexor on markers of hepatic inflammation in NASH (ALT and AST)

To determine the dose response relationship of tropifexor on liver fat content by changes in quantitative MRI determined fat

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 August 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 10 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | Canada: 5 |
| Country: Number of subjects enrolled | France: 12 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | India: 2 |
| Country: Number of subjects enrolled | Italy: 16 |
| Country: Number of subjects enrolled | Japan: 21 |
| Country: Number of subjects enrolled | Korea, Republic of: 28 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | Singapore: 13 |
| Country: Number of subjects enrolled | Slovakia: 8 |
| Country: Number of subjects enrolled | Spain: 10 |
| Country: Number of subjects enrolled | Taiwan: 26 |
| Country: Number of subjects enrolled | United States: 168 |

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 11 |
| Worldwide total number of subjects | 350 |
| EEA total number of subjects | 66 |

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) | 298 |
| From 65 to 84 years | 52 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

In total, 411 subjects were screened in Parts A and B of the study together. Of these, 198 subjects were deemed eligible to participate in the study and were subsequently randomized

### Pre-assignment

Screening details:

In Part A, 77 were randomized at baseline; 121 in Part B; and 780 were screened in Part C. Of these 152 met eligibility criteria and were randomized in nearly to receive tropifexor 140 µg (n=50) or 200 µg (n=51) or placebo (n=51)

### Period 1

| | |
|---|---|
| Period 1 title | Parts A + B (Randomized Set) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

This was a double-blind study. Subjects, investigator staff, persons performing the assessments, and Novartis clinical trial team and CRO associates involved with continued direct study site conduct (or delegates), remained blinded to the identity of study treatments from the time of randomization (until final database lock)

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | LJN452 10 µg |

Arm description:

10 micrograms of Tropifexor (Part A)

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

Dosage and administration details:

10 microgram tropifexor tablet

| | |
|---|---|
| **Arm title** | LJN452 30 µg |

Arm description:

30 micrograms of Tropifexor (Part A)

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

Dosage and administration details:

30 microgram tropifexor tablet

| | |
|---|---|
| **Arm title** | LJN452 60 µg |

Arm description:

60 micrograms of Tropifexor (Parts A+B)

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Tropifexor |
| Investigational medicinal product code | |
| Other name | LJN452 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details:<br>60 microgram tropifexor tablet | |
| **Arm title** | LJN452 90 µg |
| Arm description:<br>90 micrograms of Tropifexor (Parts A+B) | |
| Arm type | Experimental |
| Investigational medicinal product name | Tropifexor |
| Investigational medicinal product code | |
| Other name | LJN452 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details:<br>90 microgram tropifexor tablet | |
| **Arm title** | Placebo |
| Arm description:<br>Placebo A+B | |
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | Parts A+B |
| Other name | placebo |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details:<br>placebo tablet | |

| **Number of subjects in period 1[1]** | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg |
|---|---|---|---|
| Started | 14 | 16 | 37 |
| Completed | 14 | 16 | 36 |
| Not completed | 0 | 0 | 1 |
| Consent withdrawn by subject | - | - | 1 |
| Physician decision | - | - | - |
| Adverse event, non-fatal | - | - | - |

| **Number of subjects in period 1[1]** | LJN452 90 µg | Placebo |
|---|---|---|
| Started | 85 | 46 |
| Completed | 77 | 45 |
| Not completed | 8 | 1 |
| Consent withdrawn by subject | 2 | 1 |
| Physician decision | 2 | - |

| | | |
|---|---|---|
| Adverse event, non-fatal | 4 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Numbers are consistent

## Period 2

| | |
|---|---|
| Period 2 title | Part C (Randomized Set) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | LJN452 140 µg |

Arm description:

140 micrograms of Tropifexor (Part C)

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

Dosage and administration details:

140 microgram tropifexor tablet

| | |
|---|---|
| **Arm title** | LJN452 200 µg |

Arm description:

200 micrograms of Tropifexor (Part C)

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

Dosage and administration details:

200 microgram tropifexor tablet

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Placebo A+B

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | Part C |
| Other name | LJN452 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:
placebo tablet

| **Number of subjects in period 2[2]** | LJN452 140 µg | LJN452 200 µg | Placebo |
|---|---|---|---|
| Started | 50 | 51 | 51 |
| Completed | 38 | 37 | 44 |
| Not completed | 12 | 14 | 7 |
| Consent withdrawn by subject | 5 | 4 | 3 |
| Physician decision | 1 | - | 1 |
| Adverse event, non-fatal | 5 | 9 | 2 |
| Lost to follow-up | 1 | 1 | 1 |

Notes:
[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Numbers are consistent

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | LJN452 10 µg |
| Reporting group description: | |
| 10 micrograms of Tropifexor (Part A) | |
| Reporting group title | LJN452 30 µg |
| Reporting group description: | |
| 30 micrograms of Tropifexor (Part A) | |
| Reporting group title | LJN452 60 µg |
| Reporting group description: | |
| 60 micrograms of Tropifexor (Parts A+B) | |
| Reporting group title | LJN452 90 µg |
| Reporting group description: | |
| 90 micrograms of Tropifexor (Parts A+B) | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo A+B | |

| Reporting group values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg |
|---|---|---|---|
| Number of subjects | 14 | 16 | 37 |
| Age Categorical<br>Units: participants | | | |
| Parts A + B\|<=18 years | 0 | 0 | 0 |
| Part C\|<=18 years | 0 | 0 | 0 |
| Parts A + B\|Between 18 and 65 years | 14 | 14 | 33 |
| Part C\|Between 18 and 65 years | 0 | 0 | 0 |
| Parts A + B\|>=65 years | 0 | 2 | 4 |
| Part C\|>=65 years | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 48 | 49 | 50 |
| standard deviation | ± 11.7 | ± 14.4 | ± 12.5 |
| Sex: Female, Male | | | |
| Sex of participant by treatment | | | |
| Units: participants | | | |
| Parts A + B\|Female | 9 | 7 | 20 |
| Part C\|Female | 0 | 0 | 0 |
| Parts A + B\|Male | 5 | 9 | 17 |
| Part C\|Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Caucasian (Parts A + B) | 12 | 11 | 24 |
| Black (Parts A + B) | 0 | 0 | 0 |
| Asian (Parts A + B) | 2 | 5 | 12 |
| Pacific Islander (Parts A + B) | 0 | 0 | 0 |
| Other (Parts A + B) | 0 | 0 | 0 |
| Unknown (Parts A+B) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Caucasian (Part C) | 0 | 0 | 0 |
| Black (Part C) | 0 | 0 | 0 |
| Asian (Part C) | 0 | 0 | 0 |
| Pacific Islander (Part C) | 0 | 0 | 0 |
| Other (Part C) | 0 | 0 | 0 |
| Unknown (Part C) | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 48 | 49 | 50 |
| standard deviation | ± 11.7 | ± 14.4 | ± 12.5 |

| **Reporting group values** | LJN452 90 µg | Placebo | Total |
|---|---|---|---|
| Number of subjects | 85 | 46 | 198 |
| Age Categorical | | | |
| Units: participants | | | |
| Parts A + B\|<=18 years | 0 | 0 | 0 |
| Part C\|<=18 years | 0 | 0 | 0 |
| Parts A + B\|Between 18 and 65 years | 72 | 41 | 174 |
| Part C\|Between 18 and 65 years | 0 | 0 | 0 |
| Parts A + B\|>=65 years | 13 | 5 | 24 |
| Part C\|>=65 years | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 51 | 51 | |
| standard deviation | ± 13.4 | ± 12.3 | - |
| Sex: Female, Male | | | |
| Sex of participant by treatment | | | |
| Units: participants | | | |
| Parts A + B\|Female | 47 | 21 | 104 |
| Part C\|Female | 0 | 0 | 0 |
| Parts A + B\|Male | 38 | 25 | 94 |
| Part C\|Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Caucasian (Parts A + B) | 50 | 25 | 122 |
| Black (Parts A + B) | 1 | 0 | 1 |
| Asian (Parts A + B) | 31 | 20 | 70 |
| Pacific Islander (Parts A + B) | 0 | 1 | 1 |
| Other (Parts A + B) | 2 | 0 | 2 |
| Unknown (Parts A+B) | 1 | 0 | 2 |
| Caucasian (Part C) | 0 | 0 | 0 |
| Black (Part C) | 0 | 0 | 0 |
| Asian (Part C) | 0 | 0 | 0 |
| Pacific Islander (Part C) | 0 | 0 | 0 |
| Other (Part C) | 0 | 0 | 0 |
| Unknown (Part C) | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 51 | 54 | |
| standard deviation | ± 13.4 | ± 11.0 | - |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Placebo C |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Placebo Part C | |
| Subject analysis set title | Placebo A+B |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Placebo Parts A+B | |

| Reporting group values | Placebo C | Placebo A+B | |
|---|---|---|---|
| Number of subjects | 51 | 46 | |
| Age Categorical<br>Units: participants | | | |
| Parts A + B\|<=18 years | 0 | 0 | |
| Part C\|<=18 years | 0 | 0 | |
| Parts A + B\|Between 18 and 65 years | 0 | 41 | |
| Part C\|Between 18 and 65 years | 38 | 0 | |
| Parts A + B\|>=65 years | 0 | 5 | |
| Part C\|>=65 years | 8 | 0 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 54 | 51 | |
| standard deviation | ± 11.00 | ± 12.3 | |
| Sex: Female, Male | | | |
| Sex of participant by treatment | | | |
| Units: participants | | | |
| Parts A + B\|Female | 0 | 0 | |
| Part C\|Female | 32 | 21 | |
| Parts A + B\|Male | 0 | 0 | |
| Part C\|Male | 19 | 25 | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Caucasian (Parts A + B) | 0 | 25 | |
| Black (Parts A + B) | 0 | 0 | |
| Asian (Parts A + B) | 0 | 20 | |
| Pacific Islander (Parts A + B) | 0 | 1 | |
| Other (Parts A + B) | 0 | 0 | |
| Unknown (Parts A+B) | 0 | 0 | |
| Caucasian (Part C) | 38 | 0 | |
| Black (Part C) | 1 | 0 | |
| Asian (Part C) | 8 | 0 | |
| Pacific Islander (Part C) | 0 | 0 | |
| Other (Part C) | 4 | 0 | |
| Unknown (Part C) | 0 | 0 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 54 | 51 | |
| standard deviation | ± 11.0 | ± 12.3 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | LJN452 10 µg |
| Reporting group description: 10 micrograms of Tropifexor (Part A) | |
| Reporting group title | LJN452 30 µg |
| Reporting group description: 30 micrograms of Tropifexor (Part A) | |
| Reporting group title | LJN452 60 µg |
| Reporting group description: 60 micrograms of Tropifexor (Parts A+B) | |
| Reporting group title | LJN452 90 µg |
| Reporting group description: 90 micrograms of Tropifexor (Parts A+B) | |
| Reporting group title | Placebo |
| Reporting group description: Placebo A+B | |
| Reporting group title | LJN452 140 µg |
| Reporting group description: 140 micrograms of Tropifexor (Part C) | |
| Reporting group title | LJN452 200 µg |
| Reporting group description: 200 micrograms of Tropifexor (Part C) | |
| Reporting group title | Placebo |
| Reporting group description: Placebo A+B | |
| Subject analysis set title | Placebo C |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Placebo Part C | |
| Subject analysis set title | Placebo A+B |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Placebo Parts A+B | |

### Primary: Number of Nonalcoholic steatohepatitis (NASH) patients with Treatment Emergent Adverse Events (TEAE)

| | |
|---|---|
| End point title | Number of Nonalcoholic steatohepatitis (NASH) patients with Treatment Emergent Adverse Events (TEAE)[1][2] |
| End point description: Number of Nonalcoholic steatohepatitis (NASH) patients with TEAEs | |
| End point type | Primary |
| End point timeframe: End of Treatment (EoT): For Parts A&B, EoT was Week 12 (Primary Outcome Measure). For Part C, EoT was Week 48 (Secondary Outcome Measure) | |

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: No statistical analysis was planned

[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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13 | 16 | 37 | 85 |
| Units: participants | 5 | 11 | 24 | 61 |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51 | 46 |
| Units: participants | 49 | 49 | 46 | 31 |

### Statistical analyses

No statistical analyses for this end point

## Primary: Change in Transaminase levels (ALT)

| End point title | Change in Transaminase levels (ALT)[3] |
|---|---|

End point description:

Summary statistics of change in ALT from baseline to EOT by treatment. The alanine aminotransferase (ALT) test is a blood test that checks for liver damage. High levels of ALT may indicate liver damage. Normal range for ALT is typically 10 to 45 U/L or so (varies a little by age and gender). Elevation of these values indicate more liver inflammation/damage. ALT elevation is not unexpected in this patient population.

Dose relationship of tropifexor (LJN452) on ALT marker of hepatic inflammation in NASH

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

End point timeframe:

End of Treatment (EoT): For Parts A&B, EoT was Week 12 (Primary Outcome Measure). For Part C, EoT was Week 48 (Secondary Outcome Measure)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 37 | 85 |
| Units: scores | | | | |
| arithmetic mean (standard deviation) | -16.7 (± 17.53) | -12.0 (± 35.99) | -17.3 (± 28.12) | -15.4 (± 30.32) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|

| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
|---|---|---|---|---|
| Number of subjects analysed | 50 | 51 | 51 | 46 |
| Units: scores | | | | |
| arithmetic mean (standard deviation) | -27.0 (± 30.24) | -28.7 (± 25.40) | -11.7 (± 61.64) | -8.1 (± 29.37) |

## Statistical analyses

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 10 micrograms of Tropifexor vs placebo (Part A) | |
| Comparison groups | LJN452 10 µg v Placebo A+B |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.362 |
| Method | ANCOVA |
| Parameter estimate | LS mean change |
| Point estimate | -15.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -31.2 |
| upper limit | -0.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.76 |

Notes:

[4] - Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Parts A + B) (Full analysis set)

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 30 micrograms of Tropifexor vs placebo (Part A) | |
| Comparison groups | LJN452 30 µg v Placebo A+B |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | = 0.729 |
| Method | ANCOVA |
| Parameter estimate | LS mean change |
| Point estimate | -10.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.8 |
| upper limit | 3.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.12 |

Notes:
[5] - ANCOVA: ALT (U/L) change from baseline up to EOT (Parts A + B) (Full analysis set)

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor vs placebo (Parts A + B) | |
| Comparison groups | LJN452 60 µg v Placebo A+B |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.173 |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Change |
| Point estimate | -16.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.8 |
| upper limit | -7.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.73 |

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 90 micrograms of Tropifexor vs placebo (Parts A + B) | |
| Comparison groups | LJN452 90 µg v Placebo A+B |
| Number of subjects included in analysis | 131 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.185 |
| Method | ANCOVA |
| Parameter estimate | Least Square Mean Change |
| Point estimate | -14.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.3 |
| upper limit | -8.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.25 |

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 140 micrograms of Tropifexor (Part C) vs placebo | |
| Comparison groups | LJN452 140 µg v Placebo C |

| | |
|---|---|
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[6] |
| P-value | = 0.02 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Change |
| Point estimate | -31.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -46.9 |
| upper limit | -16.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.71 |

Notes:

[6] - ANCOVA: Relative change of ALT (U/L) up to EOT (Part C) (Full analysis set)

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 200 micrograms of Tropifexor vs placebo (Part C) | |
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.03 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Change |
| Point estimate | -32.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -50.6 |
| upper limit | -14.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 9.1 |

Notes:

[7] - ANCOVA: ALT (U/L) change from baseline up to EOT (Part C) (Full analysis set)

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 10 micrograms of Tropifexor vs placebo (Parts A + B + C) | |
| Comparison groups | LJN452 10 µg v Placebo C |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[8] |
| P-value | = 0.456 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -13.4 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.3 |
| upper limit | -0.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.86 |

Notes:

[8] - ANCOVA: ALT (U/L) change from baseline to Week 12 (Parts A+B+C)
Full analysis set (FAS)

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 30 micrograms of Tropifexor vs placebo (Parts A + B + C) | |
| Comparison groups | LJN452 30 µg v Placebo C |
| Number of subjects included in analysis | 67 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[9] |
| P-value | = 0.966 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -7.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.5 |
| upper limit | 4.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.27 |

Notes:

[9] - ANCOVA: ALT (U/L) change from baseline to Week 12 (Parts A + B + C)
Full analysis set (FAS)

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor vs placebo (Parts A + B + C) | |
| Comparison groups | LJN452 60 µg v Placebo C |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[10] |
| P-value | = 0.275 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -13.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.4 |
| upper limit | -5.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.93 |

Notes:

[10] - ANCOVA: ALT (U/L) change from baseline to Week 12 (Parts A + B + C)
Full analysis set (FAS)

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 90 micrograms of Tropifexor vs placebo (Parts A + B + C) | |
| Comparison groups | LJN452 90 µg v Placebo C |
| Number of subjects included in analysis | 136 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | = 0.304 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -11.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.6 |
| upper limit | -5.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.56 |

Notes:

[11] - ANCOVA: ALT (U/L) change from baseline to Week 12 (Parts A+B + C)
Full analysis set (FAS)

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 140 micrograms of Tropifexor vs placebo (Parts A + B) | |
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[12] |
| P-value | = 0.057 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -17.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.5 |
| upper limit | -9.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.45 |

Notes:

[12] - ANCOVA: ALT (U/L) change from baseline up to EOT (Parts A + B)  FAS

| **Statistical analysis title** | Change in ALT |
|---|---|
| Statistical analysis description: | |
| 200 micrograms of Tropifexor vs placebo (Parts A + B + C) | |
| Comparison groups | LJN452 200 µg v Placebo C |

| | |
|---|---|
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[13] |
| P-value | = 0.003 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -30.5 |
| upper limit | -15.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.49 |

Notes:

[13] - ANCOVA: ALT (U/L) change from baseline up to EOT (Parts A + B + C) FAS

## Primary: Change in Aspartate transaminase (AST)

| | |
|---|---|
| End point title | Change in Aspartate transaminase (AST)[14] |

End point description:

To determine the dose relationship of tropifexor (LJN452) on markers of hepatic inflammation (AST) in NASH from baseline to EoT
The alanine aminotransferase (AST) test is a blood test that checks for liver damage. High levels of AST may indicate liver damage. Normal range for AST is typically 10 to 45 U/L or so (varies a little by age and gender). Elevation of these values indicate more liver inflammation/damage

AST elevation is not unexpected in this patient population

The aspartate aminotransferase (AST) test is a blood test that checks for liver damage. Higher levels indicate more possible liver damage

Summary statistics of change in AST from baseline up to end of treatment (EOT)

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

End point timeframe:

End of Treatment (EoT): For Parts A&B, EoT was Week 12 (Primary Outcome Measure). For Part C, EoT was Week 48 (Secondary Outcome Measure)

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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 37 | 85 |
| Units: scores | | | | |
| arithmetic mean (standard deviation) | -11.3 (± 12.09) | -2.1 (± 29.62) | -10.2 (± 25.03) | -2.5 (± 24.60) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51 | 46 |

| Units: scores | | | | |
|---|---|---|---|---|
| arithmetic mean (standard deviation) | -16.7 (± 23.36) | -13.3 (± 20.14) | -13.1 (± 29.00) | -7.1 (± 23.85) |

## Statistical analyses

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description:<br>10 micrograms of Tropifexor vs placebo (Part A) | |
| Comparison groups | LJN452 10 µg v Placebo A+B |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[15] |
| P-value | = 0.722 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -9.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.9 |
| upper limit | 3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.56 |

Notes:

[15] - ANCOVA: AST (U/L) change from baseline up to EOT (Full analysis set)

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description:<br>30 micrograms of Tropifexor vs placebo (Part A) | |
| Comparison groups | LJN452 30 µg v Placebo A+B |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[16] |
| P-value | = 0.468 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14 |
| upper limit | 9.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.96 |

Notes:

[16] - ANCOVA: AST (U/L) change from baseline up to EOT (Full analysis set)

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor vs placebo (Parts A+B) | |
| Comparison groups | LJN452 60 µg v Placebo A+B |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[17] |
| P-value | = 0.774 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -8.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.7 |
| upper limit | -1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.97 |

Notes:

[17] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B) (Full analysis set)

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description: | |
| 90 micrograms of Tropifexor vs placebo (Parts A+B) | |
| Comparison groups | LJN452 90 µg v Placebo A+B |
| Number of subjects included in analysis | 131 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[18] |
| P-value | = 0.136 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6 |
| upper limit | 4.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.76 |

Notes:

[18] - ANCOVA: AST (U/L) change from baseline up to EOT (Parts A+B) (Full analysis set)

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description: | |
| 140 micrograms of Tropifexor vs placebo (Part C) | |
| Comparison groups | LJN452 140 µg v Placebo C |

| | |
|---|---|
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[19] |
| P-value | = 0.145 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -23.9 |
| upper limit | -8.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.97 |

Notes:

[19] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Part C) (Full analysis set)

| **Statistical analysis title** | Change in AST |
|---|---|

Statistical analysis description:

200 micrograms of Tropifexor vs placebo (Part C)

| | |
|---|---|
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[20] |
| P-value | = 0.236 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -15.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.2 |
| upper limit | -6.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.49 |

Notes:

[20] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Part C) (Full analysis set)

| **Statistical analysis title** | Change in AST |
|---|---|

Statistical analysis description:

10 micrograms of Tropifexor vs placebo (Parts A+B+ C)

| | |
|---|---|
| Comparison groups | LJN452 10 µg v Placebo C |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[21] |
| P-value | = 0.788 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -7.1 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.7 |
| upper limit | 4.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7 |

Notes:

[21] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description: | |
| 30 micrograms of Tropifexor vs placebo (Parts A+B+ C) | |
| Comparison groups | LJN452 30 µg v Placebo C |
| Number of subjects included in analysis | 67 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.413 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.2 |
| upper limit | 11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.43 |

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor vs placebo (Parts A+B+ C) | |
| Comparison groups | LJN452 60 µg v Placebo C |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[22] |
| P-value | = 0.833 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -6.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.4 |
| upper limit | 1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.38 |

Notes:
[22] - ANCOVA: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description: | |
| 90 micrograms of Tropifexor vs placebo (Parts A+B+ C) | |
| Comparison groups | LJN452 90 µg v Placebo C |
| Number of subjects included in analysis | 136 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[23] |
| P-value | = 0.068 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.2 |
| upper limit | 7.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.19 |

Notes:
[23] - ANCOVA: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description: | |
| 140 micrograms of Tropifexor vs placebo (Parts A+B+ C) | |
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[24] |
| P-value | = 0.269 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.6 |
| upper limit | 6.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.98 |

Notes:
[24] - ANCOVA: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

| **Statistical analysis title** | Change in AST |
|---|---|
| Statistical analysis description: | |
| 200 micrograms of Tropifexor vs placebo (Parts A+B+ C) | |
| Comparison groups | LJN452 200 µg v Placebo C |

| | |
|---|---|
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[25] |
| P-value | = 0.777 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -3.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.5 |
| upper limit | 2.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.05 |

Notes:

[25] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

## Primary: Change from baseline in percent of fat in the liver assessed using Magnetic resonance imaging (MRI)

| | |
|---|---|
| End point title | Change from baseline in percent of fat in the liver assessed using Magnetic resonance imaging (MRI)[26] |

End point description:

Repeated measures analysis: Relative change in percentage of fat in the liver assessed using MRI from baseline by visit up to EOT (Full analysis set)

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

End point timeframe:

End of Treatment (EoT): For Parts A&B, EoT was Week 12 (Primary Outcome Measure). For Part C, EoT was Week 48 (Secondary Outcome Measure)

Notes:

[26] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 37 | 85 |
| Units: scores | | | | |
| arithmetic mean (standard error) | -7.48 (± 6.174) | -14.07 (± 5.661) | -15.04 (± 3.754) | -12.34 (± 2.482) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51[27] | 46[28] |
| Units: scores | | | | |
| arithmetic mean (standard error) | -31.25 (± 5.228) | -39.54 (± 4.968) | 0.00 (± 0.00) | 0.00 (± 0.00) |

Notes:

[27] - Placebo is the reference group for repeated measures

[28] - Placebo is the reference group for repeated measures

**Statistical analyses**

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description:<br>10 microgramsof Tropifexor - Change in percentage of fat in the liver Part A | |
| Comparison groups | LJN452 10 µg v Placebo A+B |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.853 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -7.48 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.66 |
| upper limit | 4.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.174 |

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description:<br>30 micrograms of Tropifexor - Change in percentage of fat in the liver Part A | |
| Comparison groups | LJN452 30 µg v Placebo A+B |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.232 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -14.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -25.24 |
| upper limit | -2.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.661 |

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B | |
| Comparison groups | LJN452 60 µg v Placebo A+B |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[29] |
| P-value | = 0.077 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -15.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -22.45 |
| upper limit | -7.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.754 |

Notes:

[29] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description: | |
| 90 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B | |
| Comparison groups | LJN452 90 µg v Placebo A+B |
| Number of subjects included in analysis | 131 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[30] |
| P-value | = 0.141 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -12.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.23 |
| upper limit | -7.44 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.482 |

Notes:

[30] - ANCOVA: Relative change in percentage of fat in the liver from baseline

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description: | |
| 140 micrograms of Tropifexor - Change in percentage of fat in the liver Part C | |
| Comparison groups | LJN452 140 µg v Placebo C |

| | |
|---|---|
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[31] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -31.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -41.58 |
| upper limit | -20.92 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 5.228 |

Notes:

[31] - ANCOVA: Relative change in percentage of fat in the liver

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|

Statistical analysis description:

200 micrograms of Tropifexor - Change in percentage of fat in the liver Part C

| | |
|---|---|
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[32] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -39.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -49.37 |
| upper limit | -29.71 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.968 |

Notes:

[32] - ANCOVA: Relative change in percentage of fat in the liver

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|

Statistical analysis description:

10 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C

| | |
|---|---|
| Comparison groups | LJN452 10 µg v Placebo C |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[33] |
| P-value | = 0.872 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -8.09 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -19.06 |
| upper limit | 2.88 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.65 |

Notes:

[33] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description: | |
| 30 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C | |
| Comparison groups | LJN452 30 µg v Placebo C |
| Number of subjects included in analysis | 67 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[34] |
| P-value | = 0.465 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -14.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.36 |
| upper limit | -3.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.198 |

Notes:

[34] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 Parts A+B+C

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C | |
| Comparison groups | LJN452 60 µg v Placebo C |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[35] |
| P-value | = 0.228 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -15.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.75 |
| upper limit | -8.29 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.078 |

Notes:

[35] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description: | |
| 90 micrograms - Change in percentage of fat in the liver Parts A+B+C | |
| Comparison groups | LJN452 90 µg v Placebo C |
| Number of subjects included in analysis | 136 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[36] |
| P-value | = 0.37 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -12.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.04 |
| upper limit | -8.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.717 |

Notes:

[36] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description: | |
| 140 micrograms - Change in percentage of fat in the liver Parts A+B+C | |
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[37] |
| P-value | = 0.029 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -18.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.51 |
| upper limit | -12.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.517 |

Notes:

[37] - ANCOVA: Relative change in percentage of fat in the liver (Parts A+B+C)

| **Statistical analysis title** | Change in percent of fat in the liver |
|---|---|
| Statistical analysis description: | |
| 200 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C | |
| Comparison groups | LJN452 200 µg v Placebo C |

| | |
|---|---|
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[38] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | LS Mean change |
| Point estimate | -34.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -40.13 |
| upper limit | -28.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.482 |

Notes:

[38] - ANCOVA: Relative change in percentage of fat in the liver (Parts A+B+C)

## Secondary: Change from baseline in weight

| | |
|---|---|
| End point title | Change from baseline in weight[39] |

End point description:

Repeated measures for LS mean change in weight at EoT

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

End point timeframe:

End of Treatment (EoT): For Parts A&B, EoT was Week 12 (Primary Outcome Measure). For Part C, EoT was Week 48 (Secondary Outcome Measure)

Notes:

[39] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 36 | 84 |
| Units: Mean | | | | |
| arithmetic mean (standard error) | -1.79 (± 0.608) | -0.78 (± 0.567) | -1.05 (± 0.377) | -1.15 (± 0.253) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51[40] | 46[41] |
| Units: Mean | | | | |
| arithmetic mean (standard error) | -5.10 (± 0.988) | -5.89 (± 1.002) | 999 (± 999) | 999 (± 999) |

Notes:

[40] - Placebo is the reference group for repeated measures

[41] - Placebo is the reference group for repeated measures

### Statistical analyses

| **Statistical analysis title** | Change in weight |
|---|---|
| Statistical analysis description: | |
| 10 micrograms of Tropifexor (Part A) vs Placebo | |
| Comparison groups | LJN452 10 µg v Placebo A+B |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[42] |
| P-value | = 0.01 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -1.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.99 |
| upper limit | 0.59 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.608 |

Notes:

[42] - Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)

| **Statistical analysis title** | Change in weight |
|---|---|
| Statistical analysis description: | |
| 30 micrograms of Tropifexor (Part A) vs Placebo | |
| Comparison groups | LJN452 30 µg v Placebo A+B |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[43] |
| P-value | = 0.237 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | 0.34 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.567 |

Notes:

[43] - Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)

| **Statistical analysis title** | Change in weight |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor (Parts A + B) vs Placebo | |
| Comparison groups | LJN452 60 µg v Placebo A+B |

| | |
|---|---|
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[44] |
| P-value | = 0.037 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8 |
| upper limit | 0.31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.377 |

Notes:

[44] - Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)

| **Statistical analysis title** | Change in weight |
|---|---|

Statistical analysis description:

90 micrograms of Tropifexor (Parts A + B) vs Placebo

| | |
|---|---|
| Comparison groups | LJN452 90 µg v Placebo A+B |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[45] |
| P-value | = 0.007 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -1.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.65 |
| upper limit | 0.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.253 |

Notes:

[45] - Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)

| **Statistical analysis title** | Change in weight |
|---|---|

Statistical analysis description:

140 micrograms of Tropifexor (Part C) vs Placebo

| | |
|---|---|
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[46] |
| P-value | = 0.053 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -5.1 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.05 |
| upper limit | -3.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.988 |

Notes:

[46] - Repeated measures analysis: Change in weight from baseline to EOT (Parts C) (Full analysis set)

| **Statistical analysis title** | Change in weight |
|---|---|

Statistical analysis description:

200 micrograms of Tropifexor (Part C) vs Placebo

| | |
|---|---|
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[47] |
| P-value | = 0.013 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -5.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.87 |
| upper limit | -3.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.002 |

Notes:

[47] - Repeated measures analysis: Change in weight from baseline to EOT (Parts C) (Full analysis set)

## Secondary: Change in body mass index (BMI)

| | |
|---|---|
| End point title | Change in body mass index (BMI)[48] |

End point description:

Repeated measures for the LS mean change in BMI after 12 weeks of treatment. Body mass index (BMI) is a measure of body fat based on height and weight

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

End point timeframe:

12 weeks

Notes:

[48] - 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: No statistical analysis was planned

| **End point values** | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 37 | 84 |
| Units: Mean | | | | |
| arithmetic mean (standard error) | -0.64 (± 0.208) | -0.29 (± 0.194) | -0.35 (± 0.129) | -0.42 (± 0.087) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51[49] | 46[50] |
| Units: Mean | | | | |
| arithmetic mean (standard error) | -1.88 (± 0.322) | -2.11 (± 0.327) | 9.999 (± 9.999) | 9.999 (± 9.999) |

Notes:

[49] - Placebo is the reference group for repeated measures

[50] - Placebo is the reference group for repeated measures

## Statistical analyses

| Statistical analysis title | Change in BMI |
|---|---|
| Statistical analysis description: 10 micrograms of Tropifexor (Part A) vs Placebo | |
| Comparison groups | LJN452 10 µg v Placebo A+B |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[51] |
| P-value | = 0.006 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.05 |
| upper limit | 0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.208 |

Notes:

[51] - Repeated measures analysis: Change in BMI from baseline to EoT (Full analysis set)

| Statistical analysis title | Change in BMI |
|---|---|
| Statistical analysis description: 30 micrograms of Tropifexor (Part A) vs Placebo | |
| Comparison groups | LJN452 30 µg v Placebo A+B |
| Number of subjects included in analysis | 62 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[52] |
| P-value | = 0.177 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -0.29 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.67 |
| upper limit | 0.09 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.194 |

Notes:

[52] - Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)

| **Statistical analysis title** | Change in BMI |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor (Parts A + B) vs Placebo | |
| Comparison groups | LJN452 60 µg v Placebo A+B |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[53] |
| P-value | = 0.032 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -0.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.61 |
| upper limit | 0.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.129 |

Notes:

[53] - Repeated measures analysis: Change in BMI from baseline to EOT (Parts C) (Full analysis set)

| **Statistical analysis title** | Change in BMI |
|---|---|
| Statistical analysis description: | |
| 90 micrograms of Tropifexor (Parts A + B) vs Placebo | |
| Comparison groups | LJN452 90 µg v Placebo A+B |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[54] |
| P-value | = 0.003 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -0.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.59 |
| upper limit | 0.25 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.087 |

Notes:
[54] - Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)

| **Statistical analysis title** | Change in BMI |
|---|---|
| Statistical analysis description: | |
| 140 micrograms of Tropifexor (Part C) vs Placebo | |
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 101 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[55] |
| P-value | = 0.015 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -1.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.51 |
| upper limit | -1.24 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.322 |

Notes:
[55] - Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)

| **Statistical analysis title** | Change in BMI |
|---|---|
| Statistical analysis description: | |
| 200 micrograms of Tropifexor (Part C) vs Placebo | |
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[56] |
| P-value | = 0.004 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -2.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.75 |
| upper limit | -1.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.327 |

Notes:
[56] - Repeated measures analysis: Change in BMI from baseline to EOT (Parts C) (Full analysis set)

## Secondary: Change from baseline in waist to hip (WTH) ratio

| End point title | Change from baseline in waist to hip (WTH) ratio[57] |
|---|---|
| End point description: | |
| The LS mean change in waist to hip ratio after 12 weeks of treatment | |
| End point type | Secondary |

End point timeframe:

12 weeks

Notes:

[57] - 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: No statistical analysis was planned

| **End point values** | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 13 | 15 | 37 | 84 |
| Units: Mean | | | | |
| arithmetic mean (standard error) | -0.01 (± 0.009) | 0.00 (± 0.008) | -0.01 (± 0.005) | 0.00 (± 0.004) |

| **End point values** | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 49 | 51 | 51[58] | 46[59] |
| Units: Mean | | | | |
| arithmetic mean (standard error) | 0.00 (± 0.008) | -0.01 (± 0.007) | 9.999 (± 9.999) | 9.999 (± 9.999) |

Notes:

[58] - 9.999 = Placebo is the reference group for repeated measures

[59] - 9.999=Placebo is the reference group for repeated measures

## Statistical analyses

| **Statistical analysis title** | Change in WTH ratio |
|---|---|
| Statistical analysis description: | |
| 10 micrograms of Tropifexor (Part A) vs Placebo | |
| Comparison groups | LJN452 10 µg v Placebo A+B |
| Number of subjects included in analysis | 59 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[60] |
| P-value | = 0.53 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.009 |

Notes:

[60] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)

| **Statistical analysis title** | Change in WTH ratio |
|---|---|

| | |
|---|---|
| Statistical analysis description: | |
| 30 micrograms of Tropifexor (Part A) vs Placebo | |
| Comparison groups | LJN452 30 µg v Placebo A+B |
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[61] |
| P-value | = 0.857 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.008 |

Notes:

[61] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)

| **Statistical analysis title** | Change in WTH ratio |
|---|---|
| Statistical analysis description: | |
| 60 micrograms of Tropifexor (Part A) vs Placebo | |
| Comparison groups | LJN452 60 µg v Placebo A+B |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[62] |
| P-value | = 0.262 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.005 |

Notes:

[62] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)

| **Statistical analysis title** | Change in WTH ratio |
|---|---|
| Statistical analysis description: | |
| 90 micrograms of Tropifexor (Parts A + B) vs Placebo | |
| Comparison groups | LJN452 90 µg v Placebo A+B |

| | |
|---|---|
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[63] |
| P-value | = 0.323 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.004 |

Notes:

[63] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)

| **Statistical analysis title** | Change in WTH ratio |
|---|---|

Statistical analysis description:

140 micrograms of Tropifexor (Part C) vs Placebo

| | |
|---|---|
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 100 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[64] |
| P-value | = 0.1 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | 0.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.008 |

Notes:

[64] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Part C) (Full analysis set)

| **Statistical analysis title** | Change in WTH ratio |
|---|---|

Statistical analysis description:

200 micrograms of Tropifexor (Part C) vs Placebo

| | |
|---|---|
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[65] |
| P-value | = 0.693 |
| Method | Mixed models analysis |
| Parameter estimate | LS Mean change |
| Point estimate | -0.01 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03 |
| upper limit | 0 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.007 |

Notes:

[65] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Part C) (Full analysis set)

## Secondary: Change from baseline in biomarker FGF19

| | |
|---|---|
| End point title | Change from baseline in biomarker FGF19[66] |

End point description:

Dose-response relationship of tropifexor (LJN452) on FGF19 over time, a marker of FXR target engagement in the gut.

ANCOVA: Ratio of FGF19 (pg/mL) post-dose to pre-dose at Week 6

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

End point timeframe:

6 weeks

Notes:

[66] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 15 | 34 | 78 |
| Units: pg/mL | | | | |
| least squares mean (confidence interval 95%) | 1.45 (0.93 to 2.26) | 1.53 (1.00 to 2.35) | 3.82 (2.88 to 5.09) | 5.78 (4.78 to 6.98) |

| End point values | LJN452 140 µg | LJN452 200 µg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 42 | | |
| Units: pg/mL | | | | |
| least squares mean (confidence interval 95%) | 1.97 (1.48 to 2.62) | 2.23 (1.65 to 3.01) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in biomarker C4

| | |
|---|---|
| End point title | Change from baseline in biomarker C4[67] |

End point description:

Dose-response relationship of LJN452 on C4, a marker of hepatic target engagement at 4 hours post dose

C4 (ng/mL): Summary statistics by treatment and visit

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

End point timeframe:

Week 6, 4 hours post dose

Notes:

[67] - 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: No statistical analysis was planned

| **End point values** | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 15 | 37 | 85 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 38.82 (± 25.765) | 32.75 (± 23.360) | 28.38 (± 13.394) | 40.19 (± 31.356) |

| **End point values** | LJN452 140 µg | LJN452 200 µg | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 42 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 14.97 (± 20.232) | 8.54 (± 9.583) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline on markers of liver fibrosis, Fibroscan

| End point title | Change from baseline on markers of liver fibrosis, Fibroscan[68] |
|---|---|

End point description:

Dose-response relationship of tropifexor (LJN452) on markers of liver fibrosis commonly available such as Fibroscan®

Liver stiffness (kPa): Summary statistics by treatment and visit

FibroScan is a specialized ultrasound machine for measuring fibrosis (scarring) in the liver

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

End point timeframe:

End of Treatment (EoT): For Parts A&B, EoT was Week 12. For Part C, EoT was Week 48

Notes:

[68] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 37 | 85 |
| Units: mean change | | | | |
| arithmetic mean (standard deviation) | 10.94 (± 5.314) | 10.40 (± 7.663) | 9.90 (± 4.095) | 9.00 (± 4.152) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo A+B | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 50 | 51 | 46 | |
| Units: mean change | | | | |
| arithmetic mean (standard deviation) | 11.29 (± 3.677) | 12.03 (± 4.804) | 9.30 (± 4.676) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline on markers of liver fibrosis (ELF)

| End point title | Change from baseline on markers of liver fibrosis (ELF)[69] |
|---|---|

End point description:

ANCOVA: LS Mean Change in Enhanced liver fibrosis panel (ELF) score from baseline by visit up to EOT

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

End point timeframe:

End of Treatment (EoT): For Parts A&B, EoT was Week 12. For Part C, EoT was Week 48

Notes:

[69] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 34 | 78 |
| Units: scores on a scale | | | | |
| least squares mean (standard error) | 0.05 (± 0.158) | 0.00 (± 0.146) | -0.19 (± 0.097) | 0.20 (± 0.064) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51[70] | 46[71] |
| Units: scores on a scale | | | | |
| least squares mean (standard error) | -0.34 (± 0.132) | -0.24 (± 0.122) | 9.999 (± 9.999) | 9.999 (± 9.999) |

Notes:

[70] - 9.999=Placebo is the reference group for repeated measures

[71] - 9.999=Placebo is the reference group for repeated measures

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline on markers of liver fibrosis, Fibrotest (Parts A+B)

| End point title | Change from baseline on markers of liver fibrosis, Fibrotest (Parts A+B)[72] |
|---|---|

End point description:

Score of fibrosis biomarker test: Summary statistics by treatment and visit at EoT

(See Part C in separate outcomes that follows)

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

End point timeframe:

End of Treatment (EoT):12 weeks

Notes:

[72] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 37 | 85 |
| Units: mean change | | | | |
| arithmetic mean (standard deviation) | -0.23 (± 0.284) | -1.49 (± 0.852) | -1.44 (± 1.080) | -1.34 (± 1.222) |

| End point values | Placebo A+B | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 46 | | | |
| Units: mean change | | | | |
| arithmetic mean (standard deviation) | -1.23 (± 1.088) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline on markers of liver fibrosis, Fibrotest, (Part C)

| End point title | Change from baseline on markers of liver fibrosis, Fibrotest, (Part C) |
|---|---|

| End point description: | |
|---|---|
| Repeated measures analysis: Change in score of fibrosis biomarker test from baseline by visit up to EOT | |
| End point type | Secondary |
| End point timeframe: | |
| End of Treatment (EoT) was 48 weeks | |

| **End point values** | LJN452 140 µg | LJN452 200 µg | Placebo C | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 50 | 51 | 51[73] | |
| Units: mean change | | | | |
| least squares mean (standard error) | -0.42 (± 0.131) | -0.44 (± 0.135) | 9.999 (± 9.999) | |

Notes:

[73] - 9.999=Placebo is the reference group for repeated measures

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline on gamma-glutamyl transferase (GGT)

| End point title | Change from baseline on gamma-glutamyl transferase |
|---|---|
| End point description: | |
| Summary statistics of change in GGT (U/L) from baseline by visit up to EoT | |
| End point type | Secondary |
| End point timeframe: | |
| EoT for Parts A+B=12 weeks; EoT for Part C = 48 weeks | |

Notes:

[74] - 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: No statistical analysis was planned

| **End point values** | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 15 | 37 | 84 |
| Units: mean | | | | |
| least squares mean (standard error) | 1.6 (± 10.93) | -29.9 (± 10.11) | -34.2 (± 6.70) | -45.7 (± 4.52) |

| **End point values** | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51[75] | 46[76] |
| Units: mean | | | | |
| least squares mean (standard error) | -35.2 (± 11.58) | -29.9 (± 11.65) | 9.999 (± 9.999) | 9.999 (± 9.999) |

Notes:

[75] - 9.999=Placebo is the reference group for repeated measures

[76] - 9.999=Placebo is the reference group for repeated measures

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline on fasting lipid profile

| End point title | Change from baseline on fasting lipid profile[77] |
|---|---|

End point description:

Repeated measures analysis: LS geometric mean ratio of fasting lipids to baseline by visit up to EOT

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

End point timeframe:

End of Treatment (EoT): For Parts A&B, EoT was Week 12. For Part C, EoT was Week 48

Notes:

[77] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 37 | 50 |
| Units: mmol/L | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Cholesterol | 0.949 (0.888 to 1.014) | 1.003 (0.945 to 1.065) | 1.029 (0.989 to 1.070) | 1.029 (1.002 to 1.057) |
| Triglycerides | 0.920 (0.766 to 1.091) | 0.919 (0.789 to 1.071) | 0.960 (0.868 to 1.062) | 1.048 (0.978 to 1.123) |
| LDL Cholesterol | 0.923 (0.834 to 1.020) | 1.044 (0.953 to 1.142) | 1.092 (1.029 to 1.159) | 1.104 (1.060 to 1.150) |
| HDL Cholesterol | 1.019 (0.946 to 1.096) | 1.001 (0.937 to 1.069) | 0.961 (0.920 to 1.004) | 0.897 (0.870 to 0.924) |
| LDL/HDL Ratio | 0.921 (0.810 to 1.047) | 1.058 (0.942 to 1.188) | 1.139 (1.055 to 1.229) | 1.227 (1.165 to 1.293) |
| Free Glycerol | 1.0563 (0.8722 to 1.2793) | 0.9376 (0.7859 to 1.1185) | 0.9128 (0.8112 to 1.0272) | 0.9915 (0.9151 to 1.0743) |
| Free Fatty Acid | 1.082 (0.897 to 1.305) | 0.864 (0.726 to 1.028) | 0.929 (0.827 to 1.043) | 0.947 (0.874 to 1.025) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51[78] | 46[79] |
| Units: mmol/L | | | | |
| least squares mean (confidence interval 95%) | | | | |

| | | | | |
|---|---|---|---|---|
| Cholesterol | 1.032 (0.975 to 1.093) | 1.071 (1.012 to 1.133) | 9.999 (9.999 to 9.999) | 9.999 (9.999 to 9.999) |
| Triglycerides | 1.070 (0.934 to 1.226) | 1.068 (0.936 to 1.219) | 9.999 (9.999 to 9.999) | 9.999 (9.999 to 9.999) |
| LDL Cholesterol | 1.056 (0.972 to 1.147) | 1.200 (1.106 to 1.302) | 9.999 (9.999 to 9.999) | 9.999 (9.999 to 9.999) |
| HDL Cholesterol | 0.855 (0.800 to 0.913) | 0.824 (0.772 to 0.879) | 9.999 (9.999 to 9.999) | 9.999 (9.999 to 9.999) |
| LDL/HDL Ratio | 1.252 (1.128 to 1.390) | 1.478 (1.332 to 1.639) | 9.999 (9.999 to 9.999) | 9.999 (9.999 to 9.999) |
| Free Glycerol | 1.1115 (0.9721 to 1.2709) | 0.9808 (0.8571 to 1.1223) | 9.999 (9.999 to 9.999) | 9.999 (9.999 to 9.999) |
| Free Fatty Acid | 1.072 (0.951 to 1.208) | 0.887 (0.785 to 1.002) | 9.999 (9.999 to 9.999) | 9.999 (9.999 to 9.999) |

Notes:

[78] - 9.999=Placebo is the reference group for repeated measures

[79] - 9.999=Placebo is the reference group for repeated measures

### Statistical analyses

No statistical analyses for this end point

## Secondary: Itch based on a visual analog scale (VAS) rating scale

| | |
|---|---|
| End point title | Itch based on a visual analog scale (VAS) rating scale[80] |

End point description:

Repeated measures analysis: Change in VAS for Itch from baseline by visit up to EoT

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

End point timeframe:

EoT for Parts A+B=12 weeks; EoT for Part C = 48 weeks

Notes:

[80] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 36 | 78 |
| Units: mean | | | | |
| least squares mean (standard error) | -0.3 (± 0.48) | 0.2 (± 0.43) | 0.4 (± 0.28) | 0.1 (± 0.19) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51[81] | 46[82] |
| Units: mean | | | | |
| least squares mean (standard error) | 0.6 (± 0.37) | 1.1 (± 0.35) | 9.999 (± 9.999) | 9.999 (± 9.999) |

Notes:

[81] - 9.999=placebo is not complared to itself

[82] - 9.999=placebo is not complared to itself

## Statistical analyses

No statistical analyses for this end point

## Secondary: Ctrough of LJN452

| End point title | Ctrough of LJN452[83] |
|---|---|

End point description:

Summary Ctrough of tropifexor (LJN452)

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

End point timeframe:

Scheduled timepoint is zero (Parts A+B) or pre-dose (Part C )

Notes:

[83] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 16 | 37 | 85 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Profile day 7 | 0.142 (± 0.119) | 0.355 (± 0.194) | 0.638 (± 0.453) | 1.215 (± 0.593) |
| Profile day 14 | 0.216 (± 0.127) | 0.505 (± 0.328) | 0.626 (± 0.281) | 1.115 (± 0.693) |
| Profile day 28 | 0.118 (± 0.087) | 0.411 (± 0.250) | 0.639 (± 0.265) | 1.027 (± 0.700) |
| Profile day 42 | 0.161 (± 0.094) | 0.382 (± 0.150) | 0.647 (± 0.344) | 1.032 (± 0.661) |
| Profile day 56 | 0.168 (± 0.088) | 0.474 (± 0.273) | 0.637 (± 0.278) | 1.041 (± 0.701) |
| Profile day 84 | 0.118 (± 0.080) | 0.366 (± 0.147) | 0.530 (± 0.357) | 1.095 (± 0.653) |
| Profile day 168 | 0.00 (± 0.00) | 0.00 (± 0.00) | 0.00 (± 0.00) | 0.00 (± 0.00) |
| Profile day 280 | 0.00 (± 0.00) | 0.00 (± 0.00) | 0.00 (± 0.00) | 0.00 (± 0.00) |
| Profile day 336 | 0.00 (± 0.00) | 0.00 (± 0.00) | 0.00 (± 0.00) | 0.00 (± 0.00) |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | Placebo A+B |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 50 | 51 | 51[84] | 46[85] |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Profile day 7 | 0.00 (± 0.0) | 0.00 (± 0.00) | 9.999 (± 9.999) | 9.999 (± 9.999) |
| Profile day 14 | 0.00 (± 0.00) | 0.00 (± 0.00) | 9.999 (± 9.999) | 9.999 (± 9.999) |
| Profile day 28 | 0.00 (± 0.00) | 0.00 (± 0.00) | 9.999 (± 9.999) | 9.999 (± 9.999) |
| Profile day 42 | 2.821 (± 1.659) | 3.533 (± 2.356) | 9.999 (± 9.999) | 9.999 (± 9.999) |
| Profile day 56 | 0.00 (± 0.00) | 0.00 (± 0.00) | 9.999 (± 9.999) | 9.999 (± 9.999) |

| | | | | |
|---|---|---|---|---|
| Profile day 84 | 1.685 (± 0.874) | 2.286 (± 1.259) | 9.999 (± 9.999) | 9.999 (± 9.999) |
| Profile day 168 | 1.889 (± 1.340) | 2.146 (± 1.383) | 9.999 (± 9.999) | 9.999 (± 9.999) |
| Profile day 280 | 2.129 (± 1.990) | 1.990 (± 1.053) | 9.999 (± 9.999) | 9.999 (± 9.999) |
| Profile day 336 | 1.444 (± 1.077) | 1.979 (± 1.153) | 9.999 (± 9.999) | 9.999 (± 9.999) |

Notes:

[84] - 9.999=Placebo is the reference group for repeated measures. It is not compared to itself

[85] - 9.999=Placebo is the reference group for repeated measures. It is not compared to itself

### Statistical analyses

No statistical analyses for this end point

## Secondary: C2h of LJN452

| | |
|---|---|
| End point title | C2h of LJN452[86] |

End point description:

Summary C2h of tropifexor (LJN452)

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

End point timeframe:

Scheduled timepoint (Parts A+B) is 2 hours; Part C measured Post-dose

Notes:

[86] - 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: No statistical analysis was planned

| End point values | LJN452 10 µg | LJN452 30 µg | LJN452 60 µg | LJN452 90 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14[87] | 16[88] | 37 | 85 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Profile day 7 | 0.190 (± 0.143) | 0.702 (± 0.399) | 1.228 (± 0.598) | 2.193 (± 1.003) |
| Profile day 14 | 0.00 (± 0.00) | 0.00 (± 0.00) | 1.344 (± 0.727) | 2.001 (± 1.053) |

Notes:

[87] - This dosage was not measured at Day 14

[88] - This dosage was not measured at Day 14

| End point values | Placebo A+B | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 46[89] | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Profile day 7 | 0.00 (± 0.00) | | | |
| Profile day 14 | 0.00 (± 0.00) | | | |

Notes:

[89] - Placebo is the reference group and is not compared to itself

### Statistical analyses

No statistical analyses for this end point

## Secondary: Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (Part C) - total score

| | |
|---|---|
| End point title | Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (Part C) - total score |

End point description:

Number of patients who have at least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis
(total score)

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

End point timeframe:

EoT (Week 48)

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 39 | 35 | 42 | |
| Units: participants | 11 | 11 | 12 | |

### Statistical analyses

| Statistical analysis title | Biopsy-based response total score |
|---|---|

Statistical analysis description:

At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (total score)

| | |
|---|---|
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.004 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.214 |
| upper limit | 0.223 |

| Statistical analysis title | Biopsy-based response total score |
|---|---|

Statistical analysis description:

At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (total score)

| | |
|---|---|
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8074 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.029 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.196 |
| upper limit | 0.251 |

## Secondary: Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening - FDA

| | |
|---|---|
| End point title | Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening - FDA |

End point description:

Number of patients who have at least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis
(FDA)

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

End point timeframe:

EoT (Week 48)

| **End point values** | LJN452 140 µg | LJN452 200 µg | Placebo C | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 38 | 35 | 42 | |
| Units: participants | 11 | 11 | 12 | |

### Statistical analyses

| **Statistical analysis title** | Biopsy-based response - FDA |
|---|---|

Statistical analysis description:

At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (FDA)

| | |
|---|---|
| Comparison groups | LJN452 140 µg v Placebo C |

| | |
|---|---|
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.807 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.028 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.191 |
| upper limit | 0.246 |

| **Statistical analysis title** | Biopsy-based response - FDA |
|---|---|
| Statistical analysis description: | |
| At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (FDA) | |
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6233 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.052 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.173 |
| upper limit | 0.273 |

## Secondary: Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening - EMA

| End point title | Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening - EMA |
|---|---|
| End point description: | |
| Number of patients who have at least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis<br>(EMA) | |
| End point type | Secondary |
| End point timeframe: | |
| EoT (Week 48) | |

| End point values | LJN452 140 µg | LJN452 200 µg | Placebo C | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 38 | 35 | 42 | |
| Units: participants | 11 | 11 | 12 | |

**Statistical analyses**

| Statistical analysis title | Biopsy-based response - EMA |
|---|---|
| Statistical analysis description: | |
| At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (EMA) | |
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.004 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.214 |
| upper limit | 0.233 |

| Statistical analysis title | Biopsy-based response - EMA |
|---|---|
| Statistical analysis description: | |
| At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (EMA) | |
| Comparison groups | LJN452 200 µg v Placebo C |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8074 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.029 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.196 |
| upper limit | 0.251 |

**Secondary: Biopsy-based response at Week 48 compared to baseline: Difference**

| **between treatment groups (Part C) - Resolution of steatohepatitis (diagnostic category)** | |
|---|---|
| End point title | Biopsy-based response at Week 48 compared to baseline: Difference between treatment groups (Part C) - Resolution of steatohepatitis (diagnostic category) |
| End point description: | |
| Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging) | |
| End point type | Secondary |
| End point timeframe: | |
| EoT (Week 48) | |

| **End point values** | LJN452 140 µg | LJN452 200 µg | Placebo C | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 38 | 35 | 42 | |
| Units: participants | 4 | 7 | 3 | |

**Statistical analyses**

| **Statistical analysis title** | Biopsy-based response |
|---|---|
| Statistical analysis description: | |
| Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging) | |
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7028 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.034 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.184 |
| upper limit | 0.252 |

| **Statistical analysis title** | Biopsy-based response |
|---|---|
| Statistical analysis description: | |
| Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging) | |
| Comparison groups | LJN452 200 µg v Placebo C |

| | |
|---|---|
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1713 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.129 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.098 |
| upper limit | 0.345 |

## Secondary: Biopsy-based response at Week 48 compared to baseline: Difference between treatment groups (Part C) - Resolution of steatohepatitis (FDA, EMA)

| | |
|---|---|
| End point title | Biopsy-based response at Week 48 compared to baseline: Difference between treatment groups (Part C) - Resolution of steatohepatitis (FDA, EMA) |
| End point description: | |
| Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging) | |
| End point type | Secondary |
| End point timeframe: | |
| EoT (Week 48) | |

| **End point values** | LJN452 140 µg | LJN452 200 µg | Placebo C | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 38 | 35 | 42 | |
| Units: participants | 0 | 2 | 0 | |

### Statistical analyses

| **Statistical analysis title** | Biopsy-based response, FDA and EMA |
|---|---|
| Statistical analysis description: | |
| Resolution of steatohepatitis (FDA, EMA) without worsening of fibrosis (NASH CRN staging) | |
| Comparison groups | LJN452 140 µg v Placebo C |
| Number of subjects included in analysis | 80 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2033 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 0.057 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.168 |
| upper limit | 0.278 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Timeframe for AE | |
| Adverse event reporting additional description: | |
| AE additional description | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

| Reporting groups | |
|---|---|
| Reporting group title | LJN452 10 mcg |
| Reporting group description: | |
| LJN452 10 mcg | |
| Reporting group title | LJN452 60 mcg |
| Reporting group description: | |
| LJN452 60 mcg | |
| Reporting group title | LJN452 30 mcg |
| Reporting group description: | |
| LJN452 30 mcg | |
| Reporting group title | LJN452 90 mcg |
| Reporting group description: | |
| LJN452 90 mcg | |
| Reporting group title | LJN452 140 mcg |
| Reporting group description: | |
| LJN452 140 mcg | |
| Reporting group title | LJN452 200 mcg |
| Reporting group description: | |
| LJN452 200 mcg | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo | |
| Reporting group title | Total |
| Reporting group description: | |
| Total | |

| Serious adverse events | LJN452 10 mcg | LJN452 60 mcg | LJN452 30 mcg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Endometrial thickening | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trigger finger | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | LJN452 90 mcg | LJN452 140 mcg | LJN452 200 mcg |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 85 (4.71%) | 5 / 50 (10.00%) | 3 / 51 (5.88%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Endometrial thickening | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Multiple injuries | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Trigger finger | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Placebo | Total | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 97 (6.19%) | 18 / 350 (5.14%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 97 (1.03%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Endometrial thickening | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Multiple injuries | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 2 / 350 (0.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigger finger | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | LJN452 10 mcg | LJN452 60 mcg | LJN452 30 mcg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 13 (38.46%) | 16 / 37 (43.24%) | 11 / 17 (64.71%) |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Fatigue | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 3 / 17 (17.65%) |
| occurrences (all) | 0 | 1 | 3 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 37 (2.70%) | 3 / 17 (17.65%) |
| occurrences (all) | 1 | 1 | 3 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 | 1 |
| Loss of libido | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 37 (2.70%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 | 1 |
| Poor quality sleep | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 2 / 17 (11.76%) |
| occurrences (all) | 0 | 0 | 2 |
| Constipation | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 | 3 |
| Dry mouth | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 2 / 17 (11.76%) |
| occurrences (all) | 0 | 0 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Neurodermatitis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 5 / 37 (13.51%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 37 (5.41%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 37 (2.70%) | 1 / 17 (5.88%) |
| occurrences (all) | 2 | 1 | 1 |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 2 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Body tinea | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 37 (5.41%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 2 / 37 (5.41%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Viral sinusitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 37 (2.70%) | 2 / 17 (11.76%) |
| occurrences (all) | 0 | 1 | 2 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 37 (0.00%) | 0 / 17 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | LJN452 90 mcg | LJN452 140 mcg | LJN452 200 mcg |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 50 / 85 (58.82%) | 43 / 50 (86.00%) | 45 / 51 (88.24%) |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 85 (5.88%) | 7 / 50 (14.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 5 | 7 | 4 |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 85 (1.18%) | 2 / 50 (4.00%) | 1 / 51 (1.96%) |
| occurrences (all) | 1 | 2 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 4 / 50 (8.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 0 | 4 | 3 |
| Loss of libido | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 1 / 50 (2.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 3 | 2 | 3 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 4 / 50 (8.00%) | 4 / 51 (7.84%) |
| occurrences (all) | 2 | 5 | 4 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 5 / 51 (9.80%) |
| occurrences (all) | 0 | 1 | 6 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 1 / 51 (1.96%) |
| occurrences (all) | 0 | 0 | 1 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 85 (0.00%) | 3 / 50 (6.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 85 (4.71%) | 3 / 50 (6.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 7 | 3 | 6 |
| Poor quality sleep | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 5 / 50 (10.00%) | 2 / 51 (3.92%) |
| occurrences (all) | 3 | 6 | 3 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 2 / 50 (4.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 1 | 2 | 3 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 6 / 50 (12.00%) | 2 / 51 (3.92%) |
| occurrences (all) | 2 | 8 | 2 |
| Constipation | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 3 / 50 (6.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 2 | 3 | 3 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 85 (4.71%) | 3 / 50 (6.00%) | 7 / 51 (13.73%) |
| occurrences (all) | 4 | 5 | 7 |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 0 / 50 (0.00%) | 2 / 51 (3.92%) |
| occurrences (all) | 2 | 0 | 2 |
| Dyspepsia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 85 (4.71%) | 2 / 50 (4.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 5 | 2 | 3 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 5 / 50 (10.00%) | 2 / 51 (3.92%) |
| occurrences (all) | 1 | 5 | 4 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 2 / 50 (4.00%) | 2 / 51 (3.92%) |
| occurrences (all) | 1 | 2 | 2 |
| Nausea | | | |
| subjects affected / exposed | 4 / 85 (4.71%) | 6 / 50 (12.00%) | 10 / 51 (19.61%) |
| occurrences (all) | 5 | 9 | 12 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 3 / 50 (6.00%) | 4 / 51 (7.84%) |
| occurrences (all) | 6 | 6 | 5 |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neurodermatitis | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 7 / 85 (8.24%) | 26 / 50 (52.00%) | 35 / 51 (68.63%) |
| occurrences (all) | 7 | 33 | 45 |
| Rash | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 5 / 50 (10.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 2 | 7 | 4 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 2 / 50 (4.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 2 / 51 (3.92%) |
| occurrences (all) | 0 | 0 | 2 |
| Proteinuria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 85 (1.18%) | 1 / 50 (2.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 1 | 1 | 3 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 3 / 50 (6.00%) | 1 / 51 (1.96%) |
| occurrences (all) | 1 | 4 | 1 |
| Back pain | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 1 / 50 (2.00%) | 2 / 51 (3.92%) |
| occurrences (all) | 3 | 2 | 2 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Body tinea | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 3 / 50 (6.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 3 / 50 (6.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Influenza | | | |
| subjects affected / exposed | 9 / 85 (10.59%) | 1 / 50 (2.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 9 | 1 | 3 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 85 (7.06%) | 6 / 50 (12.00%) | 5 / 51 (9.80%) |
| occurrences (all) | 7 | 8 | 10 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 1 / 50 (2.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 3 / 85 (3.53%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Sinusitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 85 (1.18%) | 3 / 50 (6.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 8 / 85 (9.41%) | 9 / 50 (18.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 8 | 11 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 9 / 50 (18.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 1 | 13 | 0 |
| Viral sinusitis | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 50 (0.00%) | 0 / 51 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 1 / 50 (2.00%) | 2 / 51 (3.92%) |
| occurrences (all) | 2 | 1 | 2 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 2 / 50 (4.00%) | 1 / 51 (1.96%) |
| occurrences (all) | 2 | 2 | 1 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 85 (2.35%) | 2 / 50 (4.00%) | 3 / 51 (5.88%) |
| occurrences (all) | 2 | 2 | 3 |

| **Non-serious adverse events** | Placebo | Total | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 63 / 97 (64.95%) | 233 / 350 (66.57%) | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 97 (9.28%) | 28 / 350 (8.00%) | |
| occurrences (all) | 9 | 29 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 6 / 350 (1.71%) | |
| occurrences (all) | 1 | 6 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 8 / 350 (2.29%) | |
| occurrences (all) | 0 | 8 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 2 / 350 (0.57%) | |
| occurrences (all) | 0 | 2 | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 97 (2.06%) | 11 / 350 (3.14%) | |
| occurrences (all) | 2 | 11 | |
| Loss of libido | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 97 (3.09%) | 10 / 350 (2.86%) | |
| occurrences (all) | 3 | 11 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 97 (2.06%) | 12 / 350 (3.43%) | |
| occurrences (all) | 2 | 13 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 6 / 350 (1.71%) | |
| occurrences (all) | 0 | 7 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 2 / 350 (0.57%) | |
| occurrences (all) | 0 | 2 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 2 / 97 (2.06%) | 5 / 350 (1.43%) | |
| occurrences (all) | 2 | 5 | |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 97 (6.19%) | 19 / 350 (5.43%) | |
| occurrences (all) | 6 | 25 | |
| Poor quality sleep | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 3 / 350 (0.86%) | |
| occurrences (all) | 1 | 3 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 4 / 97 (4.12%) | 15 / 350 (4.29%) | |
| occurrences (all) | 4 | 17 | |
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 97 (8.25%) | 14 / 350 (4.00%) | |
| occurrences (all) | 9 | 15 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 2 / 350 (0.57%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 97 (3.09%) | 15 / 350 (4.29%) | |
| occurrences (all) | 3 | 17 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 97 (5.15%) | 15 / 350 (4.29%) | |
| occurrences (all) | 6 | 16 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 97 (6.19%) | 22 / 350 (6.29%) | |
| occurrences (all) | 9 | 29 | |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 97 (2.06%) | 8 / 350 (2.29%) | |
| occurrences (all) | 2 | 8 | |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 97 (4.12%) | 13 / 350 (3.71%) | |
| occurrences (all) | 4 | 14 | |
| Flatulence | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 97 (2.06%) | 10 / 350 (2.86%) | |
| occurrences (all) | 2 | 12 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 7 / 350 (2.00%) | |
| occurrences (all) | 1 | 7 | |
| Nausea | | | |
| subjects affected / exposed | 11 / 97 (11.34%) | 32 / 350 (9.14%) | |
| occurrences (all) | 13 | 40 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 97 (2.06%) | 14 / 350 (4.00%) | |
| occurrences (all) | 2 | 22 | |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences (all) | 0 | 1 | |
| Neurodermatitis | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 15 / 97 (15.46%) | 88 / 350 (25.14%) | |
| occurrences (all) | 17 | 108 | |
| Rash | | | |
| subjects affected / exposed | 4 / 97 (4.12%) | 15 / 350 (4.29%) | |
| occurrences (all) | 4 | 18 | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 4 / 350 (1.14%) | |
| occurrences (all) | 0 | 4 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 6 / 350 (1.71%) | |
| occurrences (all) | 3 | 9 | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 7 / 350 (2.00%) | |
| occurrences (all) | 0 | 8 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|---|---|---|
| Arthralgia | | | |
| subjects affected / exposed | 3 / 97 (3.09%) | 8 / 350 (2.29%) | |
| occurrences (all) | 3 | 9 | |
| Back pain | | | |
| subjects affected / exposed | 7 / 97 (7.22%) | 14 / 350 (4.00%) | |
| occurrences (all) | 7 | 15 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 3 / 350 (0.86%) | |
| occurrences (all) | 1 | 3 | |
| Infections and infestations | | | |
| Body tinea | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 3 / 350 (0.86%) | |
| occurrences (all) | 0 | 3 | |
| Bronchitis | | | |
| subjects affected / exposed | 6 / 97 (6.19%) | 10 / 350 (2.86%) | |
| occurrences (all) | 7 | 11 | |
| Influenza | | | |
| subjects affected / exposed | 4 / 97 (4.12%) | 17 / 350 (4.86%) | |
| occurrences (all) | 4 | 17 | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 97 (10.31%) | 29 / 350 (8.29%) | |
| occurrences (all) | 11 | 38 | |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 2 / 350 (0.57%) | |
| occurrences (all) | 0 | 2 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 5 / 350 (1.43%) | |
| occurrences (all) | 1 | 5 | |
| Sinusitis | | | |
| subjects affected / exposed | 7 / 97 (7.22%) | 11 / 350 (3.14%) | |
| occurrences (all) | 7 | 11 | |
| Tonsillitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 97 (0.00%) | 2 / 350 (0.57%) | |
| occurrences (all) | 0 | 2 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 10 / 97 (10.31%) | 32 / 350 (9.14%) | |
| occurrences (all) | 10 | 35 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 97 (3.09%) | 14 / 350 (4.00%) | |
| occurrences (all) | 3 | 18 | |
| Viral sinusitis | | | |
| subjects affected / exposed | 0 / 97 (0.00%) | 1 / 350 (0.29%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 9 / 350 (2.57%) | |
| occurrences (all) | 1 | 9 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 97 (1.03%) | 7 / 350 (2.00%) | |
| occurrences (all) | 1 | 7 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 2 / 97 (2.06%) | 9 / 350 (2.57%) | |
| occurrences (all) | 2 | 9 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 June 2016 | To implement recommendations from the US FDA to modify certain details of study CLJN452A2202. |
| 07 March 2017 | To ensure that the protocol text clearly outlines that a second interim analysis of Part A, to include data collected up to Week 16, would be conducted.<br><br>Additionally, the eligibility criteria were updated based on the accumulating experience from ongoing Part A, other NASH studies, input from study investigators, and review of recent literature. |
| 05 October 2017 | To add Part C to the protocol to explore doses of tropifexor (LJN452) > 90 µg. Part C enrolled patients to be treated for 48 weeks with 140 µg tropifexor or 200 µg tropifexor |

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.

No outputs were planned; and are not available for determining the effects of tropifexor on primary endpoints in the subset of patients who had historical biopsy data.

Notes: