# Clinical trial results:
# A randomized, double-blind, parallel-group, multicenter study to assess efficacy, safety, and tolerability of oral tropifexor (LJN452) & licogliflozin (LIK066) combination therapy and each monotherapy, compared with placebo for treatment of adult patients with nonalcoholic steatohepatitis (NASH) and liver fibrosis.(ELIVATE)

## Summary

| | |
|---|---|
| EudraCT number | 2019-002324-32 |
| Trial protocol | BE DE GB ES DK IT SK |
| Global end of trial date | 27 October 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 November 2023 |
| First version publication date | 11 November 2023 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CLJN452D12201C |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04065841 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

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

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 27 October 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 October 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of tropifexor + licogliflozin in combination therapy and each monotherapy treatment, as assessed by histologic improvement after 48 weeks compared to placebo in participants with NASH and stage 2 or 3 fibrosis.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 December 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 3 |
| Country: Number of subjects enrolled | Belgium: 2 |
| Country: Number of subjects enrolled | Brazil: 9 |
| Country: Number of subjects enrolled | Bulgaria: 5 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | Chile: 5 |
| Country: Number of subjects enrolled | Colombia: 4 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | Estonia: 5 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | India: 4 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Japan: 15 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Mexico: 23 |
| Country: Number of subjects enrolled | Korea, Democratic People's Republic of: 2 |
| Country: Number of subjects enrolled | Russian Federation: 5 |
| Country: Number of subjects enrolled | Singapore: 11 |

| | |
|---|---|
| Country: Number of subjects enrolled | South Africa: 5 |
| Country: Number of subjects enrolled | Spain: 12 |
| Country: Number of subjects enrolled | Taiwan: 4 |
| Country: Number of subjects enrolled | Turkey: 3 |
| Country: Number of subjects enrolled | United States: 86 |
| Worldwide total number of subjects | 233 |
| EEA total number of subjects | 45 |

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) | 186 |
| From 65 to 84 years | 47 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

234 participants were randomized at 81 sites.

### Pre-assignment

Screening details:

One of the randomized participants in the tropifexor group was not treated due to loss of interest in the study.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | tropifexor monotherapy |

Arm description:

Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally

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

Dosage and administration details:

Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally

| | |
|---|---|
| **Arm title** | licogliflozin monotherapy |

Arm description:

Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally

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

Dosage and administration details:

Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally

| | |
|---|---|
| **Arm title** | combination therapy |

Arm description:

Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally

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

| | |
|---|---|
| Investigational medicinal product name | tropifexor + licogliflozin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally

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

Arm description:

Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily

| **Number of subjects in period 1** | tropifexor monotherapy | licogliflozin monotherapy | combination therapy |
|---|---|---|---|
| Started | 53 | 55 | 84 |
| Completed | 24 | 33 | 42 |
| Not completed | 29 | 22 | 42 |
| Physician decision | 1 | - | - |
| Consent withdrawn by subject | 1 | 1 | 2 |
| Study terminated by Sponsor | 22 | 16 | 28 |
| Adverse event, non-fatal | 4 | 2 | 10 |
| Lost to follow-up | 1 | 2 | 2 |
| Protocol deviation | - | 1 | - |

| **Number of subjects in period 1** | Placebo |
|---|---|
| Started | 41 |
| Completed | 21 |
| Not completed | 20 |
| Physician decision | - |
| Consent withdrawn by subject | - |
| Study terminated by Sponsor | 17 |
| Adverse event, non-fatal | 1 |
| Lost to follow-up | 2 |
| Protocol deviation | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | tropifexor monotherapy |
| Reporting group description: | |
| Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally | |
| Reporting group title | licogliflozin monotherapy |
| Reporting group description: | |
| Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally | |
| Reporting group title | combination therapy |
| Reporting group description: | |
| Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily | |

| Reporting group values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy |
|---|---|---|---|
| Number of subjects | 53 | 55 | 84 |
| Age Categorical<br>Units: Participants | | | |
| <=18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 42 | 39 | 70 |
| >=65 years | 11 | 16 | 14 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 54.5 | 56.0 | 54.7 |
| standard deviation | ± 11.09 | ± 12.13 | ± 10.82 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 26 | 34 | 43 |
| Male | 27 | 21 | 41 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 39 | 40 | 63 |
| Black or African American | 0 | 4 | 3 |
| Asian | 9 | 10 | 17 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 0 |
| American Indian or Alaska Native | 4 | 0 | 0 |
| Unknown | 0 | 1 | 1 |

| Reporting group values | Placebo | Total | |
|---|---|---|---|
| Number of subjects | 41 | 233 | |
| Age Categorical<br>Units: Participants | | | |
| <=18 years | 0 | 0 | |
| Between 18 and 65 years | 35 | 186 | |

| | | | |
|---|---|---|---|
| >=65 years | 6 | 47 | |

| | | | |
|---|---|---|---|
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 54.9 | | |
| standard deviation | ± 10.22 | - | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 26 | 129 | |
| Male | 15 | 104 | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 32 | 174 | |
| Black or African American | 0 | 7 | |
| Asian | 5 | 41 | |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | |
| American Indian or Alaska Native | 4 | 8 | |
| Unknown | 0 | 2 | |

## End points

### End points reporting groups

| Reporting group title | tropifexor monotherapy |
|---|---|
| Reporting group description: | |
| Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally | |
| Reporting group title | licogliflozin monotherapy |
| Reporting group description: | |
| Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally | |
| Reporting group title | combination therapy |
| Reporting group description: | |
| Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily | |

### Primary: Histological improvement: Proportion of participants who responded at Week 48 compared with baseline

| End point title | Histological improvement: Proportion of participants who responded at Week 48 compared with baseline[1] |
|---|---|
| End point description: | |
| Response was defined as at least a one-stage improvement in fibrosis without worsening of nonalcoholic steatohepatitis (NASH)<br><br>Fibrosis staging and Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) based on steatosis, lobular inflammation, and hepatocyte ballooning assessment were determined by a Study Central Reader. NASH CRN fibrosis criteria: Stage 0 = no fibrosis; Stage 1 = centrilobular pericellular fibrosis (or periportal fibrosis in children); Stage 2 = centrilobular and periportal fibrosis; Stage 3 = bridging fibrosis; and Stage 4 = cirrhosis. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, Week 48 | |
| 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.<br>Justification: No statistical analysis was planned for this primary outcome. | |

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 28 | 34 | 17 |
| Units: Participants | 6 | 9 | 10 | 4 |

### Statistical analyses

No statistical analyses for this end point

## Primary: Proportion of participants with resolution of NASH and no worsening of fibrosis

| End point title | Proportion of participants with resolution of NASH and no worsening of fibrosis[2] |
|---|---|

End point description:

Fibrosis staging and Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) based on steatosis, lobular inflammation, and hepatocyte ballooning assessment were determined by a Study Central Reader. NASH CRN fibrosis criteria: Stage 0 = no fibrosis; Stage 1 = centrilobular pericellular fibrosis (or periportal fibrosis in children); Stage 2 = centrilobular and periportal fibrosis; Stage 3 = bridging fibrosis; and Stage 4 = cirrhosis.

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

End point timeframe:

48 weeks

Notes:

[2] - 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 for this primary outcome.

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 28 | 34 | 17 |
| Units: Participants | 5 | 3 | 10 | 2 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of participants with at least one stage improvement in fibrosis

| End point title | Proportion of participants with at least one stage improvement in fibrosis |
|---|---|

End point description:

Fibrosis staging and Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) based on steatosis, lobular inflammation, and hepatocyte ballooning assessment were determined by a Study Central Reader. NASH CRN fibrosis criteria: Stage 0 = no fibrosis; Stage 1 = centrilobular pericellular fibrosis (or periportal fibrosis in children); Stage 2 = centrilobular and periportal fibrosis; Stage 3 = bridging fibrosis; and Stage 4 = cirrhosis.

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

End point timeframe:

48 weeks

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 28 | 34 | 17 |
| Units: Participants | 6 | 10 | 11 | 4 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of participants who achieved resolution of NASH and no worsening of fibrosis OR improvement in fibrosis by at least one stage without worsening of NASH

| End point title | Proportion of participants who achieved resolution of NASH and no worsening of fibrosis OR improvement in fibrosis by at least one stage without worsening of NASH |
|---|---|

End point description:

Fibrosis staging and Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) based on steatosis, lobular inflammation, and hepatocyte ballooning assessment were determined by a Study Central Reader. NASH CRN fibrosis criteria: Stage 0 = no fibrosis; Stage 1 = centrilobular pericellular fibrosis (or periportal fibrosis in children); Stage 2 = centrilobular and periportal fibrosis; Stage 3 = bridging fibrosis; and Stage 4 = cirrhosis.

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

End point timeframe:

48 weeks

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 28 | 34 | 17 |
| Units: Participants | 8 | 10 | 14 | 5 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of participants with at least two stage improvement in fibrosis without worsening of NASH

| End point title | Proportion of participants with at least two stage improvement in fibrosis without worsening of NASH |
|---|---|

End point description:

Fibrosis staging and Non-alcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) based on steatosis, lobular inflammation, and hepatocyte ballooning assessment were determined by a Study Central Reader. NASH CRN fibrosis criteria: Stage 0 = no fibrosis; Stage 1 = centrilobular pericellular fibrosis (or periportal fibrosis in children); Stage 2 = centrilobular and periportal fibrosis; Stage 3 = bridging fibrosis; and Stage 4 = cirrhosis.

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

End point timeframe:

48 weeks

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 28 | 34 | 17 |
| Units: Participants | 3 | 4 | 3 | 3 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of participants achieving 5% or more reduction in body weight at Week 48 compared with baseline

| End point title | Proportion of participants achieving 5% or more reduction in body weight at Week 48 compared with baseline |
|---|---|

End point description:

Whether the participants had 5% or more reduction in body weight.

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

End point timeframe:

Baseline, Week 48

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 32 | 35 | 24 |
| Units: Participants | 12 | 9 | 28 | 3 |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline to Week 48 in percent liver fat content based on magnetic resonance imaging - proton density fat fraction (MRI - PDFF)

| End point title | Change from Baseline to Week 48 in percent liver fat content based on magnetic resonance imaging - proton density fat fraction (MRI - PDFF) |
|---|---|

End point description:

Change in liver fat content based on MRI-PDFF.

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

End point timeframe:

Baseline, Week 48

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 15 | 19 | 21 | 20 |
| Units: Percent liver fat | | | | |
| arithmetic mean (standard deviation) | -6.57 (± 5.913) | -2.64 (± 5.866) | -7.69 (± 6.702) | -2.58 (± 3.599) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change in GGT over time

| End point title | Change in GGT over time |
|---|---|

End point description:

To evaluate the relationship of investigational treatment and gamma-glutamyl transferase (GGT), a marker of cholestasis and oxidative stress. Due to early termination and a small sample size, the analysis could not be performed.

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

End point timeframe:

48 weeks

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0[3] | 0[4] | 0[5] | 0[6] |
| Units: Participants | | | | |

Notes:

[3] - Due to early termination and a small sample size, the analysis could not be performed.

[4] - Due to early termination and a small sample size, the analysis could not be performed.

[5] - Due to early termination and a small sample size, the analysis could not be performed.

[6] - Due to early termination and a small sample size, the analysis could not be performed.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change in ALT and AST over time

| End point title | Change in ALT and AST over time |
|---|---|

End point description:

To determine the relationship of investigational treatment and markers of hepatic inflammation in NASH (ALT and AST). Due to early termination and a small sample size, the analysis could not be performed.

ALT=alanine transaminase
AST=aspartate aminotransferase

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

End point timeframe:

48 weeks

| End point values | tropifexor monotherapy | licogliflozin monotherapy | combination therapy | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0[7] | 0[8] | 0[9] | 0[10] |
| Units: Participants | | | | |

Notes:

[7] - Due to early termination and a small sample size, the analysis could not be performed.

[8] - Due to early termination and a small sample size, the analysis could not be performed.

[9] - Due to early termination and a small sample size, the analysis could not be performed.

[10] - Due to early termination and a small sample size, the analysis could not be performed.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events:<br>Up to approximately 52 weeks | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 25.1 |
| **Reporting groups** | |
| Reporting group title | LJN452 |
| Reporting group description:<br>LJN452 | |
| Reporting group title | LIK066 |
| Reporting group description:<br>LIK066 | |
| Reporting group title | All Patients |
| Reporting group description:<br>All Patients | |
| Reporting group title | Placebo |
| Reporting group description:<br>Placebo | |
| Reporting group title | Combination |
| Reporting group description:<br>Combination | |

| Serious adverse events | LJN452 | LIK066 | All Patients |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 3 / 55 (5.45%) | 14 / 233 (6.01%) |
| 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) | | | |
| Ovarian cancer | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 55 (1.82%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|---|---|---|
| complications | | | |
| Post procedural fever | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 55 (1.82%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 / 53 (0.00%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoperitoneum | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemobilia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| 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 and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 0 / 55 (0.00%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 55 (1.82%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis E | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 1 / 55 (1.82%) | 1 / 233 (0.43%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Placebo | Combination | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 4 / 84 (4.76%) | |
| 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) | | | |
| Ovarian cancer | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Post procedural fever | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 / 41 (0.00%) | 1 / 84 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoperitoneum | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemobilia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 84 (1.19%) | |
| 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 | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Calculus urinary | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis E | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | LJN452 | LIK066 | All Patients |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 53 (66.04%) | 39 / 55 (70.91%) | 151 / 233 (64.81%) |
| Investigations | | | |
| Urine albumin/creatinine ratio increased | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 2 / 55 (3.64%) | 8 / 233 (3.43%) |
| occurrences (all) | 1 | 2 | 8 |
| Glucose urine present | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 3 / 55 (5.45%) | 7 / 233 (3.00%) |
| occurrences (all) | 2 | 3 | 7 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 2 / 55 (3.64%) | 7 / 233 (3.00%) |
| occurrences (all) | 4 | 2 | 8 |
| Headache | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 1 / 55 (1.82%) | 12 / 233 (5.15%) |
| occurrences (all) | 3 | 1 | 13 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 5 / 55 (9.09%) | 6 / 233 (2.58%) |
| occurrences (all) | 0 | 6 | 7 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 0 / 55 (0.00%) | 5 / 233 (2.15%) |
| occurrences (all) | 3 | 0 | 5 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 3 / 55 (5.45%) | 12 / 233 (5.15%) |
| occurrences (all) | 2 | 3 | 12 |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 4 / 55 (7.27%) | 9 / 233 (3.86%) |
| occurrences (all) | 2 | 4 | 9 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 53 (13.21%) | 21 / 55 (38.18%) | 55 / 233 (23.61%) |
| occurrences (all) | 10 | 48 | 105 |
| Abdominal pain upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 53 (7.55%) | 2 / 55 (3.64%) | 8 / 233 (3.43%) |
| occurrences (all) | 5 | 2 | 9 |
| Flatulence | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 4 / 55 (7.27%) | 11 / 233 (4.72%) |
| occurrences (all) | 4 | 4 | 13 |
| Nausea | | | |
| subjects affected / exposed | 6 / 53 (11.32%) | 4 / 55 (7.27%) | 19 / 233 (8.15%) |
| occurrences (all) | 11 | 4 | 24 |
| Vomiting | | | |
| subjects affected / exposed | 7 / 53 (13.21%) | 2 / 55 (3.64%) | 14 / 233 (6.01%) |
| occurrences (all) | 9 | 2 | 16 |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 4 / 55 (7.27%) | 5 / 233 (2.15%) |
| occurrences (all) | 0 | 4 | 5 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 20 / 53 (37.74%) | 9 / 55 (16.36%) | 55 / 233 (23.61%) |
| occurrences (all) | 26 | 11 | 68 |
| Rash | | | |
| subjects affected / exposed | 2 / 53 (3.77%) | 3 / 55 (5.45%) | 7 / 233 (3.00%) |
| occurrences (all) | 3 | 6 | 11 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 3 / 55 (5.45%) | 3 / 233 (1.29%) |
| occurrences (all) | 0 | 3 | 3 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 53 (7.55%) | 0 / 55 (0.00%) | 5 / 233 (2.15%) |
| occurrences (all) | 4 | 0 | 6 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 53 (0.00%) | 3 / 55 (5.45%) | 6 / 233 (2.58%) |
| occurrences (all) | 0 | 3 | 6 |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 53 (1.89%) | 2 / 55 (3.64%) | 6 / 233 (2.58%) |
| occurrences (all) | 1 | 2 | 6 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 53 (1.89%) | 10 / 55 (18.18%) | 29 / 233 (12.45%) |
| occurrences (all) | 1 | 10 | 29 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 53 (5.66%) | 6 / 55 (10.91%) | 15 / 233 (6.44%) |
| occurrences (all) | 6 | 10 | 27 |

| **Non-serious adverse events** | Placebo | Combination | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 41 (56.10%) | 54 / 84 (64.29%) | |
| Investigations | | | |
| Urine albumin/creatinine ratio increased | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 2 / 84 (2.38%) | |
| occurrences (all) | 3 | 2 | |
| Glucose urine present | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 84 (2.38%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 2 / 84 (2.38%) | |
| occurrences (all) | 0 | 2 | |
| Headache | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 3 / 84 (3.57%) | |
| occurrences (all) | 6 | 3 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 84 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 84 (1.19%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 5 / 84 (5.95%) | |
| occurrences (all) | 2 | 5 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 84 (2.38%) | |
| occurrences (all) | 1 | 2 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 21 / 84 (25.00%) | |
| occurrences (all) | 8 | 39 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 84 (1.19%) | |
| occurrences (all) | 1 | 1 | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 3 / 84 (3.57%) | |
| occurrences (all) | 0 | 5 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 7 / 84 (8.33%) | |
| occurrences (all) | 2 | 7 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 3 / 84 (3.57%) | |
| occurrences (all) | 2 | 3 | |
| Reproductive system and breast disorders | | | |
| Balanoposthitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 84 (1.19%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 22 / 84 (26.19%) | |
| occurrences (all) | 5 | 26 | |
| Rash | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 0 / 84 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 84 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|---|---|---|---|
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all) | 0 / 41 (0.00%)<br>0 | 1 / 84 (1.19%)<br>2 | |
| Musculoskeletal and connective tissue disorders<br>Muscle spasms<br>subjects affected / exposed<br>occurrences (all)<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 41 (2.44%)<br>1<br>3 / 41 (7.32%)<br>3 | 2 / 84 (2.38%)<br>2<br>0 / 84 (0.00%)<br>0 | |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all)<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 9 / 41 (21.95%)<br>9<br>2 / 41 (4.88%)<br>4 | 9 / 84 (10.71%)<br>9<br>4 / 84 (4.76%)<br>7 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 18 September 2020 | Included a placebo arm to minimize sources of bias and to ensure reliable inference with respect to the safety and effectiveness of the treatments; increased sample size to accommodate addition of placebo arm, change of hypothesis tests, update in response rate assumptions and to increase statistical power; provided guidance for study conduct in the context of the COVID-19 or other pandemic. |
| 30 April 2021 | Introduced the tropifexor single 140 µg hard gelatin capsule as a replacement for 3 lower dose hard gelatin capsules that made up this dose (one each of 10 µg, 30 µg and 100 µg); corrected the definition of "no worsening of NASH" to align with definitions in the FDA and EMA guidance documents; included additional emerging guidance for study conduct in the context of the COVID-19 or other public health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported