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 Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	42	39	70
>=65 years	11	16	14
Age Continuous Units: Years			
arithmetic mean	54.5	56.0	54.7
standard deviation	± 11.09	± 12.13	± 10.82
Sex: Female, Male Units: Participants			
Female	26	34	43
Male	27	21	41
Race/Ethnicity, Customized 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 Units: Participants			
<=18 years	0	0	
Between 18 and 65 years	35	186	

>=65 years	6	47	

Age Continuous Units: Years			
arithmetic mean	54.9		
standard deviation	± 10.22	-	
Sex: Female, Male Units: Participants			
Female	26	129	
Male	15	104	
Race/Ethnicity, Customized 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) 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. 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 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 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 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: 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: 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 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[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 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[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: 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: LJN452	
Reporting group title	LIK066
Reporting group description: LIK066	
Reporting group title	All Patients
Reporting group description: All Patients	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Combination
Reporting group description: 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 Insomnia subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	1 / 84 (1.19%) 2	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 1 3 / 41 (7.32%) 3	2 / 84 (2.38%) 2 0 / 84 (0.00%) 0	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	9 / 41 (21.95%) 9 2 / 41 (4.88%) 4	9 / 84 (10.71%) 9 4 / 84 (4.76%) 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