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Sponsor

Novartis

Generic Drug Name

Tropifexor and licogliflozin

Trial Indications

Nonalcoholic steatohepatitis (NASH)

Protocol Number

CLJN452D12201C

Protocol Title

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)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: December 30, 2019 (Actual)
Primary Completion Date: October 27, 2022 (Actual)
Study Completion Date: October 27, 2022 (Actual)

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Reason for Termination

The sponsor made a business decision to stop development of the trial drugs. The decision to stop the trial early was not because of any safety concerns.

Study Design/Methodology

This was a randomized, double-blind, parallel-group, multiple-arm study previously planned to assess the efficacy, safety and tolerability of tropifexor and licogliflozin combination therapy and each monotherapy, compared with placebo in participants with NASH and liver fibrosis.

The study consisted of 1) a screening period, 2) a treatment period starting from randomization on Day 0 and running to Week 48, and 3) a follow-up period of 4 weeks after the last dose of study treatment.

Centers

80 centers in 23 countries: United States(29), United Kingdom(2), Belgium(1), Spain(3), Germany(4), Japan(4), Estonia(1), Bulgaria(2), Taiwan(2), Russia(4), Turkey(1), Chile(2), India(1), Korea, Republic of(2), Singapore(2), Colombia(3), Italy(4), South Africa(2), Brazil(4), Mexico(4), Denmark(1), Argentina(1), Canada(1)

Objectives:

Primary objective:

- 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.

Secondary objectives:

- To evaluate the efficacy of combination therapy and two monotherapies in NASH or fibrosis with a composite endpoint after 48 weeks of treatment.
- To evaluate improvement in fibrosis by at least one stage after 48 weeks of treatment.

- To evaluate improvement in fibrosis by at least two stages with no worsening of NASH after 48 weeks of treatment.
- To evaluate reduction in body weight from Baseline after 48 weeks of treatment.
- To evaluate change in liver fat content after 48 weeks of treatment.
- To evaluate the relationship of investigational treatment and markers of hepatic inflammation in NASH (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) after 48 weeks of treatment.
- To evaluate the relationship of investigational treatment and gamma-glutamyltransferase (GGT), a marker of cholestasis and oxidative stress after 48 weeks of treatment.
- To evaluate the safety and tolerability of tropifexor (LJN452) in combination with licogliflozin (LIK066), and each monotherapy treatment, compared to placebo, after 48 weeks of treatment.

Test Products, Dose, and Mode of Administration

Oral capsules of tropifexor, 140 mcg

Oral tablets of licogliflozin, 30 mg

Statistical Methods

Data analysis was performed by Datamap.

For the primary endpoints, according to the current protocol (protocol amendment V02), hierarchical testing was planned to compare combination therapy and each monotherapy to placebo for the two major histological endpoints (the two previous primary endpoints). However, due to the early termination of the study, formal comparisons were not conducted. The two histological responses were summarized with frequencies and percentages for each treatment (including placebo), along with the 95% confidence intervals.

The secondary endpoints had the same analysis methods as the primary endpoints, except for the following endpoints:

- Change in liver fat content based on magnetic resonance imaging - proton density fat fraction (MRI - PDFF) (measured in 60% of patients) over time up to Week 48 compared with baseline: Summarized by treatment and visit.

- Change in ALT and AST over time up to Week 48 compared with Baseline: Due to early termination and a small sample size, the analysis could not be performed.
- Change in GGT over time up to Week 48 compared with Baseline: Due to early termination and a small sample size, the analysis could not be performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
Presence of NASH with fibrosis confirmed by central reader's evaluation of liver biopsy obtained no more than 6 months before randomization as demonstrated by the following:
(a) NASH using NAFLD Activity Score (NAS) ≥ 4 with at least 1 point each in inflammation and ballooning
and
(b) Fibrosis stage 2 or 3 using NASH CRN fibrosis criteria

Exclusion Criteria:
• Type 1 diabetes mellitus
• Uncontrolled type 2 diabetes defined as glycated hemoglobin (HbA1c) ≥ 9.0% at screening
• HbA1c < 6.5% at screening in Type 2 diabetics currently treated with insulin or sulfonylureas
• Clinical evidence of liver impairment as defined by the presence of any of the following abnormalities:

- Platelet count < LLN (see Central laboratory manual).
- Serum albumin < LLN (see Central laboratory manual).
- International Normalized Ratio (INR) > ULN (see Central laboratory manual).
- ALT or AST > 5× ULN (confirmed by 2 values during screening).
- Total bilirubin > ULN (see Central laboratory manual) (confirmed by 2 values during screening), including Gilbert's syndrome.
- Alkaline phosphatase > 300 IU/L (confirmed by 2 values during screening).
- History of esophageal varices, ascites or hepatic encephalopathy
- Splenomegaly
- MELD score >12

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Participant Flow Table

Overall Study

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo	Total
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily	
Started	54	55	84	41	234
Completed	25	33	42	21	121
Not Completed	29	22	42	20	113
Adverse Event	4	2	10	1	17
Lost to Follow-up	1	2	2	2	7
Physician Decision	1	0	0	0	1
Protocol Violation	0	1	0	0	1
Study terminated by Sponsor	22	16	28	17	83
Withdrawal by Subject	1	1	2	0	4

Baseline Characteristics

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo	Total
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg	Licogliflozin monotherapy arm: licogliflozin 30 mg	Combination therapy arm: tropifexor 140 mcg	Placebo arm: placebo matching tropifexor capsule	

	capsule (+ placebo matching licogliflozin tablet), once daily orally	tablet (+ placebo matching tropifexor capsule), once daily orally	capsule + licogliflozin 30 mg tablet, once daily orally	+ placebo matching licogliflozin tablet, once daily	
Number of Participants [units: participants]	53	55	84	41	233
Baseline Analysis Population Description	Full Analysis Set (FAS): all participants to whom study treatment was assigned by randomization and were treated				
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation					
	54.5±11.09	56.0±12.13	54.7±10.82	54.9±10.22	55.0±11.05
Age Categorical (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
<=18 years	0	0	0	0	0
Between 18 and 65 years	42	39	70	35	186
>=65 years	11	16	14	6	47
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
Female	26	34	43	26	129
Male	27	21	41	15	104
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
White	39	40	63	32	174
Black or African American	0	4	3	0	7

Asian	9	10	17	5	41
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
American Indian or Alaska Native	4	0	0	4	8
Unknown	0	1	1	0	2

Primary Outcome Result(s)

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

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.
Time Frame	Baseline, Week 48
Analysis Population Description	Full Analysis Set (FAS): all participants to whom study treatment has been assigned by randomization and had an assessment of response at Week 48. Efficacy analysis was conducted using the FAS.

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily
Number of Participants Analyzed [units: participants]	23	28	34	17

Histological improvement: Proportion of participants who responded at Week 48 compared with baseline (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Proportion who achieved at least one stage of improvement in fibrosis without worsening of NASH	6 (26.09%)	9 (32.14%)	10 (29.41%)	4 (23.53%)

Proportion of participants with resolution of NASH and no worsening of fibrosis

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.
Time Frame	48 weeks
Analysis Population Description	Full Analysis Set (FAS): all participants to whom study treatment has been assigned by randomization. Efficacy analysis was conducted using the FAS

	tropifexor monotherapy	**licogliflozin monotherapy**	**combination therapy**	**Placebo**
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily
Number of Participants Analyzed [units: participants]	23	28	34	17
Proportion of participants with resolution of NASH and no worsening of fibrosis (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	5 (21.74%)	3 (10.71%)	10 (29.41%)	2 (11.76%)

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Secondary Outcome Result(s)

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

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.
Time Frame	48 weeks
Analysis Population Description	FAS

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily
Number of Participants Analyzed [units: participants]	23	28	34	17
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 (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**

	8 (34.78%)	10 (35.71%)	14 (41.18%)	5 (29.41%)

Proportion of participants with at least one stage improvement in fibrosis

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.
Time Frame	48 weeks
Analysis Population Description	FAS

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily
Number of Participants Analyzed [units: participants]	23	28	34	17
Proportion of participants with at least one stage improvement in fibrosis (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	6 (26.09%)	10 (35.71%)	11 (32.35%)	4 (23.53%)

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

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.

Time Frame: 48 weeks

Analysis Population Description: FAS

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily
Number of Participants Analyzed [units: participants]	23	28	34	17
Proportion of participants with at least two stage improvement in fibrosis without worsening of NASH (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	3 (13.04%)	4 (14.29%)	3 (8.82%)	3 (17.65%)

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

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

Time Frame: Baseline, Week 48

Analysis Population Description: FAS

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily
Number of Participants Analyzed [units: participants]	23	32	35	24
Proportion of participants achieving 5% or more reduction in body weight at Week 48 compared with baseline (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	12 (52.17%)	9 (28.13%)	28 (80%)	3 (12.5%)

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

Description	Change in liver fat content based on MRI-PDFF.
Time Frame	Baseline, Week 48
Analysis Population Description	FAS: all participants to whom study treatment has been assigned by randomization and had an assessment at Week 48. This analysis was performed in 40% of participants.

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily

Number of Participants Analyzed [units: participants]	15	19	21	20
Change from Baseline to Week 48 in percent liver fat content based on magnetic resonance imaging - proton density fat fraction (MRI - PDFF) (units: Percent liver fat)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	-6.57 ± 5.913	-2.64 ± 5.866	-7.69 ± 6.702	-2.58 ± 3.599

Change in ALT and AST over time

Description	To determine the relationship of investigational treatment and markers of hepatic inflammation in NASH (ALT and AST). ALT=alanine transaminase AST=aspartate aminotransferase
Time Frame	48 weeks
Analysis Population Description	Due to early termination and a small sample size, the analysis could not be performed.

	tropifexor monotherapy	**licogliflozin monotherapy**	**combination therapy**	**Placebo**
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily
Number of Participants Analyzed [units: participants]	0	0	0	0
Change in ALT and AST over time (units: Participants)				
	0	0	0	0

Change in GGT over time

Description	To evaluate the relationship of investigational treatment and gamma-glutamyl transferase (GGT), a marker of cholestasis and oxidative stress.
Time Frame	48 weeks
Analysis Population Description	Due to early termination and a small sample size the analysis could not be performed.

	tropifexor monotherapy	licogliflozin monotherapy	combination therapy	Placebo
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcg capsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily
Number of Participants Analyzed [units: participants]	0	0	0	0
Change in GGT over time (units: Participants)				
	0	0	0	0

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

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Safety Results

Time Frame	Up to approximately 52 weeks
Additional Description	An AE is any untoward medical occurrence, unfavorable, or unintended sign (including an abnormal laboratory finding), symptom, disease, or injury, that ocurred during treatment period. They include events that started after the first dose of study treatment or events that were present prior to start of study treatment but increased in severity during on-treatment period.
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	LJN452 N = 53	**LIK066 N = 55**	**Combination N = 84**	**Placebo N = 41**	**All Patients N = 233**
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcgcapsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily	All Patients
Total Number Affected	0	0	0	0	0
Total Number At Risk	53	55	84	41	233

Serious Adverse Events

Time Frame	Up to approximately 52 weeks
Additional Description	An AE is any untoward medical occurrence, unfavorable, or unintended sign (including an abnormal laboratory finding), symptom, disease, or injury, that ocurred during treatment period. They include events that started after the first dose of study treatment or events that were present prior to start of study treatment but increased in severity during on-treatment period.
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

	LJN452 N = 53	**LIK066 N = 55**	**Combination N = 84**	**Placebo N = 41**	**All Patients N = 233**
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcgcapsule (+ placebo matching licogliflozin tablet), once daily orally	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo matching tropifexor capsule), once daily orally	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg tablet, once daily orally	Placebo arm: placebo matching tropifexor capsule + placebo matching licogliflozin tablet, once daily	All Patients
Total # Affected by any Serious Adverse Event	4	3	4	3	14
Total # at Risk by any Serious Adverse Event	53	55	84	41	233
Blood and lymphatic system disorders					
Anaemia	0 (0.00%)	0 (0.00%)	1 (1.19%)	0 (0.00%)	1 (0.43%)
Cardiac disorders					
Atrial fibrillation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	1 (0.43%)
Cardiac failure chronic	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.43%)

Gastrointestinal disorders					
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	1 (0.43%)
Haemoperitoneum	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Pancreatitis	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
General disorders and administration site conditions					
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	1 (1.19%)	0 (0.00%)	1 (0.43%)
Hepatobiliary disorders					
Cholecystitis	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Haemobilia	0 (0.00%)	0 (0.00%)	1 (1.19%)	0 (0.00%)	1 (0.43%)
Infections and infestations					
COVID-19 pneumonia	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Gastroenteritis	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Hepatitis E	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Injury, poisoning and procedural complications					
Post procedural fever	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Ovarian cancer	0 (0.00%)	1 (1.82%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Prostate cancer	1 (1.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.43%)
Nervous system disorders					
Sciatica	0 (0.00%)	0 (0.00%)	1 (1.19%)	0 (0.00%)	1 (0.43%)
Renal and urinary disorders					

Calculus urinary	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	1 (0.43%)
Respiratory, thoracic and mediastinal disorders					
Asthma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.44%)	1 (0.43%)

Other (Not Including Serious) Adverse Events

Time Frame	Up to approximately 52 weeks
Additional Description	An AE is any untoward medical occurrence, unfavorable, or unintended sign (including an abnormal laboratory finding), symptom, disease, or injury, that ocurred during treatment period. They include events that started after the first dose of study treatment or events that were present prior to start of study treatment but increased in severity during on-treatment period.
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LJN452 N = 53	**LIK066 N = 55**	**Combination N = 84**	**Placebo N = 41**	**All Patients N = 233**
Arm/Group Description	Tropifexor monotherapy arm: tropifexor 140 mcgcapsule (+	Licogliflozin monotherapy arm: licogliflozin 30 mg tablet (+ placebo	Combination therapy arm: tropifexor 140 mcg capsule + licogliflozin 30 mg	Placebo arm: placebo matching tropifexor capsule + placebo matching	All Patients

	placebo matching licogliflozin tablet), once daily orally	matching tropifexor capsule), once daily orally	tablet, once daily orally	licogliflozin tablet, once daily	
Total # Affected by any Other Adverse Event	35	39	54	23	151
Total # at Risk by any Other Adverse Event	53	55	84	41	233
Gastrointestinal disorders					
Abdominal distension	2 (3.77%)	3 (5.45%)	5 (5.95%)	2 (4.88%)	12 (5.15%)
Abdominal pain upper	4 (7.55%)	2 (3.64%)	1 (1.19%)	1 (2.44%)	8 (3.43%)
Diarrhoea	7 (13.21%)	21 (38.18%)	21 (25.00%)	6 (14.63%)	55 (23.61%)
Dyspepsia	2 (3.77%)	4 (7.27%)	2 (2.38%)	1 (2.44%)	9 (3.86%)
Flatulence	4 (7.55%)	4 (7.27%)	3 (3.57%)	0 (0.00%)	11 (4.72%)
Nausea	6 (11.32%)	4 (7.27%)	7 (8.33%)	2 (4.88%)	19 (8.15%)
Vomiting	7 (13.21%)	2 (3.64%)	3 (3.57%)	2 (4.88%)	14 (6.01%)
General disorders and administration site conditions					
Fatigue	3 (5.66%)	0 (0.00%)	1 (1.19%)	1 (2.44%)	5 (2.15%)
Pyrexia	0 (0.00%)	5 (9.09%)	0 (0.00%)	1 (2.44%)	6 (2.58%)
Infections and infestations					
COVID-19	1 (1.89%)	10 (18.18%)	9 (10.71%)	9 (21.95%)	29 (12.45%)
Urinary tract infection	3 (5.66%)	6 (10.91%)	4 (4.76%)	2 (4.88%)	15 (6.44%)
Investigations					
Glucose urine present	2 (3.77%)	3 (5.45%)	2 (2.38%)	0 (0.00%)	7 (3.00%)
Urine albumin/creatinine ratio increased	1 (1.89%)	2 (3.64%)	2 (2.38%)	3 (7.32%)	8 (3.43%)

Musculoskeletal and connective tissue disorders					
Back pain	1 (1.89%)	2 (3.64%)	0 (0.00%)	3 (7.32%)	6 (2.58%)
Muscle spasms	0 (0.00%)	3 (5.45%)	2 (2.38%)	1 (2.44%)	6 (2.58%)
Nervous system disorders					
Dizziness	3 (5.66%)	2 (3.64%)	2 (2.38%)	0 (0.00%)	7 (3.00%)
Headache	2 (3.77%)	1 (1.82%)	3 (3.57%)	6 (14.63%)	12 (5.15%)
Psychiatric disorders					
Insomnia	4 (7.55%)	0 (0.00%)	1 (1.19%)	0 (0.00%)	5 (2.15%)
Renal and urinary disorders					
Haematuria	0 (0.00%)	3 (5.45%)	0 (0.00%)	0 (0.00%)	3 (1.29%)
Reproductive system and breast disorders					
Balanoposthitis	0 (0.00%)	4 (7.27%)	1 (1.19%)	0 (0.00%)	5 (2.15%)
Skin and subcutaneous tissue disorders					
Pruritus	20 (37.74%)	9 (16.36%)	22 (26.19%)	4 (9.76%)	55 (23.61%)
Rash	2 (3.77%)	3 (5.45%)	0 (0.00%)	2 (4.88%)	7 (3.00%)

Other Relevant Findings

Not applicable

Conclusions:

The results were from all participants enrolled in the study who had completed their planned visits based on the early termination plan and were, therefore, limited in the scope for interpretation.

Nevertheless, based on available data, after 48 weeks of treatment there were no notable differences among the treatment groups in the proportion of participants who achieved at least one stage of improvement in fibrosis without worsening of nonalcoholic steatohepatitis (NASH). Numerical differences favoring the combination and tropifexor monotherapy groups were seen for resolution of NASH without worsening of fibrosis.

A remarkable proportion of participants on combination therapy achieved 5% or more reduction in body weight compared to baseline; and treatment with tropifexor alone or in combination with licogliflozin resulted in numerically greater reductions in liver fat content, as measured by magnetic resonance imaging - proton density fat fraction (MRI-PDFF), at Week 48.

No new or emerging safety concerns were noted upon combination of tropifexor with licogliflozin. The safety data of this study did not demonstrate any worsening of adverse drug reactions (ADRs) associated with each treatment, and the majority of events were mild to moderate in nature that did not require intervention. Although positive trends in NASH resolution, weight loss, and liver fat content were observed with one or both study drugs compared to placebo, due to the early termination of this study and, therefore, small sample size, no robust conclusions regarding efficacy can be drawn. An overall acceptable safety profile was observed.

Date of Clinical Trial Report

25 May 2023