NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Tropifexor (LJN452) cenicriviroc (CVC)

Trial Indications

Nonalcoholic steatohepatitis (NASH) and liver fibrosis

Protocol Number

CLJC242A2201J

Protocol Title

A randomized, double-blind, multicenter study to assess the safety, tolerability, and efficacy of a combination treatment of tropifexor (LJN452) and cenicriviroc (CVC) in adult patients with nonalcoholic steatohepatitis (NASH) and liver fibrosis

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: September 2018
Primary Completion Date: September 2020
Study Completion Date: October 2020

Study Design/Methodology

This was a 48-week, randomized, double-blind, multicenter study that consisted of a screening period, a treatment period starting from randomization on Day 1 and running to Week 48, and a follow up period of 4 weeks after the last dose of study treatment. The total study duration was up to 62 weeks. A protocol amendment allowed treatment to continue for up to 10 additional weeks for patients unable to attend the study site for the scheduled Week-48 End of Treatment (EOT) visit due to COVID pandemic related restriction.

Since the primary objective of the study was to determine if there was a safe combination between one of the chosen doses of tropifexor and 150 mg of CVC, all assessment results obtained, including those from eligible patients after Week 48, were included in analyses as there was no special plan to account for the treatment extension.

The screening period started from the time of the signing of informed consent and continued for up to 10 weeks when all inclusion/exclusion criteria had been evaluated and all baseline assessments had been performed.
The study was conducted in 17 countries with a total of 65 centers. Since a screening failure rate was expected to be around 66%, approximately 600 patients were to be screened.

Patients were eligible to participate in the study if they had histological evidence of NASH and liver fibrosis stage 2 or 3 (NASH clinical research network (CRN) staging criteria) demonstrated on liver biopsy during the screening period. Alternatively, a historical biopsy could be used if performed within 6 months prior to screening. For the patients who do not have an historical liver biopsy, it is recommended to review any historical available ultrasound based elastography (e.g. Transient elastography (Fibroscan), Acoustic Radiation Force Impulse Imaging (ARFI), 2D-Shear Wave Elastography, where available) prior to performing the liver biopsy. If eligibility was confirmed, and when MRI-PDFF (with or without MRE) was to be performed, it was done prior to randomization.

At baseline, approximately 200 patients whose eligibility was confirmed would be randomized in a 1:1:1:1 ratio, resulting in approximately 50 patients randomized in each of the four arms:

Arm A: tropifexor 140 mcg, once daily

Arm B: CVC 150 mg, once daily

Arm C: tropifexor 140 mcg + CVC 150 mg, once daily

Arm D: tropifexor 90 mcg + CVC 150 mg, once daily.

Centers

65 centers in 17 countries: United States (27), Singapore (2), United Kingdom (3), Spain(4), Italy (5), Latvia (1), Belgium (2), Czech Republic (1), France (3), Israel (1), Argentina (3), Canada (5), Turkey (2), India (1), Germany (2), Russia (2), Egypt (1)

Objectives

Primary objective

The primary objective for this study was to evaluate the safety and tolerability of tropifexor + CVC in patients with NASH and fibrosis (stage 2 or 3 as per NASH CRN histological score, F2/F3) by monitoring adverse events, vital signs and laboratory values during 48 weeks of treatment as compared to monotherapy with each of tropifexor and CVC.

The endpoint for the primary objective was to evaluate the occurrence of AEs, SAEs, AEs resulting in discontinuation of study treatment, AESIs, and changes in vital signs and laboratory values over 48 weeks of treatment.

Secondary objectives and estimands

The secondary objective of the study was to characterize the efficacy of tropifexor + CVC in patients with NASH with fibrosis stage F2/F3 as assessed by histological improvement after 48 weeks of treatment compared to monotherapies (tropifexor and CVC) compared to baseline biopsy.

The endpoints for the secondary objectives were to evaluate the proportion of patients who had at least a one-point improvement in fibrosis as well as the proportion of patients with resolution of steatohepatitis.

There were two estimands used to evaluate the secondary objective. The first estimand was the difference in the proportion of patients on different tropifexor + CVC regimens who achieved at least a one-point improvement in fibrosis at Week 48 compared to tropifexor and CVC monotherapy patients. Anyone who did not have a Week-48 liver biopsy or did not remain on their randomized study treatment for at least 24 weeks (even if a Week-48 biopsy was obtained) had their outcome imputed by multiple imputation (MI). For subjects who remained on their randomized study treatment for at least 24 weeks, but who discontinued study treatment prior to Week 48, the available Week-48 biopsy results were used as observed. This hypothetical strategy was to address the question “what would be the outcome if subjects had stayed at least 24 weeks on treatment and a Week 48 biopsy had been

obtained". Treatment differences between tropifexor + CVC combination therapy and monotherapy with tropifexor or CVC were evaluated using a Cochran-Mantel-Haenszel test controlling for baseline fibrosis stage (F2/F3). The estimand was evaluated in the FAS population.

The second estimand was the difference in the proportion of patients on different tropifexor + CVC regimens who achieved resolution of steatohepatitis at Week 48 relative to baseline compared to tropifexor and CVC monotherapy patients. It was assumed that anyone who did not have a Week-48 liver biopsy result or did not remain on their randomized study treatment for at least 24 weeks had their outcome imputed by MI. The handling of intercurrent events (discontinuation of assigned treatment) was equivalent to the first estimand as described above. Treatment differences between tropifexor + CVC combination therapy and monotherapy with tropifexor or CVC were evaluated using a Cochran-Mantel-Haenszel test controlling for baseline fibrosis stage (F2/F3). The estimand was evaluated in the FAS population.

Test Products, Doses, and Modes of Administration

Tropifexor was supplied to the Investigators as a dry blend in hard gelatin capsules at dose strengths of 10 mcg, 30 mcg, 90 mcg and 100 mcg with placebo supplied as a matching hard gelatin capsule. CVC was supplied to the Investigators as a coated tablet of 150 mg with placebo supplied as a matching coated tablet. The identity of the treatments was concealed by the use of placebos that were all identical in packaging, labeling, schedule of administration, appearance, taste and odor. Additional placebo capsules/tablets were given in active treatment groups when needed to maintain blinding.

Statistical Methods

Summary tables are presented by treatment group and analysis visit (as applicable) using descriptive statistics including absolute and relative frequencies for categorical variables. Continuous variables are summarized by arithmetic mean, standard deviation, minimum, maximum, median and first and third quartile per default. Where indicated, geometric mean and coefficient of variation are displayed, and the ratio instead of percentage change.

The data analysis for the CSR was performed after the clinical database lock, when all patients had completed or discontinued the study, and therefore included all collected data. Data cutoffs for safety DMC analyses occurred approximately every 6 months after start of randomization.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Written informed consent.
- Male and female patients 18 years or older (at the time of the screening visit). Patients must weigh at least 50 kg (110 lb) and no more than 200 kg (440 lb) to participate in the study.
- Able to communicate well with the investigator, to understand and comply with the requirements of the study.
- Adequate liver biopsy sample for evaluation by Central Reader.
- Presence of NASH as demonstrated by histologic evidence based on liver biopsy - NASH with fibrosis stage F2/F3, demonstrated on liver biopsy during the screening period. Alternatively, a historical biopsy can be used if performed within 6 months prior to screening.

Exclusion Criteria

- Use of other investigational drugs within 5 half-lives of enrollment or within 30 days whichever is longer.
- History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
- Previous exposure to elafibranor, CVC, tropifexor, obeticholic acid (OCA), LMB763 or other FXR agonist.
- Participated in a clinical trial and treated with any investigational product being evaluated for the treatment of liver fibrosis or NASH in the 6 months before screening.
- Patients taking medications prohibited by the protocol.
- History of treated or untreated malignancy of any organ system, other than localized basal cell carcinoma of the skin or treated cervical intraepithelial neoplasia, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential.
- Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the modified AUDIT questionnaire ≥ 8.
- Inability to reliably quantify alcohol consumption.
- History or evidence of ongoing drug abuse, within the last 6 months prior to randomization.
- Prior or planned (during the study) bariatric surgery.
- Uncontrolled diabetes defined as HbA1c ≥ 9% at screening.
- Clinical evidence of hepatic decompensation or severe liver impairment.
- Previous diagnosis of other forms of chronic liver disease.

- Calculated eGFR less than 60 mL/min (using the MDRD formula).
- History of biliary diversion.
- History of liver transplantation or planned liver transplant.
- Known positivity for HIV.
- History or current diagnosis of ECG abnormalities indicating significant risk of safety for the patient to participate.
- History of inflammatory bowel disease.
- Patients who are not candidates for liver biopsy.
- Presence of cirrhosis on liver biopsy (F4 by NASH CRN System) or medical history.
- Patients with an abnormal platelet count (referring to reference ranges from the central lab).

Participant Flow Table

Overall Study

	Arm A: Tropifexor (LJN452) - Dose 1	Arm B: Cenicriviroc (CVC)	Arm C: Tropifexor (LJN452) Dose 1 + CVC	Arm D: Tropifexor Dose 2 + CVC	Total
Arm/Group Description	tropifexor 140 mcg, once daily	CVC 150 mg, once daily	tropifexor 140 mcg + CVC 150 mg, once daily	tropifexor 90 mcg + CVC 150 mg, once daily	
Started	50	48	47	48	193
Completed	36	41	38	43	158
Not Completed	14	7	9	5	35
Protocol Violation	2	0	0	1	3
Adverse Event	9	3	8	1	21
By Subject Decision	3	4	1	3	11

Participant Flow Table

Overall Study

	Arm A: Tropifexor (LJN452) - Dose 1	Arm B: Cenicriviroc (CVC)	Arm C: Tropifexor (LJN452) Dose 1 + CVC	Arm D: Tropifexor Dose 2 + CVC	Total
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Completed	36	41	38	43	158
Not Completed	14	7	9	5	35
Protocol Violation	2	0	0	1	3
Adverse Event	9	3	8	1	21
Withdrawal by Subject	3	4	1	3	11

Baseline Characteristics

	Arm A: Tropifexor (LJN452) - Dose 1	Arm B: Cenicriviroc (CVC)	Arm C: Tropifexor (LJN452) Dose 1 + CVC	Arm D: Tropifexor Dose 2 + CVC	Total
Arm/Group Description	tropifexor 140 mcg, once daily	CVC 150 mg, once daily	tropifexor 140 mcg + CVC 150 mg, once daily	tropifexor 90 mcg + CVC 150 mg, once daily	
Number of Participants [units: participants]	50	48	47	48	193
Age Continuous (units: years) Mean ± Standard Deviation					
	54.8±13.35	53.7±11.79	54.7±12.65	54.9±12.29	54.5±12.52
Age, Customized					

(units: participants) Count of Participants					
<65	35	39	37	38	149
>=65	15	9	10	10	44
Sex/Gender, Customized (units: participants) Count of Participants					
Male	20	17	18	25	80
Female	30	31	29	23	113
Race/Ethnicity, Customized (units: participants) Count of Participants					
White	41	44	40	43	168
Asian	7	4	5	5	21
Black	1	0	2	0	3
Unknown	1	0	0	0	1

Primary Outcome Results

Number of participants with Adverse Events

(Time Frame: AEs were collected from first dose of study treatment until end of study treatment at week 48 and then up to maximum duration of 66 weeks)

	Arm A: Tropifexor (LJN452) - Dose 1	Arm B: Cenicriviroc (CVC)	Arm C: Tropifexor (LJN452) Dose 1 + CVC	Arm D: Tropifexor Dose 2 + CVC
Arm/Group Description	tropifexor 140 mcg, once daily	CVC 150 mg, once daily	tropifexor 140 mcg + CVC 150 mg, once daily	tropifexor 90 mcg + CVC 150 mg, once daily
Number of Participants Analyzed [units: participants]	50	48	47	48
Number of participants with Adverse Events (units: participants)				

Count of Participants				
Number of participants with at least one Adverse Event (AE)	42 (84%)	41 (85.42%)	40 (85.11%)	42 (87.5%)
Number of participants with at least one Serious Adverse Events (SAEs)	5 (10%)	3 (6.25%)	4 (8.51%)	10 (20.83%)
Deaths	0 (%)	0 (%)	0 (%)	0 (%)

Secondary Outcome Results

Proportion of participants who have at least a one point improvement in fibrosis

(Time Frame: baseline to 48 Weeks)

	Arm A: Tropifexor (LJN452) - Dose 1	Arm B: Cenicriviroc (CVC)	Arm C: Tropifexor (LJN452) Dose 1 + CVC	Arm D: Tropifexor Dose 2 + CVC
Arm/Group Description	tropifexor 140 mcg, once daily	CVC 150 mg, once daily	tropifexor 140 mcg + CVC 150 mg, once daily	tropifexor 90 mcg + CVC 150 mg, once daily
Number of Participants Analyzed [units: participants]	31	38	37	40
Proportion of participants who have at least a one point improvement in fibrosis (units: participants) Count of Participants				
	10 (32.26%)	12 (31.58%)	11 (29.73%)	13 (32.5%)

Statistical Analysis

Groups	Arm A: Tropifexor (LJN452) - Dose 1, Arm C: Tropifexor (LJN452) Dose 1 + CVC

P Value	0.688
Method	Cochran-Mantel-Haenszel
Odds Ratio (OR)	0.8
95% Confidence Interval 2-Sided	0.25 to 2.63

Statistical Analysis

Groups	Arm A: Tropifexor (LJN452) - Dose 1, Arm D: Tropifexor Dose 2 + CVC
P Value	0.985
Method	Cochran-Mantel-Haenszel
Odds Ratio (OR)	1.01
95% Confidence Interval 2-Sided	0.51 to 1.99

Statistical Analysis

Groups	Arm C: Tropifexor (LJN452) Dose 1 + CVC, Arm D: Tropifexor Dose 2 + CVC
P Value	0.870
Method	Cochran-Mantel-Haenszel
Odds Ratio (OR)	0.92
95% Confidence Interval 2-Sided	0.3 to 2.84

Statistical Analysis

Groups	Arm B: Cenicriviroc (CVC), Arm D: Tropifexor Dose 2 + CVC
P Value	0.710
Method	Cochran-Mantel-Haenszel
Odds Ratio (OR)	1.21
95% Confidence Interval 2-Sided	0.41 to 3.61

Proportion of participants with resolution of steatohepatitis

(Time Frame: baseline to 48 weeks)

	Arm A: Tropifexor (LJN452) - Dose 1	Arm B: Cenicriviroc (CVC)	Arm C: Tropifexor (LJN452) Dose 1 + CVC	Arm D: Tropifexor Dose 2 + CVC
Arm/Group Description	tropifexor 140 mcg, once daily	CVC 150 mg, once daily	tropifexor 140 mcg + CVC 150 mg, once daily	tropifexor 90 mcg + CVC 150 mg, once daily
Number of Participants Analyzed [units: participants]	31	38	37	40
Proportion of participants with resolution of steatohepatitis (units: participants) Count of Participants				
	8 (25.81%)	8 (21.05%)	5 (13.51%)	9 (22.5%)

Statistical Analysis

Groups	Arm A: Tropifexor (LJN452) - Dose 1, Arm C: Tropifexor (LJN452) Dose 1 + CVC
P Value	0.136
Method	Cochran-Mantel-Haenszel

Odds Ratio (OR)	0.37
95% Confidence Interval 2-Sided	0.08 to 1.61

Statistical Analysis

Groups	Arm A: Tropifexor (LJN452) - Dose 1, Arm D: Tropifexor Dose 2 + CVC
P Value	0.747
Method	Cochran-Mantel-Haenszel
Odds Ratio (OR)	0.83
95% Confidence Interval 2-Sided	0.24 to 2.9

Statistical Analysis

Groups	Arm B: Cenicriviroc (CVC), Arm C: Tropifexor (LJN452) Dose 1 + CVC
P Value	0.784
Method	Cochran-Mantel-Haenszel
Odds Ratio (OR)	0.84
95% Confidence Interval 2-Sided	0.18 to 3.63

Statistical Analysis

Groups	Arm B: Cenicriviroc (CVC), Arm D: Tropifexor Dose 2 + CVC
P Value	0.521
Method	Cochran-Mantel-Haenszel

Odds Ratio (OR)	1.45
95% Confidence Interval 2-Sided	0.4 to 5.69

Safety Results

All-Cause Mortality

	Tropifexor 140mcg N = 50	CVC 150mg N = 48	Tropifexor 140mcg + CVC 150mg N = 47	Tropifexor 90mcg + CVC 150mg N = 48
Arm/Group Description	Tropifexor 140mcg	CVC 150mg	Tropifexor 140mcg + CVC 150mg	Tropifexor 90mcg + CVC 150mg
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	AEs were collected from first dose of study treatment until end of study treatment at week 48 and then up to maximum duration of 66 weeks
Additional Description	Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment and up to of 66 weeks
Source Vocabulary for Table Default	MedDRA (23.1)
Assessment Type for Table Default	Systematic Assessment

	Tropifexor 140mcg N = 50	CVC 150mg N = 48	Tropifexor 140mcg + CVC 150mg N = 47	Tropifexor 90mcg + CVC 150mg N = 48
Arm/Group Description	Tropifexor 140mcg	CVC 150mg	Tropifexor 140mcg + CVC 150mg	Tropifexor 90mcg + CVC 150mg
Total participants affected	5 (10.00%)	3 (6.25%)	4 (8.51%)	10 (20.83%)
Cardiac disorders				
Coronary artery disease	0 (0.00%)	1 (2.08%)	0 (0.00%)	0 (0.00%)
Myocardial infarction	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.08%)
Gastrointestinal disorders				
Duodenal ulcer	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastritis	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophageal ulcer	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pancreatitis acute	0 (0.00%)	1 (2.08%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions				
Non-cardiac chest pain	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders				
Biliary dyskinesia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.08%)
Gallbladder polyp	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations				
Appendicitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.08%)
COVID-19	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.17%)
COVID-19 pneumonia	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Sepsis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.08%)
Injury, poisoning and procedural complications				
Anaesthetic complication	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.08%)
Cervical vertebral fracture	0 (0.00%)	1 (2.08%)	0 (0.00%)	0 (0.00%)
Road traffic accident	0 (0.00%)	1 (2.08%)	0 (0.00%)	0 (0.00%)
Spinal compression fracture	0 (0.00%)	1 (2.08%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders				
Euglycaemic diabetic ketoacidosis	0 (0.00%)	1 (2.08%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Spondylitis	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Acute lymphocytic leukaemia	0 (0.00%)	0 (0.00%)	1 (2.13%)	0 (0.00%)
Colon cancer	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders				
Cerebrovascular accident	0 (0.00%)	0 (0.00%)	1 (2.13%)	1 (2.08%)
Syncope	1 (2.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Psychiatric disorders				
Depression suicidal	0 (0.00%)	0 (0.00%)	1 (2.13%)	0 (0.00%)
Reproductive system and breast disorders				
Benign prostatic hyperplasia	0 (0.00%)	0 (0.00%)	1 (2.13%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Pneumonitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.08%)
Surgical and medical procedures				
Cataract operation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.08%)

Other Adverse Events by System Organ Class

Time Frame	AEs were collected from first dose of study treatment until end of study treatment at week 48 and then up to maximum duration of 66 weeks
Additional Description	Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment and up to of 66 weeks
Source Vocabulary for Table Default	MedDRA (23.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Tropifexor 140mcg N = 50	**CVC 150mg N = 48**	**Tropifexor 140mcg + CVC 150mg N = 47**	**Tropifexor 90mcg + CVC 150mg N = 48**
Arm/Group Description	Tropifexor 140mcg	CVC 150mg	Tropifexor 140mcg +	Tropifexor 90mcg + CVC

			CVC 150mg	150mg
Total participants affected	39 (78.00%)	30 (62.50%)	33 (70.21%)	32 (66.67%)
Eye disorders				
Cataract	0 (0.00%)	3 (6.25%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders				
Abdominal distension	2 (4.00%)	3 (6.25%)	1 (2.13%)	4 (8.33%)
Abdominal pain	5 (10.00%)	3 (6.25%)	5 (10.64%)	2 (4.17%)
Abdominal pain upper	3 (6.00%)	2 (4.17%)	5 (10.64%)	2 (4.17%)
Constipation	5 (10.00%)	2 (4.17%)	6 (12.77%)	3 (6.25%)
Diarrhoea	2 (4.00%)	7 (14.58%)	4 (8.51%)	0 (0.00%)
Dyspepsia	1 (2.00%)	0 (0.00%)	3 (6.38%)	2 (4.17%)
Flatulence	1 (2.00%)	1 (2.08%)	3 (6.38%)	2 (4.17%)
Nausea	2 (4.00%)	6 (12.50%)	7 (14.89%)	6 (12.50%)
General disorders and administration site conditions				
Asthenia	4 (8.00%)	2 (4.17%)	5 (10.64%)	3 (6.25%)
Fatigue	7 (14.00%)	4 (8.33%)	5 (10.64%)	4 (8.33%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (8.33%)
Infections and infestations				
Bronchitis	1 (2.00%)	0 (0.00%)	3 (6.38%)	1 (2.08%)
Ear infection	0 (0.00%)	0 (0.00%)	3 (6.38%)	0 (0.00%)
Gastroenteritis	1 (2.00%)	1 (2.08%)	3 (6.38%)	3 (6.25%)
Nasopharyngitis	2 (4.00%)	3 (6.25%)	2 (4.26%)	2 (4.17%)

Sinusitis	2 (4.00%)	1 (2.08%)	4 (8.51%)	3 (6.25%)
Upper respiratory tract infection	3 (6.00%)	2 (4.17%)	5 (10.64%)	5 (10.42%)
Urinary tract infection	7 (14.00%)	3 (6.25%)	2 (4.26%)	4 (8.33%)
Injury, poisoning and procedural complications				
Ligament sprain	2 (4.00%)	0 (0.00%)	0 (0.00%)	3 (6.25%)
Investigations				
Blood alkaline phosphatase increased	3 (6.00%)	0 (0.00%)	1 (2.13%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Arthralgia	6 (12.00%)	3 (6.25%)	6 (12.77%)	1 (2.08%)
Back pain	1 (2.00%)	3 (6.25%)	5 (10.64%)	4 (8.33%)
Muscle spasms	1 (2.00%)	2 (4.17%)	3 (6.38%)	1 (2.08%)
Osteoarthritis	1 (2.00%)	0 (0.00%)	3 (6.38%)	0 (0.00%)
Pain in extremity	0 (0.00%)	3 (6.25%)	0 (0.00%)	1 (2.08%)
Nervous system disorders				
Dizziness	2 (4.00%)	3 (6.25%)	2 (4.26%)	1 (2.08%)
Psychiatric disorders				
Insomnia	1 (2.00%)	1 (2.08%)	3 (6.38%)	1 (2.08%)
Skin and subcutaneous tissue disorders				
Pruritus	20 (40.00%)	10 (20.83%)	15 (31.91%)	10 (20.83%)

Conclusion

This study was a 48-week, randomized, double-blind, multicenter trial that consisted of a screening period, a treatment period starting from randomization on Day 1 and running to Week 48, and a follow up period of 4 weeks after the last dose of study treatment. The total study duration was up to 62 weeks. A protocol amendment necessitated by the COVID-19 pandemic allowed treatment to be extended by up to 8 additional weeks, for a total maximum duration of 67 weeks. Subjects were randomized to one of the following treatment groups: tropifexor 140 mcg, once daily; CVC 150 mg, once daily; tropifexor 140 mcg + CVC 150 mg, once daily; tropifexor 90 mcg + CVC 150 mg, once daily.

Safety was the primary objective of this study and the safety profiles of the combination therapies were similar to those of each monotherapy, with no additional emergent safety signals compared to those and reported in previous monotherapy studies.

In the efficacy analysis (secondary objective), there was no evidence that tropifexor + CVC combination therapy had a higher likelihood of at least a one-point improvement in fibrosis (NASH CRN staging) after 48 weeks of treatment or of achieving resolution of steatohepatitis after 48 weeks of treatment compared with that of monotherapy treatment. Overall efficacy performance of tropifexor monotherapy in this study was similar to that observed in Study CLJN452A2202 (FLIGHT-FXR).

Pruritus was frequent and increases in LDL-C and decreases in HDL-C were seen in the tropifexor monotherapy and combination therapy treatment groups

Date of Clinical Trial Report

5 July 2021