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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

LJN452 (tropifexor)

Trial Indications

non-alcoholic steatohepatitis (NASH)

Protocol Number

CLJN452A2202

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: August 2016
Primary Completion Date: April 2020
Study Completion Date: April 2020

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose finding, 3-part (Parts A, B, and C), adaptive design study to assess the safety, tolerability, and efficacy of six doses of tropifexor as compared to placebo in subjects with NASH.

Each study part had a screening period followed by a double-blind, randomized, treatment period, and a post-treatment follow-up period.

In Part A, 77 subjects were randomized at baseline to receive tropifexor (10 µg, 30 µg, 60 µg or 90 µg) or placebo for 12 weeks. After ≥ 90% of the subjects from Part A completed 8 weeks of treatment, the first interim analysis of all Part A data was performed and the Data Monitoring Committee (DMC) recommended evaluation of 90 µg tropifexor (safe and efficacious) in Part B. The treatment arms of Part A were completed through Week 16.

Randomization for Part B was started after the DMC recommendation of testing the 90 ug dose. As planned in the study protocol, since the DMC selected only one dose (90 µg) to be tested in Part B, one of the other originally planned treatment arms (60 µg) was included with a smaller sample size to confirm the earlier findings of this dose observed in Part A. Therefore, in Part B, 121 subjects, were randomized at baseline to receive tropifexor (90 µg and 60 µg) or placebo (Arms F, G and H) for 12 weeks. Part B ended at Week 16.

Part C was introduced

Centers

84 centers in 17 countries: United States (34), Taiwan (5), Australia (2), Austria (2), Canada (3), Netherlands (1), Slovakia (Slovak Republic) (4), Korea, Republic of (5), Germany (5), Belgium (3), Italy (3), Spain (5), Singapore (1), France (3), Japan (4), Argentina (3), India (1)

Objectives

Primary objectives of the study were:

- To determine safety and tolerability of different doses of tropifexor
- To determine the dose-response relationship of tropifexor on markers of hepatic inflammation in NASH (ALT and AST)
- To determine the dose response relationship of tropifexor on liver fat content by changes in quantitative MRI determined fat

Secondary objectives of the study were:

- To determine the effect of different doses of tropifexor on anthropometric assessments (weight, BMI, waist-to-hip (WHR) ratio) after 12 weeks of treatment
- To determine the dose-response relationship of tropifexor on FGF19 over time, a marker of FXR target engagement in the gut, and C4, a marker of hepatic target engagement
- To determine the dose-response relationship of tropifexor on markers of liver fibrosis commonly available such as Fibroscan®, enhanced liver fibrosis panel (ELF), and fibrosis biomarker test (originally known as Fibrotest®/ FibroSure®)

Test Product, Dose, and Mode of Administration

The test drug (tropifexor) was supplied to the investigators as 10 µg, 30 µg and 100 µg oral capsules. Placebo was also supplied as capsules.

Statistical Methods

There were no pre-specified hypotheses and statistical models in this study. The methods to analyze the primary safety and efficacy variables are outlined below.

Variable	Method of analysis
Occurrence of SAE	Summary table of absolute and relative frequency, overall and by preferred term
Occurrence of AE resulting in discontinuation or dose reduction of study treatment	Summary table of absolute and relative frequency, overall and by preferred term
Occurrence of AE of special interest	Summary table of absolute and relative frequency, overall and by type of AE (risk definition as per DSPP)
Change from baseline to Week 12 of ALT	Baseline adjusted mean estimates and pairwise differences from repeated measures ANCOVA, descriptive statistics
Change from baseline to Week 12 of AST	Baseline adjusted mean estimates and pairwise differences from repeated measures ANCOVA, descriptive statistics
Relative change from baseline to Week 12 in percentage of fat in the liver assessed using MRI	Baseline adjusted mean estimates and pairwise differences from ANCOVA, descriptive statistics

An overview of the secondary efficacy variables and planned analysis is as below:

Variable	Analysis
Absolute and relative change from baseline by visit in percentage of fat in the liver assessed using MRI	Baseline adjusted mean estimates and pairwise differences from ANCOVA (repeated measures for Part C), descriptive statistics
Weight BMI Waist-to-hip (WTH) ratio	Descriptive statistics by visit, including change from baseline, pairwise differences versus placebo with 95% CI from repeated measures ANCOVA (weight and BMI) or simple ANCOVA (WTH ratio)
FGF19	Descriptive statistics (statset2) by visit, including change from baseline, pairwise ratio versus placebo with 95% CI from ANCOVA (ratio post-dose versus pre-dose (and versus baseline for C4) at week 6 back-transformed from log scale)
C4	Descriptive statistics (statset2) by visit, including change from baseline, pairwise ratio versus placebo with 95% CI from ANCOVA (ratio post-dose versus pre-dose (and versus baseline for C4) at week 6 back-transformed from log scale)
Liver stiffness (in kPa) by Fibroscan® Enhanced liver fibrosis panel (ELF) score Score of fibrosis biomarker test (originally known as Fibrotest®/ FibroSure®)	Descriptive statistics by visit (including change from baseline), pairwise differences versus placebo with 95% CI from ANCOVA (repeated measures for Part C)
GGT	Descriptive statistics by visit (including change from baseline), pairwise differences versus placebo with 95% CI from repeated measures ANCOVA
Fasting lipids, mainly: Total cholesterol Triglycerides LDL and HDL cholesterol LDL-C / HDL-C ratio Free glycerol Free fatty acids	Descriptive statistics (statset2) by visit (including % change and log transformed ratio to baseline), and pairwise ratio versus placebo with 95% CI from repeated measures ANCOVA (ratio to baseline back transformed from log scale) Additional covariate: use of lipid reducing concomitant medication.
At least a one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis at Week 48 compared to baseline	Descriptive statistics (absolute and relative frequency), differences, odds ratio and relative risk reduction versus placebo with 95% CI
At least a two point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis at Week 48 compared to baseline	Descriptive statistics (absolute and relative frequency), differences, odds ratio and relative risk reduction versus placebo with 95% CI
Resolution of steatohepatitis without worsening of fibrosis (NASH CRN staging) at Week 48 compared to baseline	Descriptive statistics (absolute and relative frequency), differences, odds ratio and relative risk reduction versus placebo with 95% CI
Change of NAS from baseline to Week 48	Descriptive statistics

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- male/female patients, 18 years or older
- written informed consent
- Part A and B patients : presence of NASH by histological evidence (liver biopsy obtained 2 years or less prior to randomization) with fibrosis level of F1, F2 or F3 (fibrosis in the absence of cirrhosis) and no diagnosis of chronic liver disease and elevated alanine aminotransferase (ALT) OR phenotypic diagnosis based on elevated ALT, BMI and diagnosis of Type 2 diabetes mellitus (DM)
- Part C patients: presence of NASH by histological evidence (liver biopsy obtained during the Screening period or 6 months or less prior to randomization) with fibrosis level of F2 or F3 and no diagnosis of chronic liver disease

And (All Parts):
- ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females)
- Liver fat equal to or higher than 10% by MRI

Exclusion Criteria:

- previous exposure to OCA
- patients taking prohibited medications
- patients taking the following medicines UNLESS on a stable dose (within 25% of baseline dose) for at least 1 month before randomization: (for Part C patients, dose must be stable for at least 1 month prior to biopsy through Screening : anti- diabetic medications, insulin, beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, vitamin E (if doses > 200 IU/day; doses

800 IU/day are prohibited), thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control
- pregnant or nursing (lactating) women
- current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening
- uncontrolled diabetes mellitus
- new use of GLP-1 agonists such as liraglutide, exenatide, lixisenatide, albiglutide or dulaglutide within 3 months of screening
- presence of cirrhosis
- hepatic decompensation or severe liver impairment
- previous diagnosis of other forms of chronic liver disease

- patients with contraindications to MRI imaging

Participant Flow Table

Parts A + B (Randomized Set)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo C	Total
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A+B)	90 micrograms of Tropifexor (Parts A + B)	Placebo A+B	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)	
Started	14	16	37	85	46	0	0	0	198
Completed	14	16	36	77	45	0	0	0	188
Not Completed	0	0	1	8	1	0	0	0	10
Withdrawal by Subject	0	0	1	2	1	0	0	0	4
Physician Decision	0	0	0	2	0	0	0	0	2
Adverse Event	0	0	0	4	0	0	0	0	4

Part C (Randomized Set)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo C	Total
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A+B)	90 micrograms of Tropifexor (Parts A + B)	Placebo A+B	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)	
Started	0	0	0	0	0	50	51	51	152
Completed	0	0	0	0	0	38	37	44	119

Not Completed	0	0	0	0	0	12	14	7	33
Adverse Event	0	0	0	0	0	5	9	2	16
Lost to Follow-up	0	0	0	0	0	1	1	1	3
Physician Decision	0	0	0	0	0	1	0	1	2
Withdrawal by Subject	0	0	0	0	0	5	4	3	12

Baseline Characteristics

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo C	Total
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A+B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	(Placebo Part C)	
Number of Participants [units: participants]	14	16	37	85	46	50	51	51	350
Sex: Female, Male[1] (units: participants) Count of Participants									
Parts A + B : Female	9	7	20	47	21	0	0	0	104
Parts A + B : Male	5	9	17	38	25	0	0	0	94
Part C : Female	0	0	0	0	0	36	29	32	97
Part C : Male	0	0	0	0	0	14	22	19	55

Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)									
Caucasian (Parts A + B)	12	11	24	50	25	0	0	0	122
Black (Parts A + B)	0	0	0	1	0	0	0	0	1
Asian (Parts A + B)	2	5	12	31	20	0	0	0	70
Pacific Islander (Parts A + B)	0	0	0	0	1	0	0	0	1
Other (Parts A + B)	0	0	0	2	0	0	0	0	2
Unknown (Parts A+B)	0	1	1	1	0	0	0	0	3
Caucasian (Part C)	0	0	0	0	0	37	38	38	113
Black (Part C)	0	0	0	0	0	0	0	1	1
Asian (Part C)	0	0	0	0	0	10	10	8	28
Pacific Islander (Part C)	0	0	0	0	0	1	0	0	1
Other (Part C)	0	0	0	0	0	2	3	4	9
Age Continuous (units: years) Mean ± Standard Deviation									
Parts A + B	48±11.7	49±14.4	50±12.5	51±13.4	51±12.3				51±12.8
Part C						56±11.41	55±10.8	54±11.0	55±11.0
Age Categorical (units: participants) Count of Participants (Not Applicable)									
Parts A + B : <=18 years	0	0	0	0	0	0	0	0	0
Parts A + B : Between 18 and 65 years	14	14	33	72	41	0	0	0	174

Parts A + B : >=65 years	0	2	4	13	5	0	0	0	24
Part C : <=18 years	0	0	0	0	0	0	0	0	0
Part C : Between 18 and 65 years	0	0	0	0	0	40	41	43	167
Part C : >=65 years	0	0	0	0	8	10	10	8	36

[1] Sex of participant by treatment

Primary Outcome Results

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

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

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LNJ452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A+B)	90 micrograms of Tropifexor (Parts A+B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	13	17	37	85	46	50	51	51
Number of Nonalcoholic steatohepatitis (NASH) patients with Treatment Emergent Adverse Events (TEAE) (units: participants) Count of Participants (Not Applicable)								
Number of participants with at least one AE	5 (38.46%)	11 (64.71%)	24 (64.86%)	61 (71.76%)	31 (67.39%)	49 (98%)	49 (96.08%)	46 (90.2%)

Change in Transaminase levels (ALT)

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

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LNJ452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	16	37	85	46	50	51	51
Change in Transaminase levels (ALT) (units: IU/L) Mean ± Standard Deviation								
	-16.7 ± 17.53	-12.0 ± 35.99	-17.3 ± 28.12	-15.4 ± 30.32	-8.1 ± 29.37	-27.0 ± 30.24	-28.7 ± 25.40	-11.7 ± 61.64

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B	10 micrograms of Tropifexor vs placebo (Part A)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Parts A + B) (Full analysis set)
P Value	0.362	
Method	ANCOVA	
LS mean change	-15.9	
Standard Error of the mean	7.76	

95% Confidence Interval 2-Sided	-31.2 to -0.6

Statistical Analysis

Groups	LJN452 30 µg, Placebo A+B	30 micrograms of Tropifexor vs placebo (Part A)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Parts A + B) (Full analysis set)
P Value	0.729	
Method	ANCOVA	
LS mean change	-10.7	
Standard Error of the mean	7.12	
95% Confidence Interval 2-Sided	-24.8 to 3.3	

Statistical Analysis

Groups	LJN452 60 µg, Placebo A+B	60 micrograms of Tropifexor vs placebo (Parts A + B)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Parts A + B) (Full analysis set)
P Value	0.173	
Method	ANCOVA	
Least Square Mean Change	-16.5	
Standard Error of the mean	4.73	
95% Confidence Interval 2-Sided	-25.8 to -7.1	

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B	90 micrograms of Tropifexor vs placebo (Parts A + B)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Parts A + B) (Full analysis set)
P Value	0.185	
Method	ANCOVA	
Least Square Mean Change	-14.9	
Standard Error of the mean	3.25	
95% Confidence Interval 2-Sided	-21.3 to -8.5	

Statistical Analysis

Groups	LJN452 140 µg, Placebo Part C	140 micrograms of Tropifexor (Part C) vs placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Part C) (Full analysis set)
P Value	0.020	
Method	ANCOVA	
LS Mean Change	-31.6	
Standard Error of the mean	7.71	
95% Confidence Interval 2-Sided	-46.9 to -16.3	

Statistical Analysis

Groups	LNJ452 200 µg, Placebo Part C	200 micrograms of Tropifexor vs placebo (Part C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Part C) (Full analysis set)
P Value	0.030	
Method	ANCOVA	
LS Mean Change	-32.5	
Standard Error of the mean	9.10	
95% Confidence Interval 2-Sided	-50.6 to -14.5	

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B, Placebo Part C	10 micrograms of Tropifexor vs placebo (Parts A + B + C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline to Week 12 (Parts A+B+C) Full analysis set (FAS)
P Value	0.456	
Method	ANCOVA	
LS Mean change	-13.4	
Standard Error of the mean	7.86	
95% Confidence Interval 2-Sided	-26.3 to -0.4	

Statistical Analysis

Groups	LJN452 30 µg, Placebo A+B, Placebo Part C	30 micrograms of Tropifexor vs placebo (Parts A + B + C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline to Week 12 (Parts A+B+C) Full analysis set (FAS)
P Value	0.966	
Method	ANCOVA	
LS Mean change	-7.5	
Standard Error of the mean	7.27	
95% Confidence Interval 2-Sided	-19.5 to 4.4	

Statistical Analysis

Groups	LJN452 60 µg, Placebo A+B, Placebo Part C	60 micrograms of Tropifexor vs placebo (Parts A + B + C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline to Week 12 (Parts A+B+C) Full analysis set (FAS)
P Value	0.275	
Method	ANCOVA	
LS Mean change	-13.3	
Standard Error of the mean	4.93	
95% Confidence Interval 2-Sided	-21.4 to -5.2	

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B,	90 micrograms of Tropifexor vs placebo (Parts A + B + C)

	Placebo Part C	
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline to Week 12 (Parts A+B+C) Full analysis set (FAS)
P Value	0.304	
Method	ANCOVA	
LS Mean change	-11.8	
Standard Error of the mean	3.56	
95% Confidence Interval 2-Sided	-17.6 to -5.9	

Statistical Analysis

Groups	Placebo A+B, LJN452 140 µg, Placebo Part C	140 micrograms of Tropifexor vs placebo (Parts A + B + C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Parts A + B) FAS
P Value	0.057	
Method	ANCOVA	
LS Mean change	-17.1	
Standard Error of the mean	4.45	
95% Confidence Interval 2-Sided	-24.5 to -9.8	

Statistical Analysis

Groups	Placebo A+B,	200 micrograms of Tropifexor vs placebo (Parts A + B + C)

	LNJ452 200 µg, Placebo Part C	
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Parts A + B + C) FAS
P Value	0.003	
Method	ANCOVA	
LS Mean change	-23.0	
Standard Error of the mean	4.49	
95% Confidence Interval 2-Sided	-30.5 to -15.6	

Change in Aspartate transaminase (AST)

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

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	16	37	85	46	50	51	51
Change in Aspartate transaminase (AST) (units: U/L) Mean ± Standard Deviation	-11.3 ± 12.09	-2.1 ± 29.62	-10.2 ± 25.03	-2.5 ± 24.60	-7.1 ± 23.85	-16.7 ± 23.36	-13.3 ± 20.14	-13.1 ± 29.00

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B	10 micrograms of Tropifexor vs placebo (Part A)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Full analysis set)
P Value	0.722	
Method	ANCOVA	
LS Mean change	-9.9	
Standard Error of the mean	6.56	
95% Confidence Interval 2-Sided	-22.9 to 3.0	

Statistical Analysis

Groups	LJN452 30 µg, Placebo A+B	30 micrograms of Tropifexor vs placebo (Part A)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Full analysis set)
P Value	0.468	
Method	ANCOVA	
LS Mean change	-2.2	
Standard Error of the mean	5.96	
95% Confidence Interval 2-Sided	-14.0 to 9.5	

Statistical Analysis

Groups	LJN452 60 µg, Placebo A+B	60 micrograms of Tropifexor vs placebo (Parts A+B)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B) (Full analysis set)
P Value	0.774	
Method	ANCOVA	
LS Mean change	-8.8	
Standard Error of the mean	3.97	
95% Confidence Interval 2-Sided	-16.7 to -1.0	

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B	90 micrograms of Tropifexor vs placebo (Parts A+B)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B) (Full analysis set)
P Value	0.136	
Method	ANCOVA	
LS Mean change	-0.6	
Standard Error of the mean	2.76	
95% Confidence Interval 2-Sided	-6.0 to 4.9	

Statistical Analysis

Groups	LJN452 140 µg, Placebo Part C	140 micrograms of Tropifexor vs placebo (Part C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Part C) (Full analysis set)
P Value	0.145	
Method	ANCOVA	
LS Mean change	-16.0	
Standard Error of the mean	3.97	
95% Confidence Interval 2-Sided	-23.9 to -8.2	

Statistical Analysis

Groups	LJN452 200 µg, Placebo Part C	200 micrograms of Tropifexor vs placebo (Part C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Part C) (Full analysis set)
P Value	0.236	
Method	ANCOVA	
LS Mean change	-15.3	
Standard Error of the mean	4.49	
95% Confidence Interval 2-Sided	-24.2 to -6.4	

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B, Placebo Part C	10 micrograms of Tropifexor vs placebo (Parts A+B+ C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)
P Value	0.788	
Method	ANCOVA	
LS Mean change	-7.1	
Standard Error of the mean	7.00	
95% Confidence Interval 2-Sided	-18.7 to 4.4	

Statistical Analysis

Groups	LJN452 30 µg, Placebo A+B, Placebo Part C	30 micrograms of Tropifexor vs placebo (Parts A+B+ C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)
P Value	0.413	
Method	ANCOVA	
LS Mean change	0.4	
Standard Error of the mean	6.43	
95% Confidence Interval 2-Sided	-10.2 to 11.0	

Statistical Analysis

Groups	LJN452 60 µg, Placebo A+B, Placebo Part C	60 micrograms of Tropifexor vs placebo (Parts A+B+ C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)
P Value	0.833	
Method	ANCOVA	
LS Mean change	-6.2	
Standard Error of the mean	4.38	
95% Confidence Interval 2-Sided	-13.4 to 1.0	

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B, Placebo Part C	90 micrograms of Tropifexor vs placebo (Parts A+B+ C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)
P Value	0.068	
Method	ANCOVA	
LS Mean change	2.0	
Standard Error of the mean	3.19	
95% Confidence Interval 2-Sided	-3.2 to 7.3	

Statistical Analysis

Groups	Placebo A+B, LJN452 140 µg, Placebo Part C	140 micrograms of Tropifexor vs placebo (Parts A+B+ C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)
P Value	0.269	
Method	ANCOVA	
LS Mean change	-0.1	
Standard Error of the mean	3.98	
95% Confidence Interval 2-Sided	-6.6 to 6.5	

Statistical Analysis

Groups	Placebo A+B, LJN452 200 µg, Placebo Part C	200 micrograms of Tropifexor vs placebo (Parts A+B+ C)
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)
P Value	0.777	
Method	ANCOVA	
LS Mean change	-3.8	
Standard Error of the mean	4.05	
95% Confidence Interval 2-Sided	-10.5 to 2.9	

Change from baseline in % of fat in the liver assessed using Magnetic resonance imaging (MRI)

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

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	16	37	85	46	50	51	51
Change from baseline in % of fat in the liver assessed using Magnetic resonance imaging (MRI) (units: percentage of fat in the liver) Mean ± Standard Error								
	-7.48 ± 6.174	-14.07 ± 5.661	-15.04 ± 3.754	-12.34 ± 2.482	-6.19 ± 3.381	-31.25 ± 5.228	-39.54 ± 4.968	-3.58 ± 4.718

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B	10 microgramsof Tropifexor - Change in percentage of fat in the liver Part A
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12
P Value	0.853	

Method	ANCOVA
LS Mean change	-7.48
Standard Error of the mean	6.174
95% Confidence Interval 2-Sided	-19.66 to 4.70

Statistical Analysis

Groups	LJN452 30 µg, Placebo A+B	30 micrograms of Tropifexor - Change in percentage of fat in the liver Part A
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12
P Value	0.232	
Method	ANCOVA	
LS Mean change	-14.07	
Standard Error of the mean	5.661	
95% Confidence Interval 2-Sided	-25.24 to -2.91	

Statistical Analysis

Groups	LJN452 60 µg, Placebo A+B	60 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12

P Value	0.077
Method	ANCOVA
LS Mean change	-15.04
Standard Error of the mean	3.754
95% Confidence Interval 2-Sided	-22.45 to -7.64

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B	90 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline

P Value	0.141
Method	ANCOVA
LS Mean change	-12.34
Standard Error of the mean	2.482
95% Confidence Interval 2-Sided	-17.23 to -7.44

Statistical Analysis

Groups	LJN452 140 µg, Placebo Part C	140 micrograms of Tropifexor - Change in percentage of fat in the liver Part C
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12

P Value	<0.001
Method	ANCOVA
LS Mean change	-31.25
Standard Error of the mean	5.228
95% Confidence Interval 2-Sided	-41.58 to -20.92

Statistical Analysis

Groups	LJN452 200 µg, Placebo Part C	200 micrograms of Tropifexor - Change in percentage of fat in the liver Part C
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)
P Value	<0.001	
Method	ANCOVA	
LS Mean change	-39.54	
Standard Error of the mean	4.968	
95 % Confidence Interval 2-Sided	-49.37 to -29.71	

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B, Placebo Part C	10 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C

Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)
P Value	0.872	
Method	ANCOVA	
LS Mean change	-8.09	
Standard Error of the mean	6.650	
95% Confidence Interval 2-Sided	-19.06 to 2.88	

Statistical Analysis

Groups	LJN452 30 µg, Placebo A+B, Placebo Part C	30 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)
P Value	0.465	
Method	ANCOVA	
LS Mean change	-14.14	
Standard Error of the mean	6.198	
95% Confidence Interval 2-Sided	-24.36 to -3.91	

Statistical Analysis

Groups	LJN452 60 µg,	60 micrograms of Tropifexor - Change in percentage of fat in the liver

	Placebo A+B, Placebo Part C	Parts A+B+C
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)
P Value	0.228	
Method	ANCOVA	
LS Mean change	-15.02	
Standard Error of the mean	4.078	
95% Confidence Interval 2-Sided	-21.75 to -8.29	

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B, Placebo Part C	90 micrograms - Change in percentage of fat in the liver Parts A+B+C
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)
P Value	0.370	
Method	ANCOVA	
LS Mean change	-12.56	
Standard Error of the mean	2.717	
95% Confidence Interval 2-Sided	-17.04 to -8.08	

Statistical Analysis

Groups	Placebo A+B, LJN452 140 µg, Placebo Part C	140 micrograms - Change in percentage of fat in the liver Parts A+B+C
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)
P Value	0.029	
Method	ANCOVA	
LS Mean change	-18.71	
Standard Error of the mean	3.517	
95% Confidence Interval 2-Sided	-24.51 to -12.91	

Statistical Analysis

Groups	Placebo A+B, LJN452 200 µg, Placebo Part C	200 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C
Non-Inferiority/Equivalence Test	Superiority	ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)
P Value	<0.001	
Method	ANCOVA	
LS Mean change	-34.38	
Standard Error of the mean	3.482	
95% Confidence Interval 2-Sided	-40.13 to -28.64	

Secondary Outcome Results

Change from baseline in weight

(Time Frame: 48 weeks)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A) vs placebo	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	16	36	84	46	50	51	51
Change from baseline in weight (units: kg) Mean ± Standard Error								
	-1.79 ± 0.608	-0.78 ± 0.567	-1.05 ± 0.377	-1.15 ± 0.253	0.00 ± 0.338	-5.10 ± 0.988	-5.89 ± 1.002	-2.48 ± 0.915

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B	10 micrograms of Tropifexor (Part A) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)
P Value	0.010	
Method	Mixed Models Analysis	
LS Mean change	-1.79	
Standard Error of the mean	0.608	
95% Confidence Interval 2-Sided	-2.99 to 0.59	

Groups	LJN452 30 µg, Placebo A+B	30 micrograms of Tropifexor (Part A) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)
P Value	0.237	
Method	Mixed Models Analysis	
LS Mean change	-0.78	
Standard Error of the mean	0.567	
95% Confidence Interval 2-Sided	-1.90 to 0.34	

Statistical Analysis

Groups	LJN452 60 µg, Placebo A+B	60 micrograms of Tropifexor (Parts A + B) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)
P Value	0.037	
Method	Mixed Models Analysis	
LS Mean change	-1.05	
Standard Error of the mean	0.377	
95% Confidence Interval	-1.80 to 0.31	

2-Sided

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B	90 micrograms of Tropifexor (Parts A + B) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)
P Value	0.007	
Method	Mixed Models Analysis	
LS Mean change	-1.15	
Standard Error of the mean	0.253	
95% Confidence Interval 2-Sided	-1.65 to 0.65	

Statistical Analysis

Groups	LJN452 140 µg, Placebo Part C	140 micrograms of Tropifexor (Part C) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in weight from baseline to EOT (Parts C) (Full analysis set)
P Value	0.053	
Method	Mixed Models Analysis	
LS Mean change	-5.10	
Standard Error of the mean	0.988	

95% Confidence Interval 2-Sided	-7.05 to -3.14

Statistical Analysis

Groups	LJN452 200 µg, Placebo Part C	200 micrograms of Tropifexor (Part C) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in weight from baseline to EOT (Parts C) (Full analysis set)
P Value	0.013	
Method	Mixed Models Analysis	
LS Mean change	-5.89	
Standard Error of the mean	1.002	
95% Confidence Interval 2-Sided	-7.87 to -3.91	

Change in body mass index (BMI)

(Time Frame: 12 weeks)

	LJN452 10 µg	**LJN452 30 µg**	**LJN452 60 µg**	**LJN452 90 µg**	**Placebo A+B**	**LJN452 140 µg**	**LJN452 200 µg**	**Placebo Part C**
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	16	37	84	46	50	51	51
Change in body mass index (BMI) (units: kg/m2)								

Mean ± Standard Error								
	-0.64 ± 0.208	-0.29 ± 0.194	-0.35 ± 0.129	-0.42 ± 0.087	0.02 ± 0.116	-1.88 ± 0.322	-2.11 ± 0.327	-0.80 ± 0.299

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B	10 micrograms of Tropifexor (Part A) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)
P Value	0.006	
Method	Mixed Models Analysis	
LS Mean change	-0.64	
Standard Error of the mean	0.208	
95% Confidence Interval 2-Sided	-1.05 to 0.23	

Statistical Analysis

Groups	LJN452 30 µg, Placebo A+B	30 micrograms of Tropifexor (Part A) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)
P Value	0.177	
Method	Mixed Models Analysis	
LS Mean change	-0.29	
Standard Error of the mean	0.194	
95% Confidence Interval	-0.67 to 0.09	

2-Sided

Statistical Analysis

Groups	LJN452 60 µg, Placebo A+B	60 micrograms of Tropifexor (Parts A + B) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in BMI from baseline to EOT (Parts C) (Full analysis set)
P Value	0.032	
Method	Mixed Models Analysis	
LS Mean change	-0.35	
Standard Error of the mean	0.129	
95% Confidence Interval 2-Sided	-0.61 to 0.10	

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B	90 micrograms of Tropifexor (Parts A + B) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)
P Value	0.003	
Method	Mixed Models Analysis	
LS Mean change	-0.42	
Standard Error of the mean	0.087	
95% Confidence Interval	-0.59 to 0.25	

2-Sided

Statistical Analysis

Groups	LJN452 140 µg, Placebo Part C	140 micrograms of Tropifexor (Part C) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)
P Value	0.015	
Method	Mixed Models Analysis	
LS Mean change	-1.88	
Standard Error of the mean	0.322	
95% Confidence Interval 2-Sided	-2.51 to -1.24	

Statistical Analysis

Groups	LJN452 200 µg, Placebo Part C	200 micrograms of Tropifexor (Part C) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in BMI from baseline to EOT (Parts C) (Full analysis set)
P Value	0.004	
Method	Mixed Models Analysis	
LS Mean change	-2.11	
Standard Error of the mean	0.327	
95% Confidence Interval 2-Sided	-2.75 to -1.46	

Change from baseline in waist to hip (WTH) ratio

(Time Frame: 12 weeks)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	13	15	37	84	46	49	37	51
Change from baseline in waist to hip (WTH) ratio (units: ratio) Mean ± Standard Error	-0.01 ± 0.009	0.00 ± 0.008	-0.01 ± 0.005	0.00 ± 0.004	0.00 ± 0.005	0.00 ± 0.008	-0.01 ± 0.007	-0.02 ± 0.007

Statistical Analysis

Groups	LJN452 10 µg, Placebo A+B	10 micrograms of Tropifexor (Part A) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)
P Value	0.530	
Method	Mixed Models Analysis	
LS Mean change	-0.01	
Standard Error of the mean	0.009	

95% Confidence Interval 2-Sided	-0.03 to 0.01

Statistical Analysis

Groups	LJN452 30 µg, Placebo A+B	30 micrograms of Tropifexor (Part A) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)
P Value	0.857	
Method	Mixed Models Analysis	
LS Mean change	0.00	
Standard Error of the mean	0.008	
95% Confidence Interval 2-Sided	-0.02 to 0.01	

Statistical Analysis

Groups	LJN452 60 µg, Placebo A+B	60 micrograms of Tropifexor (Part A) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)
P Value	0.262	
Method	Mixed Models Analysis	
LS Mean change	-0.01	
Standard Error of the mean	0.005	

95% Confidence Interval 2-Sided	-0.02 to 0.00

Statistical Analysis

Groups	LJN452 90 µg, Placebo A+B	90 micrograms of Tropifexor (Parts A + B) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)
P Value	0.323	
Method	Mixed Models Analysis	
LS Mean change	0.00	
Standard Error of the mean	0.004	
95% Confidence Interval 2-Sided	0.00 to 0.01	

Statistical Analysis

Groups	LJN452 140 µg, Placebo Part C	140 micrograms of Tropifexor (Part C) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in WTH ratio from baseline to EOT (Part C) (Full analysis set)
P Value	0.100	
Method	Mixed Models Analysis	
LS Mean change	0.01	
Standard Error of the mean	0.008	
95% Confidence Interval 2-Sided	-0.02 to 0.01	

Statistical Analysis

Groups	LJN452 200 µg, Placebo Part C	200 micrograms of Tropifexor (Part C) vs Placebo
Non-Inferiority/Equivalence Test	Superiority	Repeated measures analysis: Change in WTH ratio from baseline to EOT (Part C) (Full analysis set)
P Value	0.693	
Method	Mixed Models Analysis	
LS Mean change	-0.01	
Standard Error of the mean	0.007	
95% Confidence Interval 2-Sided	-0.03 to 0.00	

Change from baseline in biomarker FGF19

(Time Frame: baseline, week 6)

	LJN452 10 µg	**LJN452 30 µg**	**LJN452 60 µg**	**LJN452 90 µg**	**Placebo A+B**	**LJN452 140 µg**	**LJN452 200 µg**	**Placebo Part C**
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	15	34	78	42	47	42	42
Change from baseline in biomarker FGF19 (units: pg/mL) Geometric Least Squares Mean (95% Confidence								

Interval)								
	1.45 (0.93 to 2.26)	1.53 (1.00 to 2.35)	3.82 (2.88 to 5.09)	5.78 (4.78 to 6.98)	1.33 (1.03 to 1.73)	1.97 (1.48 to 2.62)	2.23 (1.65 to 3.01)	1.22 (0.92 to 1.61)

Change from baseline in biomarker C4

(Time Frame: Week 6, 4 hours post dose)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	15	37	85	46	47	42	51
Change from baseline in biomarker C4 (units: ng/mL) Mean ± Standard Deviation								
	38.82 ± 25.765	32.75 ± 23.360	28.38 ± 13.394	40.19 ± 31.356	47.70 ± 25.524	14.97 ± 20.232	8.54 ± 9.583	38.40 ± 24.552

Change from baseline on markers of liver fibrosis, Fibroscan

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

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo (Part C)
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)

Number of Participants Analyzed [units: participants]	14	16	37	85	46	46	42	51
Change from baseline on markers of liver fibrosis, Fibroscan (units: scores) Mean ± Standard Deviation								
	10.94 ± 5.314	10.40 ± 7.663	9.90 ± 4.095	9.00 ± 4.152	9.30 ± 4.676	11.29 ± 3.677	12.03 ± 4.804	11.26 ± 4.027

Change from baseline on markers of liver fibrosis panel (ELF) score

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

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Parts A + B)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C) vs placebo	200 micrograms of Tropifexor (Part C)	(Part C)
Number of Participants Analyzed [units: participants]	14	16	34	78	46	47	42	51
Change from baseline on markers of liver fibrosis panel (ELF) score (units: scores on a scale) Least Squares Mean ± Standard Error								
	0.05 ± 0.158	0.00 ± 0.146	-0.19 ± 0.097	0.20 ± 0.064	0.08 ± 0.087	-0.34 ± 0.132	-0.24 ± 0.122	-0.08 ± 0.115

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

(Time Frame: End of Treatment (EoT):12 weeks)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo (A+B)
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)
Number of Participants Analyzed [units: participants]	14	16	37	85	46
Change from baseline on markers of liver fibrosis, Fibrotest (Parts A+B) (units: scores) Mean ± Standard Deviation					
	-0.23 ± 0.284	-1.49 ± 0.852	-1.44 ± 1.080	-1.34 ± 1.222	-1.23 ± 1.088

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

(Time Frame: End of Treatment (EoT) was 48 weeks)

	LJN452 140 µg	LJN452 200 µg	Placebo
Arm/Group Description	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo
Number of Participants Analyzed [units: participants]	34	28	37
Change from baseline on markers of liver fibrosis, Fibrotest, (Part C)			

(units: scores) Least Squares Mean ± Standard Error			
	-0.42 ± 0.131	-0.44 ± 0.135	-0.17 ± 0.119

Change from baseline on gamma-glutamyl transferase (GGT)

(Time Frame: EoT for Parts A+B=12 weeks; EoT for Part C = 48 weeks)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	15	37	84	78	51	42	36
Change from baseline on gamma-glutamyl transferase (GGT) (units: IU/L) Least Squares Mean ± Standard Error								
	1.6 ± 10.93	-29.9 ± 10.11	-34.2 ± 6.70	-45.7 ± 4.52	-5.0 ± 6.10	-35.2 ± 11.58	-29.9 ± 11.65	9.0 ± 10.72

Change from baseline on fasting lipid profile

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

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	Placebo (Parts A+B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)

Number of Participants Analyzed [units: participants]	14	16	37	50	46	46	42	37
Change from baseline on fasting lipid profile (units: mmol/L) Geometric Least Squares Mean (95% Confidence Interval)								
Cholesterol	0.949 (0.888 to 1.014)	1.003 (0.945 to 1.065)	1.029 (0.989 to 1.070)	1.029 (1.002 to 1.057)	0.956 (0.923 to 0.991)	1.032 (0.975 to 1.093)	1.071 (1.012 to 1.133)	0.977 (0.928 to 1.029)
Triglycerides	0.920 (0.766 to 1.091)	0.919 (0.789 to 1.071)	0.960 (0.868 to 1.062)	1.048 (0.978 to 1.123)	0.991 (0.904 to 1.085)	1.070 (0.934 to 1.226)	1.068 (0.936 to 1.219)	0.883 (0.782 to 0.998)
LDL Cholesterol	0.923 (0.834 to 1.020)	1.044 (0.953 to 1.142)	1.092 (1.029 to 1.159)	1.104 (1.060 to 1.150)	0.943 (0.893 to 0.995)	1.056 (0.972 to 1.147)	1.200 (1.106 to 1.302)	0.973 (0.903 to 1.049)
HDL Cholesterol	1.019 (0.946 to 1.096)	1.001 (0.937 to 1.069)	0.961 (0.920 to 1.004)	0.897 (0.870 to 0.924)	0.959 (0.922 to 0.998)	0.855 (0.800 to 0.913)	0.824 (0.772 to 0.879)	1.033 (0.973 to 1.096)
LDL/HDL Ratio	0.921 (0.810 to 1.047)	1.058 (0.942 to 1.188)	1.139 (1.055 to 1.229)	1.227 (1.165 to 1.293)	0.980 (0.915 to 1.051)	1.252 (1.128 to 1.390)	1.478 (1.332 to 1.639)	0.947 (0.862 to 1.041)
Free Glycerol	1.0563 (0.8722 to 1.2793)	0.9376 (0.7859 to 1.1185)	0.9128 (0.8112 to 1.0272)	0.9915 (0.9151 to 1.0743)	0.9604 (0.8641 to 1.0674)	1.1115 (0.9721 to 1.2709)	0.9808 (0.8571 to 1.1223)	0.9846 (0.8722 to 1.11116)
Free Fatty Acid	1.082 (0.897 to 1.305)	0.864 (0.726 to 1.028)	0.929 (0.827 to 1.043)	0.947 (0.874 to 1.025)	0.936 (0.844 to 1.038)	1.072 (0.951 to 1.208)	0.887 (0.785 to 1.002)	0.977 (0.928 to 1.029)

Itch based on a visual analog scale (VAS) rating scale

(Time Frame: EoT for Parts A+B=12 weeks; EoT for Part C = 48 weeks)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	Placebo A+B	LJN452 140 µg	LJN452 200 µg	Placebo Part C
Arm/Group Description	10 micrograms of Tropifexor (Part A)	30 micrograms of Tropifexor (Part A) vs placebo	60 micrograms of Tropifexor (Parts A + B) vs placebo	90 micrograms of Tropifexor (Parts A + B)	Placebo for parts A + B	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Part C)
Number of Participants Analyzed [units: participants]	14	16	36	78	39	47	42	37
Itch based on a visual analog scale (VAS) rating scale (units: scores) Least Squares Mean ± Standard Error								
	-0.3 ± 0.48	0.2 ± 0.43	0.4 ± 0.28	0.1 ± 0.19	0.6 ± 0.27	0.6 ± 0.37	1.1 ± 0.35	0.3 ± 0.33

Pre-dose Trough Concentration (C_{trough}) of LJN452

(Time Frame: In Parts A and B, LJN452 Ctrough was measured on Study Days 7, 14, 28, 42, 56, and 84. In Part C LJN452 C_{trough} was measured on Study Days 42, 84, 168, 280 and 336)

	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg	LJN452 140 µg	LJN452 200 µg
Arm/Group Description	10 micrograms of Tropifexor (Parts A + B)	30 micrograms of Tropifexor (Parts A + B)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)
Number of Participants Analyzed [units: participants]	14	16	37	85	37	51
Pre-dose Trough Concentration (Ctrough) of LJN452 (units: ng/mL)						

Mean ± Standard Deviation						
Profile day 7	0.142 ± 0.119	0.355 ± 0.194	0.638 ± 0.453	1.215 ± 0.593		
Profile day 14	0.216 ± 0.127	0.505 ± 0.328	0.626 ± 0.281	1.115 ± 0.693		
Profile day 28	0.118 ± 0.087	0.411 ± 0.250	0.639 ± 0.265	1.027 ± 0.700		
Profile day 42	0.161 ± 0.094	0.382 ± 0.150	0.647 ± 0.344	1.032 ± 0.661	2.821 ± 1.659	3.533 ± 2.356
Profile day 56	0.168 ± 0.088	0.474 ± 0.273	0.637 ± 0.278	1.041 ± 0.701		
Profile day 84	0.118 ± 0.080	0.366 ± 0.147	0.530 ± 0.357	1.095 ± 0.653	1.685 ± 0.874	2.286 ± 1.259
Profile day 168					1.889 ± 1.340	2.146 ± 1.383
Profile day 280					2.129 ± 1.257	1.990 ± 1.053
Profile day 336					1.444 ± 1.077	1.979 ± 1.153

C2h (steady-state drug levels 2 hours postdose) of LJN452

(Time Frame: Days 7 and 14 (10 and 30µg LJN452 C2h was not measured day 14))

	LJN452 10 µg	**LJN452 30 µg**	**LJN452 60 µg**	**LJN452 90 µg**
Arm/Group Description	10 micrograms of Tropifexor (Parts A + B)	30 micrograms of Tropifexor (Parts A + B)	60 micrograms of Tropifexor (Parts A + B)	90 micrograms of Tropifexor (Parts A + B)
Number of Participants Analyzed [units: participants]	14	16	37	85
C2h (steady-state drug levels 2 hours postdose) of LJN452 (units: ng/mL) Mean ± Standard Deviation				
Profile day 7	0.190 ± 0.143	0.702 ± 0.399	1.228 ± 0.598	2.193 ± 1.003
Profile day 14			1.344 ± 0.727	2.001 ± 1.053

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

(Time Frame: EoT (Week 48))

	LJN452 140 µg	LNJ452 200 µg	Placebo A+B
Arm/Group Description	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo A+B
Number of Participants Analyzed [units: participants]	39	35	42
Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (Part C) - total score (units: participants) Count of Participants			
	11 (28.21%)	11 (31.43%)	12 (28.57%)

Statistical Analysis

Groups	LJN452 140 µg, Placebo A+B	At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (total score)
P Value	1.0000	
Method	Mixed Models Analysis	
Risk Difference (RD)	0.004	
95% Confidence Interval 2-Sided	-0.214 to 0.223	

Statistical Analysis

Groups	LNJ452 200 µg, Placebo A+B	At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (total score)
P Value	0.8074	
Method	Mixed Models Analysis	
Risk Difference (RD)	0.029	
95% Confidence Interval 2-Sided	-0.196 to 0.251	

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

(Time Frame: EoT (Week 48))

	LJN452 140 µg	LNJ452 200 µg	Placebo A+B
Arm/Group Description	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo A+B
Number of Participants Analyzed [units: participants]	38	35	42
Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening - FDA (units: participants) Count of Participants			
	11 (28.95%)	11 (31.43%)	11 (26.19%)

Statistical Analysis

Groups	LJN452 140 µg, Placebo A+B	At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (FDA)
P Value	0.8070	
Method	Mixed Models Analysis	
Risk Difference (RD)	0.028	
95% Confidence Interval 2-Sided	-0.191 to 0.246	

Statistical Analysis

Groups	LNJ452 200 µg, Placebo A+B	At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (FDA)
P Value	0.6233	
Method	Mixed Models Analysis	
Risk Difference (RD)	0.052	
95% Confidence Interval 2-Sided	-0.173 to 0.273	

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

(Time Frame: EoT (Week 48))

	LJN452 140 µg	LNJ452 200 µg	Placebo A+B

Arm/Group Description	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo (Parts A+B)
Number of Participants Analyzed [units: participants]	38	35	42
Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening - EMA (units: participants) Count of Participants			
	11 (28.95%)	11 (31.43%)	12 (28.57%)

Statistical Analysis

Groups	LJN452 140 µg, Placebo A+B	At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (EMA)
P Value	1.0000	
Method	Mixed Models Analysis	
Risk Difference (RD)	0.004	
95 % Confidence Interval 2-Sided	-0.214 to 0.233	

Statistical Analysis

Groups	LNJ452 200 µg, Placebo A+B	At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (EMA)

P Value	0.8074
Method	Mixed Models Analysis
Risk Difference (RD)	0.029
95% Confidence Interval 2-Sided	-0.196 to 0.251

Biopsy-based response at Week 48 compared to baseline: Difference between treatment groups (Part C) - Resolution of steatohepatitis (diagnostic category)

(Time Frame: EoT (Week 48))

	LJN452 140 µg	LNJ452 200 µg	Placebo A+B
Arm/Group Description	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo A+B
Number of Participants Analyzed [units: participants]	38	35	42
Biopsy-based response at Week 48 compared to baseline: Difference between treatment groups (Part C) - Resolution of steatohepatitis (diagnostic category) (units: participants) Count of Participants			
	4 (10.53%)	7 (20%)	3 (7.14%)

Statistical Analysis

Groups	LJN452 140 µg,	Resolution of steatohepatitis (diagnostic category) without

	Placebo A+B	worsening of fibrosis (NASH CRN staging)
P Value	0.7028	
Method	Mixed Models Analysis	
Risk Difference (RD)	0.034	
95% Confidence Interval 2-Sided	-0.184 to 0.252	

Statistical Analysis

Groups	LNJ452 200 µg, Placebo A+B	Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging)
P Value	0.1713	
Method	Mixed Models Analysis	
Risk Difference (RD)	0.129	
95% Confidence Interval 2-Sided	-0.098 to 0.345	

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

(Time Frame: EoT (Week 48))

	LJN452 140 µg	**LNJ452 200 µg**	**Placebo A+B**
Arm/Group Description	140 micrograms of Tropifexor (Part C)	200 micrograms of Tropifexor (Part C)	Placebo A+B
Number of Participants Analyzed [units: participants]	38	35	42
Biopsy-based response at Week 48 compared to baseline: Difference between treatment groups (Part C) - Resolution of steatohepatitis (FDA, EMA)			

(units: participants)
Count of Participants

	0 (%)	2 (5.71%)	0 (%)

Statistical Analysis

Groups	LNJ452 200 µg, Placebo A+B	Resolution of steatohepatitis (FDA, EMA) without worsening of fibrosis (NASH CRN staging)
P Value	0.2033	
Method	Mixed Models Analysis	
Risk Difference (RD)	0.057	
95% Confidence Interval 2-Sided	-0.168 to 0.278	

Safety Results

All-Cause Mortality

	LJN452 10 µg N = 13	LJN452 30 µg N = 17	LJN452 60 µg N = 37	LJN452 90 µg N = 85	LJN452 140 µg N = 50	LJN452 200 µg N = 51	Placebo A+B+C N = 97	Total N = 350
Arm/Group Description	LJN452 10 mcg (Part A)	30 micrograms of Tropifexor (Part A)	LJN452 60 mcg (Parts A+B)	90 micrograms of Tropifexor (Parts A + B)	LJN452 140 mcg (Part C)	LJN452 200 mcg (Part C)	Placebo A+B	Total
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	To End of Treatment (EoT): For Parts A&B, EoT was Week 12; For Part C, EoT was Week 48
Additional Description	AEs are any untoward sign or symptom that occurred during the study treatment period 350 patients were randomized. One patient was treated at 2 sites, so 351 enrolled may appearr in some places.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

	LJN452 10 µg N = 13	**LJN452 30 µg N = 17**	**LJN452 60 µg N = 37**	**LJN452 90 µg N = 85**	**LJN452 140 µg N = 50**	**LJN452 200 µg N = 51**	**Placebo A+B+C N = 97**	**Total N = 350**
Arm/Group Description	LJN452 10 mcg (Part A)	30 micrograms of Tropifexor (Part A)	LJN452 60 mcg (Parts A+B)	90 micrograms of Tropifexor (Parts A + B)	LJN452 140 mcg (Part C)	LJN452 200 mcg (Part C)	Placebo A+B	Total
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.71%)	5 (10.00%)	3 (5.88%)	6 (6.19%)	18 (5.14%)
Cardiac disorders								
Angina pectoris	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (1.96%)	0 (0.00%)	2 (0.57%)
Tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Gastrointestinal disorders								
Haematochezia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
General disorders and administration site conditions								
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Hepatobiliary disorders								

Cholecystitis acute	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	1 (0.29%)
Infections and infestations								
Gastroenteritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	1 (0.29%)
Injury, poisoning and procedural complications								
Animal bite	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Multiple injuries	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	1 (0.29%)
Investigations								
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Metabolism and nutrition disorders								
Hyperglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.96%)	0 (0.00%)	1 (0.29%)
Musculoskeletal and connective tissue disorders								
Arthralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Synovial cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Trigger finger	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Malignant melanoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	1 (0.29%)
Nervous system disorders								
Transient ischaemic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	1 (0.29%)

attack								
Product issues								
Device dislocation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	1 (0.29%)
Renal and urinary disorders								
Nephrolithiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.96%)	0 (0.00%)	1 (0.29%)
Renal impairment	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Reproductive system and breast disorders								
Endometrial thickening	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Respiratory, thoracic and mediastinal disorders								
Haemothorax	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	1 (0.29%)

Other Adverse Events by System Organ Class

Time Frame	To End of Treatment (EoT): For Parts A&B, EoT was Week 12; For Part C, EoT was Week 48
Additional Description	AEs are any untoward sign or symptom that occurred during the study treatment period 350 patients were randomized. One patient was treated at 2 sites, so 351 enrolled may appearr in some places.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LJN452 10 µg N = 13	**LJN452 30 µg N = 17**	**LJN452 60 µg N = 37**	**LJN452 90 µg N = 85**	**LJN452 140 µg N = 50**	**LJN452 200 µg N = 51**	**Placebo A+B+C N = 97**	**Total N = 350**

Arm/Group Description	LJN452 10 mcg (Part A)	30 micrograms of Tropifexor (Part A)	LJN452 60 mcg (Parts A+B)	90 micrograms of Tropifexor (Parts A + B)	LJN452 140 mcg (Part C)	LJN452 200 mcg (Part C)	Placebo A+B	Total
Total participants affected	5 (38.46%)	11 (64.71%)	16 (43.24%)	50 (58.82%)	43 (86.00%)	45 (88.24%)	63 (64.95%)	233 (66.57%)
Blood and lymphatic system disorders								
Anaemia	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	1 (1.03%)	3 (0.86%)
Gastrointestinal disorders								
Abdominal distension	0 (0.00%)	0 (0.00%)	1 (2.70%)	3 (3.53%)	5 (10.00%)	2 (3.92%)	4 (4.12%)	15 (4.29%)
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	2 (4.00%)	3 (5.88%)	8 (8.25%)	14 (4.00%)
Abdominal pain lower	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	2 (0.57%)
Abdominal pain upper	0 (0.00%)	2 (11.76%)	0 (0.00%)	2 (2.35%)	6 (12.00%)	2 (3.92%)	3 (3.09%)	15 (4.29%)
Constipation	0 (0.00%)	1 (5.88%)	1 (2.70%)	2 (2.35%)	3 (6.00%)	3 (5.88%)	5 (5.15%)	15 (4.29%)
Diarrhoea	0 (0.00%)	1 (5.88%)	1 (2.70%)	4 (4.71%)	3 (6.00%)	7 (13.73%)	6 (6.19%)	22 (6.29%)
Dry mouth	0 (0.00%)	1 (5.88%)	1 (2.70%)	2 (2.35%)	0 (0.00%)	2 (3.92%)	2 (2.06%)	8 (2.29%)
Dyspepsia	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (4.71%)	2 (4.00%)	3 (5.88%)	4 (4.12%)	13 (3.71%)
Flatulence	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	5 (10.00%)	2 (3.92%)	2 (2.06%)	10 (2.86%)
Gastrooesophageal reflux disease	0 (0.00%)	1 (5.88%)	0 (0.00%)	1 (1.18%)	2 (4.00%)	2 (3.92%)	1 (1.03%)	7 (2.00%)
Nausea	0 (0.00%)	0 (0.00%)	1 (2.70%)	4 (4.71%)	6 (12.00%)	10 (19.61%)	11 (11.34%)	32 (9.14%)
Vomiting	0 (0.00%)	2 (11.76%)	0 (0.00%)	3 (3.53%)	3 (6.00%)	4 (7.84%)	2 (2.06%)	14 (4.00%)
General disorders and administration site conditions								
Fatigue	0 (0.00%)	3 (17.65%)	1 (2.70%)	5 (5.88%)	7 (14.00%)	3 (5.88%)	9 (9.28%)	28 (8.00%)
Pyrexia	1 (7.69%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	2 (4.00%)	1 (1.96%)	1 (1.03%)	6 (1.71%)

Infections and infestations								
Body tinea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	0 (0.00%)	0 (0.00%)	3 (0.86%)
Bronchitis	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	0 (0.00%)	6 (6.19%)	10 (2.86%)
Influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	9 (10.59%)	1 (2.00%)	3 (5.88%)	4 (4.12%)	17 (4.86%)
Laryngitis	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	2 (5.41%)	6 (7.06%)	6 (12.00%)	5 (9.80%)	10 (10.31%)	29 (8.29%)
Periodontitis	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	2 (0.57%)
Rhinitis	0 (0.00%)	1 (5.88%)	0 (0.00%)	3 (3.53%)	0 (0.00%)	0 (0.00%)	1 (1.03%)	5 (1.43%)
Sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	3 (6.00%)	0 (0.00%)	7 (7.22%)	11 (3.14%)
Tonsillitis	1 (7.69%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.57%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	2 (5.41%)	8 (9.41%)	9 (18.00%)	3 (5.88%)	10 (10.31%)	32 (9.14%)
Urinary tract infection	1 (7.69%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	9 (18.00%)	0 (0.00%)	3 (3.09%)	14 (4.00%)
Viral sinusitis	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Injury, poisoning and procedural complications								
Contusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	0 (0.00%)	2 (2.06%)	5 (1.43%)
Investigations								
Alanine aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (3.53%)	1 (2.00%)	3 (5.88%)	3 (3.09%)	10 (2.86%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.35%)	4 (8.00%)	4 (7.84%)	2 (2.06%)	12 (3.43%)
Blood alkaline phosphatase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	5 (9.80%)	0 (0.00%)	6 (1.71%)

Blood creatinine increased	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.96%)	0 (0.00%)	2 (0.57%)
Platelet count decreased	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Metabolism and nutrition disorders								
Decreased appetite	0 (0.00%)	2 (11.76%)	1 (2.70%)	2 (2.35%)	1 (2.00%)	2 (3.92%)	1 (1.03%)	9 (2.57%)
Diabetes mellitus	1 (7.69%)	0 (0.00%)	0 (0.00%)	2 (2.35%)	2 (4.00%)	1 (1.96%)	1 (1.03%)	7 (2.00%)
Type 2 diabetes mellitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.35%)	2 (4.00%)	3 (5.88%)	2 (2.06%)	9 (2.57%)
Musculoskeletal and connective tissue disorders								
Arthralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.18%)	3 (6.00%)	1 (1.96%)	3 (3.09%)	8 (2.29%)
Back pain	0 (0.00%)	1 (5.88%)	0 (0.00%)	3 (3.53%)	1 (2.00%)	2 (3.92%)	7 (7.22%)	14 (4.00%)
Musculoskeletal pain	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	1 (1.03%)	3 (0.86%)
Nervous system disorders								
Headache	1 (7.69%)	1 (5.88%)	1 (2.70%)	4 (4.71%)	3 (6.00%)	3 (5.88%)	6 (6.19%)	19 (5.43%)
Poor quality sleep	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Psychiatric disorders								
Anxiety	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	0 (0.00%)	0 (0.00%)	2 (0.57%)
Insomnia	0 (0.00%)	1 (5.88%)	1 (2.70%)	0 (0.00%)	4 (8.00%)	3 (5.88%)	2 (2.06%)	11 (3.14%)
Loss of libido	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Renal and urinary disorders								
Haematuria	1 (7.69%)	1 (5.88%)	1 (2.70%)	0 (0.00%)	0 (0.00%)	2 (3.92%)	1 (1.03%)	6 (1.71%)
Proteinuria	1 (7.69%)	1 (5.88%)	0 (0.00%)	1 (1.18%)	1 (2.00%)	3 (5.88%)	0 (0.00%)	7 (2.00%)

Respiratory, thoracic and mediastinal disorders								
Oropharyngeal pain	1 (7.69%)	3 (17.65%)	1 (2.70%)	3 (3.53%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	8 (2.29%)
Skin and subcutaneous tissue disorders								
Hyperhidrosis	0 (0.00%)	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Neurodermatitis	1 (7.69%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.29%)
Pruritus	0 (0.00%)	0 (0.00%)	5 (13.51%)	7 (8.24%)	26 (52.00%)	35 (68.63%)	15 (15.46%)	88 (25.14%)
Rash	0 (0.00%)	0 (0.00%)	1 (2.70%)	2 (2.35%)	5 (10.00%)	3 (5.88%)	4 (4.12%)	15 (4.29%)
Rash pruritic	0 (0.00%)	0 (0.00%)	2 (5.41%)	0 (0.00%)	2 (4.00%)	0 (0.00%)	0 (0.00%)	4 (1.14%)

Conclusion

- A dose response relationship of tropifexor on decrease in ALT and liver fat was evident in all three study parts (A, B, and C) combined. No dose response relationship of tropifexor on decrease in AST was evident.
- Decreases in weight and BMI from baseline to EOT were greater with tropifexor when compared to placebo in all three study parts.
- Decreases in GGT from baseline to EOT were greater with tropifexor when compared to placebo in all three study parts.
- Proportion of subjects with at least one or two point improvement in fibrosis without worsening of NASH or resolution of steatohepatitis, without worsening of fibrosis was not significantly different between tropifexor (140 µg or 200 µg) groups and placebo group.

- Overall, no safety signals emerged in this study. The incidence and nature of SAEs did not indicate significant or dose dependent concerns.

- Consistent with the known class effects of FXR agonists, pruritus and dyslipidemia were reported with tropifexor and both are considered detectable and manageable. Pruritus was the most frequently reported AE; incidence and severity increased with dose, but most subjects were able to continue on treatment.

- Dyslipidemia was also dose dependent, but did not lead to study drug discontinuation

Date of Clinical Trial Report

5 March 2021