



Clinical trial results:

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

Summary

EudraCT number	2015-005215-33
Trial protocol	SK IT DE NL BE AT ES
Global end of trial date	06 April 2020

Results information

Result version number	v1 (current)
This version publication date	28 April 2021
First version publication date	28 April 2021

Trial information

Trial identification

Sponsor protocol code	CLJN452A2202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02855164
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma AG, 1 8627788300, novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	India: 2
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Singapore: 13
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Taiwan: 26
Country: Number of subjects enrolled	United States: 168

Country: Number of subjects enrolled	Argentina: 11
Worldwide total number of subjects	350
EEA total number of subjects	66

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	298
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 411 subjects were screened in Parts A and B of the study together. Of these, 198 subjects were deemed eligible to participate in the study and were subsequently randomized

Pre-assignment

Screening details:

In Part A, 77 were randomized at baseline; 121 in Part B; and 780 were screened in Part C. Of these 152 met eligibility criteria and were randomized in nearly to receive tropifexor 140 µg (n=50) or 200 µg (n=51) or placebo (n=51)

Period 1

Period 1 title	Parts A + B (Randomized Set)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This was a double-blind study. Subjects, investigator staff, persons performing the assessments, and Novartis clinical trial team and CRO associates involved with continued direct study site conduct (or delegates), remained blinded to the identity of study treatments from the time of randomization (until final database lock)

Arms

Are arms mutually exclusive?	Yes
Arm title	LJN452 10 µg

Arm description:

10 micrograms of Tropifexor (Part A)

Arm type	Experimental
Investigational medicinal product name	Tropifexor
Investigational medicinal product code	
Other name	LJN452
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 microgram tropifexor tablet

Arm title	LJN452 30 µg
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Arm description:

30 micrograms of Tropifexor (Part A)

Arm type	Experimental
Investigational medicinal product name	Tropifexor
Investigational medicinal product code	
Other name	LJN452
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30 microgram tropifexor tablet

Arm title	LJN452 60 µg
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Arm description:

60 micrograms of Tropifexor (Parts A+B)

Arm type	Experimental
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Investigational medicinal product name	Tropifexor
Investigational medicinal product code	
Other name	LJN452
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 60 microgram tropifexor tablet	
Arm title	LJN452 90 µg
Arm description: 90 micrograms of Tropifexor (Parts A+B)	
Arm type	Experimental
Investigational medicinal product name	Tropifexor
Investigational medicinal product code	
Other name	LJN452
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 90 microgram tropifexor tablet	
Arm title	Placebo
Arm description: Placebo A+B	
Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	Parts A+B
Other name	placebo
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: placebo tablet	

Number of subjects in period 1^[1]	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg
Started	14	16	37
Completed	14	16	36
Not completed	0	0	1
Consent withdrawn by subject	-	-	1
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1^[1]	LJN452 90 µg	Placebo
Started	85	46
Completed	77	45
Not completed	8	1
Consent withdrawn by subject	2	1
Physician decision	2	-

Adverse event, non-fatal	4	-
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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Numbers are consistent

Period 2

Period 2 title	Part C (Randomized Set)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LJN452 140 µg

Arm description:

140 micrograms of Tropifexor (Part C)

Arm type	Experimental
Investigational medicinal product name	Tropifexor
Investigational medicinal product code	
Other name	LJN452
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

140 microgram tropifexor tablet

Arm title	LJN452 200 µg
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Arm description:

200 micrograms of Tropifexor (Part C)

Arm type	Experimental
Investigational medicinal product name	Tropifexor
Investigational medicinal product code	
Other name	LJN452
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 microgram tropifexor tablet

Arm title	Placebo
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Arm description:

Placebo A+B

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	Part C
Other name	LJN452
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
placebo tablet

Number of subjects in period 2^[2]	LJN452 140 µg	LJN452 200 µg	Placebo
Started	50	51	51
Completed	38	37	44
Not completed	12	14	7
Physician decision	1	-	1
Consent withdrawn by subject	5	4	3
Adverse event, non-fatal	5	9	2
Lost to follow-up	1	1	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Numbers are consistent

Baseline characteristics

Reporting groups

Reporting group title	LJN452 10 µg
Reporting group description: 10 micrograms of Tropifexor (Part A)	
Reporting group title	LJN452 30 µg
Reporting group description: 30 micrograms of Tropifexor (Part A)	
Reporting group title	LJN452 60 µg
Reporting group description: 60 micrograms of Tropifexor (Parts A+B)	
Reporting group title	LJN452 90 µg
Reporting group description: 90 micrograms of Tropifexor (Parts A+B)	
Reporting group title	Placebo
Reporting group description: Placebo A+B	

Reporting group values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg
Number of subjects	14	16	37
Age Categorical			
Units: participants			
Parts A + B <=18 years	0	0	0
Part C <=18 years	0	0	0
Parts A + B Between 18 and 65 years	14	14	33
Part C Between 18 and 65 years	0	0	0
Parts A + B >=65 years	0	2	4
Part C >=65 years	0	0	0
Age Continuous			
Units: years			
arithmetic mean	48	49	50
standard deviation	± 11.7	± 14.4	± 12.5
Sex: Female, Male			
Sex of participant by treatment			
Units: participants			
Parts A + B Female	9	7	20
Part C Female	0	0	0
Parts A + B Male	5	9	17
Part C Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian (Parts A + B)	12	11	24
Black (Parts A + B)	0	0	0
Asian (Parts A + B)	2	5	12
Pacific Islander (Parts A + B)	0	0	0
Other (Parts A + B)	0	0	0
Unknown (Parts A+B)	0	0	1

Caucasian (Part C)	0	0	0
Black (Part C)	0	0	0
Asian (Part C)	0	0	0
Pacific Islander (Part C)	0	0	0
Other (Part C)	0	0	0
Unknown (Part C)	0	0	0
Age Continuous			
Units: years			
arithmetic mean	48	49	50
standard deviation	± 11.7	± 14.4	± 12.5

Reporting group values	LJN452 90 µg	Placebo	Total
Number of subjects	85	46	198
Age Categorical			
Units: participants			
Parts A + B <=18 years	0	0	0
Part C <=18 years	0	0	0
Parts A + B Between 18 and 65 years	72	41	174
Part C Between 18 and 65 years	0	0	0
Parts A + B >=65 years	13	5	24
Part C >=65 years	0	0	0
Age Continuous			
Units: years			
arithmetic mean	51	51	-
standard deviation	± 13.4	± 12.3	-
Sex: Female, Male			
Sex of participant by treatment			
Units: participants			
Parts A + B Female	47	21	104
Part C Female	0	0	0
Parts A + B Male	38	25	94
Part C Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian (Parts A + B)	50	25	122
Black (Parts A + B)	1	0	1
Asian (Parts A + B)	31	20	70
Pacific Islander (Parts A + B)	0	1	1
Other (Parts A + B)	2	0	2
Unknown (Parts A+B)	1	0	2
Caucasian (Part C)	0	0	0
Black (Part C)	0	0	0
Asian (Part C)	0	0	0
Pacific Islander (Part C)	0	0	0
Other (Part C)	0	0	0
Unknown (Part C)	0	0	0
Age Continuous			
Units: years			
arithmetic mean	51	54	-
standard deviation	± 13.4	± 11.0	-

Subject analysis sets

Subject analysis set title	Placebo C
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo Part C	
Subject analysis set title	Placebo A+B
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo Parts A+B	

Reporting group values	Placebo C	Placebo A+B	
Number of subjects	51	46	
Age Categorical Units: participants			
Parts A + B <=18 years	0	0	
Part C <=18 years	0	0	
Parts A + B Between 18 and 65 years	0	41	
Part C Between 18 and 65 years	38	0	
Parts A + B >=65 years	0	5	
Part C >=65 years	8	0	
Age Continuous Units: years			
arithmetic mean	54	51	
standard deviation	± 11.00	± 12.3	
Sex: Female, Male			
Sex of participant by treatment			
Units: participants			
Parts A + B Female	0	0	
Part C Female	32	21	
Parts A + B Male	0	0	
Part C Male	19	25	
Race/Ethnicity, Customized Units: Subjects			
Caucasian (Parts A + B)	0	25	
Black (Parts A + B)	0	0	
Asian (Parts A + B)	0	20	
Pacific Islander (Parts A + B)	0	1	
Other (Parts A + B)	0	0	
Unknown (Parts A+B)	0	0	
Caucasian (Part C)	38	0	
Black (Part C)	1	0	
Asian (Part C)	8	0	
Pacific Islander (Part C)	0	0	
Other (Part C)	4	0	
Unknown (Part C)	0	0	
Age Continuous Units: years			
arithmetic mean	54	51	
standard deviation	± 11.0	± 12.3	

End points

End points reporting groups

Reporting group title	LJN452 10 µg
Reporting group description:	10 micrograms of Tropifexor (Part A)
Reporting group title	LJN452 30 µg
Reporting group description:	30 micrograms of Tropifexor (Part A)
Reporting group title	LJN452 60 µg
Reporting group description:	60 micrograms of Tropifexor (Parts A+B)
Reporting group title	LJN452 90 µg
Reporting group description:	90 micrograms of Tropifexor (Parts A+B)
Reporting group title	Placebo
Reporting group description:	Placebo A+B
Reporting group title	LJN452 140 µg
Reporting group description:	140 micrograms of Tropifexor (Part C)
Reporting group title	LJN452 200 µg
Reporting group description:	200 micrograms of Tropifexor (Part C)
Reporting group title	Placebo
Reporting group description:	Placebo A+B
Subject analysis set title	Placebo C
Subject analysis set type	Intention-to-treat
Subject analysis set description:	Placebo Part C
Subject analysis set title	Placebo A+B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	Placebo Parts A+B

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

End point title	Number of Nonalcoholic steatohepatitis (NASH) patients with Treatment Emergent Adverse Events (TEAE) ^{[1][2]}
End point description:	Number of Nonalcoholic steatohepatitis (NASH) patients with TEAEs
End point type	Primary
End point timeframe:	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)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the

baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	16	37	85
Units: participants	5	11	24	61

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51	46
Units: participants	49	49	46	31

Statistical analyses

No statistical analyses for this end point

Primary: Change in Transaminase levels (ALT)

End point title	Change in Transaminase levels (ALT) ^[3]
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End point description:

Summary statistics of change in ALT from baseline to EOT by treatment. The alanine aminotransferase (ALT) test is a blood test that checks for liver damage. High levels of ALT may indicate liver damage. Normal range for ALT is typically 10 to 45 U/L or so (varies a little by age and gender). Elevation of these values indicate more liver inflammation/damage. ALT elevation is not unexpected in this patient population.

Dose relationship of tropifexor (LJN452) on ALT marker of hepatic inflammation in NASH

End point type	Primary
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End point timeframe:

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)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	37	85
Units: scores				
arithmetic mean (standard deviation)	-16.7 (± 17.53)	-12.0 (± 35.99)	-17.3 (± 28.12)	-15.4 (± 30.32)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
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Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51	46
Units: scores				
arithmetic mean (standard deviation)	-27.0 (\pm 30.24)	-28.7 (\pm 25.40)	-11.7 (\pm 61.64)	-8.1 (\pm 29.37)

Statistical analyses

Statistical analysis title	Change in ALT
Statistical analysis description: 10 micrograms of Tropifexor vs placebo (Part A)	
Comparison groups	LJN452 10 µg v Placebo A+B
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.362
Method	ANCOVA
Parameter estimate	LS mean change
Point estimate	-15.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.2
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	7.76

Notes:

[4] - Repeated measures analysis: ALT (U/L) change from baseline up to EOT (Parts A + B) (Full analysis set)

Statistical analysis title	Change in ALT
Statistical analysis description: 30 micrograms of Tropifexor vs placebo (Part A)	
Comparison groups	LJN452 30 µg v Placebo A+B
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.729
Method	ANCOVA
Parameter estimate	LS mean change
Point estimate	-10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.8
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	7.12

Notes:

[5] - ANCOVA: ALT (U/L) change from baseline up to EOT (Parts A + B) (Full analysis set)

Statistical analysis title	Change in ALT
Statistical analysis description: 60 micrograms of Tropifexor vs placebo (Parts A + B)	
Comparison groups	LJN452 60 µg v Placebo A+B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.173
Method	ANCOVA
Parameter estimate	Least Square Mean Change
Point estimate	-16.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.8
upper limit	-7.1
Variability estimate	Standard error of the mean
Dispersion value	4.73

Statistical analysis title	Change in ALT
Statistical analysis description: 90 micrograms of Tropifexor vs placebo (Parts A + B)	
Comparison groups	LJN452 90 µg v Placebo A+B
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.185
Method	ANCOVA
Parameter estimate	Least Square Mean Change
Point estimate	-14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.3
upper limit	-8.5
Variability estimate	Standard error of the mean
Dispersion value	3.25

Statistical analysis title	Change in ALT
Statistical analysis description: 140 micrograms of Tropifexor (Part C) vs placebo	
Comparison groups	LJN452 140 µg v Placebo C

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.02
Method	ANCOVA
Parameter estimate	LS Mean Change
Point estimate	-31.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.9
upper limit	-16.3
Variability estimate	Standard error of the mean
Dispersion value	7.71

Notes:

[6] - ANCOVA: Relative change of ALT (U/L) up to EOT (Part C) (Full analysis set)

Statistical analysis title	Change in ALT
Statistical analysis description:	
200 micrograms of Tropifexor vs placebo (Part C)	
Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.03
Method	ANCOVA
Parameter estimate	LS Mean Change
Point estimate	-32.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.6
upper limit	-14.5
Variability estimate	Standard error of the mean
Dispersion value	9.1

Notes:

[7] - ANCOVA: ALT (U/L) change from baseline up to EOT (Part C) (Full analysis set)

Statistical analysis title	Change in ALT
Statistical analysis description:	
10 micrograms of Tropifexor vs placebo (Parts A + B + C)	
Comparison groups	LJN452 10 µg v Placebo C
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.456
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-13.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.3
upper limit	-0.4
Variability estimate	Standard error of the mean
Dispersion value	7.86

Notes:

[8] - ANCOVA: ALT (U/L) change from baseline to Week 12 (Parts A+B+C)
Full analysis set (FAS)

Statistical analysis title	Change in ALT
Statistical analysis description:	
30 micrograms of Tropifexor vs placebo (Parts A + B + C)	
Comparison groups	LJN452 30 µg v Placebo C
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.966
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-7.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.5
upper limit	4.4
Variability estimate	Standard error of the mean
Dispersion value	7.27

Notes:

[9] - ANCOVA: ALT (U/L) change from baseline to Week 12 (Parts A + B + C)
Full analysis set (FAS)

Statistical analysis title	Change in ALT
Statistical analysis description:	
60 micrograms of Tropifexor vs placebo (Parts A + B + C)	
Comparison groups	LJN452 60 µg v Placebo C
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.275
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.4
upper limit	-5.2
Variability estimate	Standard error of the mean
Dispersion value	4.93

Notes:

[10] - ANCOVA: ALT (U/L) change from baseline to Week 12 (Parts A + B + C)
Full analysis set (FAS)

Statistical analysis title	Change in ALT
Statistical analysis description: 90 micrograms of Tropifexor vs placebo (Parts A + B + C)	
Comparison groups	LJN452 90 µg v Placebo C
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.304
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	-5.9
Variability estimate	Standard error of the mean
Dispersion value	3.56

Notes:

[11] - ANCOVA: ALT (U/L) change from baseline to Week 12 (Parts A+B + C)
Full analysis set (FAS)

Statistical analysis title	Change in ALT
Statistical analysis description: 140 micrograms of Tropifexor vs placebo (Parts A + B)	
Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.057
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-17.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.5
upper limit	-9.8
Variability estimate	Standard error of the mean
Dispersion value	4.45

Notes:

[12] - ANCOVA: ALT (U/L) change from baseline up to EOT (Parts A + B) FAS

Statistical analysis title	Change in ALT
Statistical analysis description: 200 micrograms of Tropifexor vs placebo (Parts A + B + C)	
Comparison groups	LJN452 200 µg v Placebo C

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.003
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.5
upper limit	-15.6
Variability estimate	Standard error of the mean
Dispersion value	4.49

Notes:

[13] - ANCOVA: ALT (U/L) change from baseline up to EOT (Parts A + B + C) FAS

Primary: Change in Aspartate transaminase (AST)

End point title	Change in Aspartate transaminase (AST) ^[14]
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End point description:

To determine the dose relationship of tropifexor (LJN452) on markers of hepatic inflammation (AST) in NASH from baseline to EoT

The alanine aminotransferase (AST) test is a blood test that checks for liver damage. High levels of AST may indicate liver damage. Normal range for AST is typically 10 to 45 U/L or so (varies a little by age and gender). Elevation of these values indicate more liver inflammation/damage

AST elevation is not unexpected in this patient population

The aspartate aminotransferase (AST) test is a blood test that checks for liver damage. Higher levels indicate more possible liver damage

Summary statistics of change in AST from baseline up to end of treatment (EOT)

End point type	Primary
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End point timeframe:

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)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	37	85
Units: scores				
arithmetic mean (standard deviation)	-11.3 (± 12.09)	-2.1 (± 29.62)	-10.2 (± 25.03)	-2.5 (± 24.60)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51	46

Units: scores				
arithmetic mean (standard deviation)	-16.7 (\pm 23.36)	-13.3 (\pm 20.14)	-13.1 (\pm 29.00)	-7.1 (\pm 23.85)

Statistical analyses

Statistical analysis title	Change in AST
Statistical analysis description: 10 micrograms of Tropifexor vs placebo (Part A)	
Comparison groups	LJN452 10 µg v Placebo A+B
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.722
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.9
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	6.56

Notes:

[15] - ANCOVA: AST (U/L) change from baseline up to EOT (Full analysis set)

Statistical analysis title	Change in AST
Statistical analysis description: 30 micrograms of Tropifexor vs placebo (Part A)	
Comparison groups	LJN452 30 µg v Placebo A+B
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
P-value	= 0.468
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	9.5
Variability estimate	Standard error of the mean
Dispersion value	5.96

Notes:

[16] - ANCOVA: AST (U/L) change from baseline up to EOT (Full analysis set)

Statistical analysis title	Change in AST
Statistical analysis description: 60 micrograms of Tropifexor vs placebo (Parts A+B)	
Comparison groups	LJN452 60 µg v Placebo A+B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.774
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.7
upper limit	-1
Variability estimate	Standard error of the mean
Dispersion value	3.97

Notes:

[17] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B) (Full analysis set)

Statistical analysis title	Change in AST
Statistical analysis description: 90 micrograms of Tropifexor vs placebo (Parts A+B)	
Comparison groups	LJN452 90 µg v Placebo A+B
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	= 0.136
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	4.9
Variability estimate	Standard error of the mean
Dispersion value	2.76

Notes:

[18] - ANCOVA: AST (U/L) change from baseline up to EOT (Parts A+B) (Full analysis set)

Statistical analysis title	Change in AST
Statistical analysis description: 140 micrograms of Tropifexor vs placebo (Part C)	
Comparison groups	LJN452 140 µg v Placebo C

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	= 0.145
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.9
upper limit	-8.2
Variability estimate	Standard error of the mean
Dispersion value	3.97

Notes:

[19] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Part C) (Full analysis set)

Statistical analysis title	Change in AST
Statistical analysis description:	
200 micrograms of Tropifexor vs placebo (Part C)	
Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	= 0.236
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	-6.4
Variability estimate	Standard error of the mean
Dispersion value	4.49

Notes:

[20] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Part C) (Full analysis set)

Statistical analysis title	Change in AST
Statistical analysis description:	
10 micrograms of Tropifexor vs placebo (Parts A+B+ C)	
Comparison groups	LJN452 10 µg v Placebo C
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	= 0.788
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-7.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.7
upper limit	4.4
Variability estimate	Standard error of the mean
Dispersion value	7

Notes:

[21] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

Statistical analysis title	Change in AST
Statistical analysis description:	
30 micrograms of Tropifexor vs placebo (Parts A+B+ C)	
Comparison groups	LJN452 30 µg v Placebo C
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.413
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	11
Variability estimate	Standard error of the mean
Dispersion value	6.43

Statistical analysis title	Change in AST
Statistical analysis description:	
60 micrograms of Tropifexor vs placebo (Parts A+B+ C)	
Comparison groups	LJN452 60 µg v Placebo C
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority ^[22]
P-value	= 0.833
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	4.38

Notes:

[22] - ANCOVA: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

Statistical analysis title	Change in AST
Statistical analysis description: 90 micrograms of Tropifexor vs placebo (Parts A+B+ C)	
Comparison groups	LJN452 90 µg v Placebo C
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	= 0.068
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	7.3
Variability estimate	Standard error of the mean
Dispersion value	3.19

Notes:

[23] - ANCOVA: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

Statistical analysis title	Change in AST
Statistical analysis description: 140 micrograms of Tropifexor vs placebo (Parts A+B+ C)	
Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority ^[24]
P-value	= 0.269
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	6.5
Variability estimate	Standard error of the mean
Dispersion value	3.98

Notes:

[24] - ANCOVA: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

Statistical analysis title	Change in AST
Statistical analysis description: 200 micrograms of Tropifexor vs placebo (Parts A+B+ C)	
Comparison groups	LJN452 200 µg v Placebo C

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	= 0.777
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	4.05

Notes:

[25] - Repeated measures analysis: AST (U/L) change from baseline up to EOT (Parts A+B+C) Full analysis set (FAS)

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

End point title	Change from baseline in percent of fat in the liver assessed using Magnetic resonance imaging (MRI) ^[26]
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End point description:

Repeated measures analysis: Relative change in percentage of fat in the liver assessed using MRI from baseline by visit up to EOT (Full analysis set)

End point type	Primary
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End point timeframe:

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)

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	37	85
Units: scores				
arithmetic mean (standard error)	-7.48 (± 6.174)	-14.07 (± 5.661)	-15.04 (± 3.754)	-12.34 (± 2.482)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51 ^[27]	46 ^[28]
Units: scores				
arithmetic mean (standard error)	-31.25 (± 5.228)	-39.54 (± 4.968)	0.00 (± 0.00)	0.00 (± 0.00)

Notes:

[27] - Placebo is the reference group for repeated measures

Statistical analyses

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
10 microgramsof Tropifexor - Change in percentage of fat in the liver Part A	
Comparison groups	LJN452 10 µg v Placebo A+B
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.853
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-7.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.66
upper limit	4.7
Variability estimate	Standard error of the mean
Dispersion value	6.174

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
30 micrograms of Tropifexor - Change in percentage of fat in the liver Part A	
Comparison groups	LJN452 30 µg v Placebo A+B
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.232
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-14.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.24
upper limit	-2.91
Variability estimate	Standard error of the mean
Dispersion value	5.661

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
60 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B	
Comparison groups	LJN452 60 µg v Placebo A+B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority ^[29]
P-value	= 0.077
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-15.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.45
upper limit	-7.64
Variability estimate	Standard error of the mean
Dispersion value	3.754

Notes:

[29] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
90 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B	
Comparison groups	LJN452 90 µg v Placebo A+B
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority ^[30]
P-value	= 0.141
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-12.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.23
upper limit	-7.44
Variability estimate	Standard error of the mean
Dispersion value	2.482

Notes:

[30] - ANCOVA: Relative change in percentage of fat in the liver from baseline

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
140 micrograms of Tropifexor - Change in percentage of fat in the liver Part C	
Comparison groups	LJN452 140 µg v Placebo C

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-31.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.58
upper limit	-20.92
Variability estimate	Standard error of the mean
Dispersion value	5.228

Notes:

[31] - ANCOVA: Relative change in percentage of fat in the liver

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
200 micrograms of Tropicexor - Change in percentage of fat in the liver Part C	
Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-39.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.37
upper limit	-29.71
Variability estimate	Standard error of the mean
Dispersion value	4.968

Notes:

[32] - ANCOVA: Relative change in percentage of fat in the liver

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
10 micrograms of Tropicexor - Change in percentage of fat in the liver Parts A+B+C	
Comparison groups	LJN452 10 µg v Placebo C
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	= 0.872
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-8.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.06
upper limit	2.88
Variability estimate	Standard error of the mean
Dispersion value	6.65

Notes:

[33] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
30 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C	
Comparison groups	LJN452 30 µg v Placebo C
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority ^[34]
P-value	= 0.465
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-14.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.36
upper limit	-3.91
Variability estimate	Standard error of the mean
Dispersion value	6.198

Notes:

[34] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 Parts A+B+C

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
60 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C	
Comparison groups	LJN452 60 µg v Placebo C
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	= 0.228
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-15.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.75
upper limit	-8.29
Variability estimate	Standard error of the mean
Dispersion value	4.078

Notes:

[35] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
90 micrograms - Change in percentage of fat in the liver Parts A+B+C	
Comparison groups	LJN452 90 µg v Placebo C
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority ^[36]
P-value	= 0.37
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-12.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.04
upper limit	-8.08
Variability estimate	Standard error of the mean
Dispersion value	2.717

Notes:

[36] - ANCOVA: Relative change in percentage of fat in the liver from baseline to Week 12 (Parts A+B+C)

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
140 micrograms - Change in percentage of fat in the liver Parts A+B+C	
Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority ^[37]
P-value	= 0.029
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-18.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.51
upper limit	-12.91
Variability estimate	Standard error of the mean
Dispersion value	3.517

Notes:

[37] - ANCOVA: Relative change in percentage of fat in the liver (Parts A+B+C)

Statistical analysis title	Change in percent of fat in the liver
Statistical analysis description:	
200 micrograms of Tropifexor - Change in percentage of fat in the liver Parts A+B+C	
Comparison groups	LJN452 200 µg v Placebo C

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[38]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS Mean change
Point estimate	-34.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.13
upper limit	-28.64
Variability estimate	Standard error of the mean
Dispersion value	3.482

Notes:

[38] - ANCOVA: Relative change in percentage of fat in the liver (Parts A+B+C)

Secondary: Change from baseline in weight

End point title	Change from baseline in weight ^[39]
End point description:	
Repeated measures for LS mean change in weight at EoT	
End point type	Secondary
End point timeframe:	
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)	

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	36	84
Units: Mean				
arithmetic mean (standard error)	-1.79 (± 0.608)	-0.78 (± 0.567)	-1.05 (± 0.377)	-1.15 (± 0.253)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51 ^[40]	46 ^[41]
Units: Mean				
arithmetic mean (standard error)	-5.10 (± 0.988)	-5.89 (± 1.002)	999 (± 999)	999 (± 999)

Notes:

[40] - Placebo is the reference group for repeated measures

[41] - Placebo is the reference group for repeated measures

Statistical analyses

Statistical analysis title	Change in weight
Statistical analysis description: 10 micrograms of Tropifexor (Part A) vs Placebo	
Comparison groups	LJN452 10 µg v Placebo A+B
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority ^[42]
P-value	= 0.01
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.99
upper limit	0.59
Variability estimate	Standard error of the mean
Dispersion value	0.608

Notes:

[42] - Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)

Statistical analysis title	Change in weight
Statistical analysis description: 30 micrograms of Tropifexor (Part A) vs Placebo	
Comparison groups	LJN452 30 µg v Placebo A+B
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority ^[43]
P-value	= 0.237
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.567

Notes:

[43] - Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)

Statistical analysis title	Change in weight
Statistical analysis description: 60 micrograms of Tropifexor (Parts A + B) vs Placebo	
Comparison groups	LJN452 60 µg v Placebo A+B

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority ^[44]
P-value	= 0.037
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.31
Variability estimate	Standard error of the mean
Dispersion value	0.377

Notes:

[44] - Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)

Statistical analysis title	Change in weight
Statistical analysis description:	
90 micrograms of Tropifexor (Parts A + B) vs Placebo	
Comparison groups	LJN452 90 µg v Placebo A+B
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority ^[45]
P-value	= 0.007
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	0.253

Notes:

[45] - Repeated measures analysis: Change in weight from baseline to EOT (Parts A + B) (Full analysis set)

Statistical analysis title	Change in weight
Statistical analysis description:	
140 micrograms of Tropifexor (Part C) vs Placebo	
Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority ^[46]
P-value	= 0.053
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-5.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.05
upper limit	-3.14
Variability estimate	Standard error of the mean
Dispersion value	0.988

Notes:

[46] - Repeated measures analysis: Change in weight from baseline to EOT (Parts C) (Full analysis set)

Statistical analysis title	Change in weight
Statistical analysis description: 200 micrograms of Tropifexor (Part C) vs Placebo	
Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[47]
P-value	= 0.013
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-5.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.87
upper limit	-3.91
Variability estimate	Standard error of the mean
Dispersion value	1.002

Notes:

[47] - Repeated measures analysis: Change in weight from baseline to EOT (Parts C) (Full analysis set)

Secondary: Change in body mass index (BMI)

End point title	Change in body mass index (BMI) ^[48]
End point description: Repeated measures for the LS mean change in BMI after 12 weeks of treatment. Body mass index (BMI) is a measure of body fat based on height and weight	
End point type	Secondary
End point timeframe: 12 weeks	

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	37	84
Units: Mean				
arithmetic mean (standard error)	-0.64 (± 0.208)	-0.29 (± 0.194)	-0.35 (± 0.129)	-0.42 (± 0.087)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51 ^[49]	46 ^[50]
Units: Mean				
arithmetic mean (standard error)	-1.88 (± 0.322)	-2.11 (± 0.327)	9.999 (± 9.999)	9.999 (± 9.999)

Notes:

[49] - Placebo is the reference group for repeated measures

[50] - Placebo is the reference group for repeated measures

Statistical analyses

Statistical analysis title	Change in BMI
Statistical analysis description: 10 micrograms of Tropifexor (Part A) vs Placebo	
Comparison groups	LJN452 10 µg v Placebo A+B
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority ^[51]
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.208

Notes:

[51] - Repeated measures analysis: Change in BMI from baseline to EoT (Full analysis set)

Statistical analysis title	Change in BMI
Statistical analysis description: 30 micrograms of Tropifexor (Part A) vs Placebo	
Comparison groups	LJN452 30 µg v Placebo A+B
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority ^[52]
P-value	= 0.177
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.194

Notes:

[52] - Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)

Statistical analysis title	Change in BMI
Statistical analysis description:	
60 micrograms of Tropifexor (Parts A + B) vs Placebo	
Comparison groups	LJN452 60 µg v Placebo A+B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority ^[53]
P-value	= 0.032
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.129

Notes:

[53] - Repeated measures analysis: Change in BMI from baseline to EOT (Parts C) (Full analysis set)

Statistical analysis title	Change in BMI
Statistical analysis description:	
90 micrograms of Tropifexor (Parts A + B) vs Placebo	
Comparison groups	LJN452 90 µg v Placebo A+B
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority ^[54]
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.087

Notes:

[54] - Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)

Statistical analysis title	Change in BMI
Statistical analysis description: 140 micrograms of Tropifexor (Part C) vs Placebo	
Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority ^[55]
P-value	= 0.015
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	-1.24
Variability estimate	Standard error of the mean
Dispersion value	0.322

Notes:

[55] - Repeated measures analysis: Change in BMI from baseline to EOT (Full analysis set)

Statistical analysis title	Change in BMI
Statistical analysis description: 200 micrograms of Tropifexor (Part C) vs Placebo	
Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[56]
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.75
upper limit	-1.46
Variability estimate	Standard error of the mean
Dispersion value	0.327

Notes:

[56] - Repeated measures analysis: Change in BMI from baseline to EOT (Parts C) (Full analysis set)

Secondary: Change from baseline in waist to hip (WTH) ratio

End point title	Change from baseline in waist to hip (WTH) ratio ^[57]
End point description: The LS mean change in waist to hip ratio after 12 weeks of treatment	
End point type	Secondary

End point timeframe:

12 weeks

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	15	37	84
Units: Mean				
arithmetic mean (standard error)	-0.01 (± 0.009)	0.00 (± 0.008)	-0.01 (± 0.005)	0.00 (± 0.004)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	49	51	51 ^[58]	46 ^[59]
Units: Mean				
arithmetic mean (standard error)	0.00 (± 0.008)	-0.01 (± 0.007)	9.999 (± 9.999)	9.999 (± 9.999)

Notes:

[58] - 9.999 = Placebo is the reference group for repeated measures

[59] - 9.999=Placebo is the reference group for repeated measures

Statistical analyses

Statistical analysis title	Change in WTH ratio
Statistical analysis description: 10 micrograms of Tropifexor (Part A) vs Placebo	
Comparison groups	LJN452 10 µg v Placebo A+B
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority ^[60]
P-value	= 0.53
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.009

Notes:

[60] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)

Statistical analysis title	Change in WTH ratio
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Statistical analysis description:

30 micrograms of Tropifexor (Part A) vs Placebo

Comparison groups	LJN452 30 µg v Placebo A+B
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority ^[61]
P-value	= 0.857
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.008

Notes:

[61] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)

Statistical analysis title	Change in WTH ratio
Statistical analysis description:	
60 micrograms of Tropifexor (Part A) vs Placebo	
Comparison groups	LJN452 60 µg v Placebo A+B
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority ^[62]
P-value	= 0.262
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.005

Notes:

[62] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)

Statistical analysis title	Change in WTH ratio
Statistical analysis description:	
90 micrograms of Tropifexor (Parts A + B) vs Placebo	
Comparison groups	LJN452 90 µg v Placebo A+B

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority ^[63]
P-value	= 0.323
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.004

Notes:

[63] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Parts A+B) (Full analysis set)

Statistical analysis title	Change in WTH ratio
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Statistical analysis description:

140 micrograms of Tropifexor (Part C) vs Placebo

Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority ^[64]
P-value	= 0.1
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.008

Notes:

[64] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Part C) (Full analysis set)

Statistical analysis title	Change in WTH ratio
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Statistical analysis description:

200 micrograms of Tropifexor (Part C) vs Placebo

Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority ^[65]
P-value	= 0.693
Method	Mixed models analysis
Parameter estimate	LS Mean change
Point estimate	-0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.007

Notes:

[65] - Repeated measures analysis: Change in WTH ratio from baseline to EOT (Part C) (Full analysis set)

Secondary: Change from baseline in biomarker FGF19

End point title	Change from baseline in biomarker FGF19 ^[66]
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End point description:

Dose-response relationship of tropifexor (LJN452) on FGF19 over time, a marker of FXR target engagement in the gut.

ANCOVA: Ratio of FGF19 (pg/mL) post-dose to pre-dose at Week 6

End point type	Secondary
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End point timeframe:

6 weeks

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	34	78
Units: pg/mL				
least squares mean (confidence interval 95%)	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)

End point values	LJN452 140 µg	LJN452 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	42		
Units: pg/mL				
least squares mean (confidence interval 95%)	1.97 (1.48 to 2.62)	2.23 (1.65 to 3.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in biomarker C4

End point title	Change from baseline in biomarker C4 ^[67]
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End point description:

Dose-response relationship of LJN452 on C4, a marker of hepatic target engagement at 4 hours post dose

C4 (ng/mL): Summary statistics by treatment and visit

End point type	Secondary
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End point timeframe:

Week 6, 4 hours post dose

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	37	85
Units: ng/mL				
arithmetic mean (standard deviation)	38.82 (± 25.765)	32.75 (± 23.360)	28.38 (± 13.394)	40.19 (± 31.356)

End point values	LJN452 140 µg	LJN452 200 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	42		
Units: ng/mL				
arithmetic mean (standard deviation)	14.97 (± 20.232)	8.54 (± 9.583)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline on markers of liver fibrosis, Fibroscan

End point title	Change from baseline on markers of liver fibrosis, Fibroscan ^[68]
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End point description:

Dose-response relationship of tropifexor (LJN452) on markers of liver fibrosis commonly available such as Fibroscan®

Liver stiffness (kPa): Summary statistics by treatment and visit

FibroScan is a specialized ultrasound machine for measuring fibrosis (scarring) in the liver

End point type	Secondary
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End point timeframe:

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

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	37	85
Units: mean change				
arithmetic mean (standard deviation)	10.94 (± 5.314)	10.40 (± 7.663)	9.90 (± 4.095)	9.00 (± 4.152)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo A+B	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	50	51	46	
Units: mean change				
arithmetic mean (standard deviation)	11.29 (± 3.677)	12.03 (± 4.804)	9.30 (± 4.676)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline on markers of liver fibrosis (ELF)

End point title	Change from baseline on markers of liver fibrosis (ELF) ^[69]
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End point description:

ANCOVA: LS Mean Change in Enhanced liver fibrosis panel (ELF) score from baseline by visit up to EOT

End point type	Secondary
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End point timeframe:

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

Notes:

[69] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	34	78
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)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51 ^[70]	46 ^[71]
Units: scores on a scale				
least squares mean (standard error)	-0.34 (± 0.132)	-0.24 (± 0.122)	9.999 (± 9.999)	9.999 (± 9.999)

Notes:

[70] - 9.999=Placebo is the reference group for repeated measures

[71] - 9.999=Placebo is the reference group for repeated measures

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from baseline on markers of liver fibrosis, Fibrotest (Parts A+B) ^[72]
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End point description:

Score of fibrosis biomarker test: Summary statistics by treatment and visit at EoT

(See Part C in separate outcomes that follows)

End point type	Secondary
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End point timeframe:

End of Treatment (EoT):12 weeks

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	37	85
Units: mean change				
arithmetic mean (standard deviation)	-0.23 (± 0.284)	-1.49 (± 0.852)	-1.44 (± 1.080)	-1.34 (± 1.222)

End point values	Placebo A+B			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: mean change				
arithmetic mean (standard deviation)	-1.23 (± 1.088)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from baseline on markers of liver fibrosis, Fibrotest, (Part C)
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End point description:	
Repeated measures analysis: Change in score of fibrosis biomarker test from baseline by visit up to EOT	
End point type	Secondary
End point timeframe:	
End of Treatment (EoT) was 48 weeks	

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	50	51	51 ^[73]	
Units: mean change				
least squares mean (standard error)	-0.42 (± 0.131)	-0.44 (± 0.135)	9.999 (± 9.999)	

Notes:

[73] - 9.999=Placebo is the reference group for repeated measures

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline on gamma-glutamyl transferase (GGT)

End point title	Change from baseline on gamma-glutamyl transferase
End point description:	
Summary statistics of change in GGT (U/L) from baseline by visit up to EoT	
End point type	Secondary
End point timeframe:	
EoT for Parts A+B=12 weeks; EoT for Part C = 48 weeks	

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	15	37	84
Units: mean				
least squares mean (standard error)	1.6 (± 10.93)	-29.9 (± 10.11)	-34.2 (± 6.70)	-45.7 (± 4.52)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51 ^[75]	46 ^[76]
Units: mean				
least squares mean (standard error)	-35.2 (± 11.58)	-29.9 (± 11.65)	9.999 (± 9.999)	9.999 (± 9.999)

Notes:

[75] - 9.999=Placebo is the reference group for repeated measures

[76] - 9.999=Placebo is the reference group for repeated measures

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline on fasting lipid profile

End point title	Change from baseline on fasting lipid profile ^[77]
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End point description:

Repeated measures analysis: LS geometric mean ratio of fasting lipids to baseline by visit up to EOT

End point type	Secondary
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End point timeframe:

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

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	37	50
Units: mmol/L				
least squares mean (confidence interval 95%)				
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)
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)
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)
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)
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)
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)
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)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51 ^[78]	46 ^[79]
Units: mmol/L				
least squares mean (confidence interval 95%)				

Cholesterol	1.032 (0.975 to 1.093)	1.071 (1.012 to 1.133)	9.999 (9.999 to 9.999)	9.999 (9.999 to 9.999)
Triglycerides	1.070 (0.934 to 1.226)	1.068 (0.936 to 1.219)	9.999 (9.999 to 9.999)	9.999 (9.999 to 9.999)
LDL Cholesterol	1.056 (0.972 to 1.147)	1.200 (1.106 to 1.302)	9.999 (9.999 to 9.999)	9.999 (9.999 to 9.999)
HDL Cholesterol	0.855 (0.800 to 0.913)	0.824 (0.772 to 0.879)	9.999 (9.999 to 9.999)	9.999 (9.999 to 9.999)
LDL/HDL Ratio	1.252 (1.128 to 1.390)	1.478 (1.332 to 1.639)	9.999 (9.999 to 9.999)	9.999 (9.999 to 9.999)
Free Glycerol	1.1115 (0.9721 to 1.2709)	0.9808 (0.8571 to 1.1223)	9.999 (9.999 to 9.999)	9.999 (9.999 to 9.999)
Free Fatty Acid	1.072 (0.951 to 1.208)	0.887 (0.785 to 1.002)	9.999 (9.999 to 9.999)	9.999 (9.999 to 9.999)

Notes:

[78] - 9.999=Placebo is the reference group for repeated measures

[79] - 9.999=Placebo is the reference group for repeated measures

Statistical analyses

No statistical analyses for this end point

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

End point title	Itch based on a visual analog scale (VAS) rating scale ^[80]
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End point description:

Repeated measures analysis: Change in VAS for Itch from baseline by visit up to EoT

End point type	Secondary
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End point timeframe:

EoT for Parts A+B=12 weeks; EoT for Part C = 48 weeks

Notes:

[80] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	36	78
Units: mean				
least squares mean (standard error)	-0.3 (± 0.48)	0.2 (± 0.43)	0.4 (± 0.28)	0.1 (± 0.19)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51 ^[81]	46 ^[82]
Units: mean				
least squares mean (standard error)	0.6 (± 0.37)	1.1 (± 0.35)	9.999 (± 9.999)	9.999 (± 9.999)

Notes:

[81] - 9.999=placebo is not compared to itself

[82] - 9.999=placebo is not compared to itself

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough of LJN452

End point title Ctrough of LJN452^[83]

End point description:

Summary Ctrough of tropifexor (LJN452)

End point type Secondary

End point timeframe:

Scheduled timepoint is zero (Parts A+B) or pre-dose (Part C)

Notes:

[83] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	37	85
Units: ng/mL				
arithmetic 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)
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)
Profile day 168	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)
Profile day 280	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)
Profile day 336	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	Placebo A+B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	51	51 ^[84]	46 ^[85]
Units: ng/mL				
arithmetic mean (standard deviation)				
Profile day 7	0.00 (± 0.0)	0.00 (± 0.00)	9.999 (± 9.999)	9.999 (± 9.999)
Profile day 14	0.00 (± 0.00)	0.00 (± 0.00)	9.999 (± 9.999)	9.999 (± 9.999)
Profile day 28	0.00 (± 0.00)	0.00 (± 0.00)	9.999 (± 9.999)	9.999 (± 9.999)
Profile day 42	2.821 (± 1.659)	3.533 (± 2.356)	9.999 (± 9.999)	9.999 (± 9.999)
Profile day 56	0.00 (± 0.00)	0.00 (± 0.00)	9.999 (± 9.999)	9.999 (± 9.999)

Profile day 84	1.685 (± 0.874)	2.286 (± 1.259)	9.999 (± 9.999)	9.999 (± 9.999)
Profile day 168	1.889 (± 1.340)	2.146 (± 1.383)	9.999 (± 9.999)	9.999 (± 9.999)
Profile day 280	2.129 (± 1.990)	1.990 (± 1.053)	9.999 (± 9.999)	9.999 (± 9.999)
Profile day 336	1.444 (± 1.077)	1.979 (± 1.153)	9.999 (± 9.999)	9.999 (± 9.999)

Notes:

[84] - 9.999=Placebo is the reference group for repeated measures. It is not compared to itself

[85] - 9.999=Placebo is the reference group for repeated measures. It is not compared to itself

Statistical analyses

No statistical analyses for this end point

Secondary: C2h of LJN452

End point title	C2h of LJN452 ^[86]
End point description:	
Summary C2h of tropifexor (LJN452)	
End point type	Secondary
End point timeframe:	
Scheduled timepoint (Parts A+B) is 2 hours; Part C measured Post-dose	

Notes:

[86] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis was planned

End point values	LJN452 10 µg	LJN452 30 µg	LJN452 60 µg	LJN452 90 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14 ^[87]	16 ^[88]	37	85
Units: ng/mL				
arithmetic 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	0.00 (± 0.00)	0.00 (± 0.00)	1.344 (± 0.727)	2.001 (± 1.053)

Notes:

[87] - This dosage was not measured at Day 14

[88] - This dosage was not measured at Day 14

End point values	Placebo A+B			
Subject group type	Subject analysis set			
Number of subjects analysed	46 ^[89]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Profile day 7	0.00 (± 0.00)			
Profile day 14	0.00 (± 0.00)			

Notes:

[89] - Placebo is the reference group and is not compared to itself

Statistical analyses

Secondary: 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

End point title	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
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End point description:

Number of patients who have at least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (total score)

End point type	Secondary
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End point timeframe:

EoT (Week 48)

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	39	35	42	
Units: participants	11	11	12	

Statistical analyses

Statistical analysis title	Biopsy-based response total score
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Statistical analysis description:

At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (total score)

Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.214
upper limit	0.223

Statistical analysis title	Biopsy-based response total score
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Statistical analysis description:

At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (total score)

Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8074
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.196
upper limit	0.251

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

End point title	Biopsy-based response at Week 48 compared to baseline: At least one point improvement in fibrosis (NASH CRN staging) without worsening - FDA
End point description:	
Number of patients who have at least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (FDA)	
End point type	Secondary
End point timeframe:	
EoT (Week 48)	

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	38	35	42	
Units: participants	11	11	12	

Statistical analyses

Statistical analysis title	Biopsy-based response - FDA
Statistical analysis description:	
At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (FDA)	
Comparison groups	LJN452 140 µg v Placebo C

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.807
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.191
upper limit	0.246

Statistical analysis title	Biopsy-based response - FDA
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Statistical analysis description:

At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (FDA)

Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6233
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.173
upper limit	0.273

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

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

Number of patients who have at least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (EMA)

End point type	Secondary
End point timeframe:	
EoT (Week 48)	

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	38	35	42	
Units: participants	11	11	12	

Statistical analyses

Statistical analysis title	Biopsy-based response - EMA
Statistical analysis description: At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (EMA)	
Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.214
upper limit	0.233

Statistical analysis title	Biopsy-based response - EMA
Statistical analysis description: At least one point improvement in fibrosis (NASH CRN staging) without worsening of steatohepatitis (EMA)	
Comparison groups	LJN452 200 µg v Placebo C
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8074
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.196
upper limit	0.251

Secondary: Biopsy-based response at Week 48 compared to baseline: Difference

between treatment groups (Part C) - Resolution of steatohepatitis (diagnostic category)

End point title	Biopsy-based response at Week 48 compared to baseline: Difference between treatment groups (Part C) - Resolution of steatohepatitis (diagnostic category)
End point description: Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging)	
End point type	Secondary
End point timeframe: EoT (Week 48)	

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	38	35	42	
Units: participants	4	7	3	

Statistical analyses

Statistical analysis title	Biopsy-based response
Statistical analysis description: Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging)	
Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7028
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.184
upper limit	0.252

Statistical analysis title	Biopsy-based response
Statistical analysis description: Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging)	
Comparison groups	LJN452 200 µg v Placebo C

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1713
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.098
upper limit	0.345

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

End point title	Biopsy-based response at Week 48 compared to baseline: Difference between treatment groups (Part C) - Resolution of steatohepatitis (FDA, EMA)
End point description:	Resolution of steatohepatitis (diagnostic category) without worsening of fibrosis (NASH CRN staging)
End point type	Secondary
End point timeframe:	
EoT (Week 48)	

End point values	LJN452 140 µg	LJN452 200 µg	Placebo C	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	38	35	42	
Units: participants	0	2	0	

Statistical analyses

Statistical analysis title	Biopsy-based response, FDA and EMA
Statistical analysis description:	Resolution of steatohepatitis (FDA, EMA) without worsening of fibrosis (NASH CRN staging)
Comparison groups	LJN452 140 µg v Placebo C
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2033
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.057

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.168
upper limit	0.278

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	LJN452 10 mcg
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Reporting group description:

LJN452 10 mcg

Reporting group title	LJN452 60 mcg
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Reporting group description:

LJN452 60 mcg

Reporting group title	LJN452 30 mcg
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Reporting group description:

LJN452 30 mcg

Reporting group title	LJN452 90 mcg
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Reporting group description:

LJN452 90 mcg

Reporting group title	LJN452 140 mcg
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Reporting group description:

LJN452 140 mcg

Reporting group title	LJN452 200 mcg
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Reporting group description:

LJN452 200 mcg

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	Total
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Reporting group description:

Total

Serious adverse events	LJN452 10 mcg	LJN452 60 mcg	LJN452 30 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			

subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometrial thickening			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Multiple injuries			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			

subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigger finger			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LJN452 90 mcg	LJN452 140 mcg	LJN452 200 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 85 (4.71%)	5 / 50 (10.00%)	3 / 51 (5.88%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			

subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometrial thickening			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Multiple injuries			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			

subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigger finger			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo	Total	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 97 (6.19%)	18 / 350 (5.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			

subjects affected / exposed	1 / 97 (1.03%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial thickening			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	1 / 97 (1.03%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 97 (1.03%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple injuries			
subjects affected / exposed	1 / 97 (1.03%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 97 (0.00%)	2 / 350 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 97 (1.03%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haematochezia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 97 (1.03%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 97 (1.03%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LJN452 10 mcg	LJN452 60 mcg	LJN452 30 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 13 (38.46%)	16 / 37 (43.24%)	11 / 17 (64.71%)
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 37 (2.70%) 1	3 / 17 (17.65%) 3
Pyrexia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 37 (2.70%) 1	3 / 17 (17.65%) 3
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 37 (0.00%) 0	1 / 17 (5.88%) 1
Insomnia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 37 (2.70%) 1	1 / 17 (5.88%) 1
Loss of libido subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 37 (0.00%) 0	1 / 17 (5.88%) 1
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 37 (0.00%) 0	0 / 17 (0.00%) 0

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)	1 / 37 (2.70%)	1 / 17 (5.88%)
occurrences (all)	1	1	1
Poor quality sleep			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 37 (2.70%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 37 (2.70%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 37 (2.70%)	1 / 17 (5.88%)
occurrences (all)	0	1	3
Dry mouth			

subjects affected / exposed	0 / 13 (0.00%)	1 / 37 (2.70%)	1 / 17 (5.88%)
occurrences (all)	0	1	1
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 37 (2.70%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	2 / 17 (11.76%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Neurodermatitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 13 (0.00%)	5 / 37 (13.51%)	0 / 17 (0.00%)
occurrences (all)	0	6	0
Rash			
subjects affected / exposed	0 / 13 (0.00%)	1 / 37 (2.70%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	0 / 13 (0.00%)	2 / 37 (5.41%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 13 (7.69%)	1 / 37 (2.70%)	1 / 17 (5.88%)
occurrences (all)	2	1	1
Proteinuria			
subjects affected / exposed	1 / 13 (7.69%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Infections and infestations			
Body tinea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 37 (5.41%)	0 / 17 (0.00%)
occurrences (all)	0	2	0
Periodontitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Rhinitis			

subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	2 / 37 (5.41%)	0 / 17 (0.00%)
occurrences (all)	0	3	0
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Viral sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 13 (0.00%)	1 / 37 (2.70%)	2 / 17 (11.76%)
occurrences (all)	0	1	2
Diabetes mellitus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 13 (0.00%)	0 / 37 (0.00%)	0 / 17 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	LJN452 90 mcg	LJN452 140 mcg	LJN452 200 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 85 (58.82%)	43 / 50 (86.00%)	45 / 51 (88.24%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 85 (5.88%)	7 / 50 (14.00%)	3 / 51 (5.88%)
occurrences (all)	5	7	4
Pyrexia			

subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 1	2 / 50 (4.00%) 2	1 / 51 (1.96%) 1
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 85 (3.53%) 3	0 / 50 (0.00%) 0	0 / 51 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Loss of libido subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0 0 / 85 (0.00%) 0 0 / 85 (0.00%) 0	1 / 50 (2.00%) 1 4 / 50 (8.00%) 4 0 / 50 (0.00%) 0	0 / 51 (0.00%) 0 3 / 51 (5.88%) 3 0 / 51 (0.00%) 0
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all)	3 / 85 (3.53%) 3 2 / 85 (2.35%) 2 0 / 85 (0.00%) 0 0 / 85 (0.00%) 0 0 / 85 (0.00%) 0	1 / 50 (2.00%) 2 4 / 50 (8.00%) 5 1 / 50 (2.00%) 1 0 / 50 (0.00%) 0 0 / 50 (0.00%) 0	3 / 51 (5.88%) 3 4 / 51 (7.84%) 4 5 / 51 (9.80%) 6 1 / 51 (1.96%) 1 0 / 51 (0.00%) 0
Injury, poisoning and procedural complications Contusion			

subjects affected / exposed occurrences (all)	0 / 85 (0.00%) 0	3 / 50 (6.00%) 3	0 / 51 (0.00%) 0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 85 (4.71%)	3 / 50 (6.00%)	3 / 51 (5.88%)
occurrences (all)	7	3	6
Poor quality sleep			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 85 (3.53%)	5 / 50 (10.00%)	2 / 51 (3.92%)
occurrences (all)	3	6	3
Abdominal pain			
subjects affected / exposed	1 / 85 (1.18%)	2 / 50 (4.00%)	3 / 51 (5.88%)
occurrences (all)	1	2	3
Abdominal pain lower			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	2 / 85 (2.35%)	6 / 50 (12.00%)	2 / 51 (3.92%)
occurrences (all)	2	8	2
Constipation			
subjects affected / exposed	2 / 85 (2.35%)	3 / 50 (6.00%)	3 / 51 (5.88%)
occurrences (all)	2	3	3
Diarrhoea			
subjects affected / exposed	4 / 85 (4.71%)	3 / 50 (6.00%)	7 / 51 (13.73%)
occurrences (all)	4	5	7
Dry mouth			
subjects affected / exposed	2 / 85 (2.35%)	0 / 50 (0.00%)	2 / 51 (3.92%)
occurrences (all)	2	0	2
Dyspepsia			

subjects affected / exposed	4 / 85 (4.71%)	2 / 50 (4.00%)	3 / 51 (5.88%)
occurrences (all)	5	2	3
Flatulence			
subjects affected / exposed	1 / 85 (1.18%)	5 / 50 (10.00%)	2 / 51 (3.92%)
occurrences (all)	1	5	4
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 85 (1.18%)	2 / 50 (4.00%)	2 / 51 (3.92%)
occurrences (all)	1	2	2
Nausea			
subjects affected / exposed	4 / 85 (4.71%)	6 / 50 (12.00%)	10 / 51 (19.61%)
occurrences (all)	5	9	12
Vomiting			
subjects affected / exposed	3 / 85 (3.53%)	3 / 50 (6.00%)	4 / 51 (7.84%)
occurrences (all)	6	6	5
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Neurodermatitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	7 / 85 (8.24%)	26 / 50 (52.00%)	35 / 51 (68.63%)
occurrences (all)	7	33	45
Rash			
subjects affected / exposed	2 / 85 (2.35%)	5 / 50 (10.00%)	3 / 51 (5.88%)
occurrences (all)	2	7	4
Rash pruritic			
subjects affected / exposed	0 / 85 (0.00%)	2 / 50 (4.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	2
Proteinuria			

subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 1	1 / 50 (2.00%) 1	3 / 51 (5.88%) 3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 85 (1.18%)	3 / 50 (6.00%)	1 / 51 (1.96%)
occurrences (all)	1	4	1
Back pain			
subjects affected / exposed	3 / 85 (3.53%)	1 / 50 (2.00%)	2 / 51 (3.92%)
occurrences (all)	3	2	2
Musculoskeletal pain			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Body tinea			
subjects affected / exposed	0 / 85 (0.00%)	3 / 50 (6.00%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Bronchitis			
subjects affected / exposed	0 / 85 (0.00%)	3 / 50 (6.00%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Influenza			
subjects affected / exposed	9 / 85 (10.59%)	1 / 50 (2.00%)	3 / 51 (5.88%)
occurrences (all)	9	1	3
Laryngitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	6 / 85 (7.06%)	6 / 50 (12.00%)	5 / 51 (9.80%)
occurrences (all)	7	8	10
Periodontitis			
subjects affected / exposed	0 / 85 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	3 / 85 (3.53%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
Sinusitis			

subjects affected / exposed	1 / 85 (1.18%)	3 / 50 (6.00%)	0 / 51 (0.00%)
occurrences (all)	1	3	0
Tonsillitis			
subjects affected / exposed	1 / 85 (1.18%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	8 / 85 (9.41%)	9 / 50 (18.00%)	3 / 51 (5.88%)
occurrences (all)	8	11	3
Urinary tract infection			
subjects affected / exposed	1 / 85 (1.18%)	9 / 50 (18.00%)	0 / 51 (0.00%)
occurrences (all)	1	13	0
Viral sinusitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 85 (2.35%)	1 / 50 (2.00%)	2 / 51 (3.92%)
occurrences (all)	2	1	2
Diabetes mellitus			
subjects affected / exposed	2 / 85 (2.35%)	2 / 50 (4.00%)	1 / 51 (1.96%)
occurrences (all)	2	2	1
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 85 (2.35%)	2 / 50 (4.00%)	3 / 51 (5.88%)
occurrences (all)	2	2	3

Non-serious adverse events	Placebo	Total	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 97 (64.95%)	233 / 350 (66.57%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 97 (9.28%)	28 / 350 (8.00%)	
occurrences (all)	9	29	
Pyrexia			
subjects affected / exposed	1 / 97 (1.03%)	6 / 350 (1.71%)	
occurrences (all)	1	6	
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	8 / 350 (2.29%) 8	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	2 / 350 (0.57%) 2	
Insomnia subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	11 / 350 (3.14%) 11	
Loss of libido subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 350 (0.29%) 1	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 97 (3.09%) 3	10 / 350 (2.86%) 11	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	12 / 350 (3.43%) 13	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	6 / 350 (1.71%) 7	
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	2 / 350 (0.57%) 2	
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 350 (0.29%) 1	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	5 / 350 (1.43%) 5	
Nervous system disorders Headache			

subjects affected / exposed	6 / 97 (6.19%)	19 / 350 (5.43%)	
occurrences (all)	6	25	
Poor quality sleep			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 97 (1.03%)	3 / 350 (0.86%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 97 (4.12%)	15 / 350 (4.29%)	
occurrences (all)	4	17	
Abdominal pain			
subjects affected / exposed	8 / 97 (8.25%)	14 / 350 (4.00%)	
occurrences (all)	9	15	
Abdominal pain lower			
subjects affected / exposed	0 / 97 (0.00%)	2 / 350 (0.57%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	3 / 97 (3.09%)	15 / 350 (4.29%)	
occurrences (all)	3	17	
Constipation			
subjects affected / exposed	5 / 97 (5.15%)	15 / 350 (4.29%)	
occurrences (all)	6	16	
Diarrhoea			
subjects affected / exposed	6 / 97 (6.19%)	22 / 350 (6.29%)	
occurrences (all)	9	29	
Dry mouth			
subjects affected / exposed	2 / 97 (2.06%)	8 / 350 (2.29%)	
occurrences (all)	2	8	
Dyspepsia			
subjects affected / exposed	4 / 97 (4.12%)	13 / 350 (3.71%)	
occurrences (all)	4	14	
Flatulence			

subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	10 / 350 (2.86%) 12	
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	7 / 350 (2.00%) 7	
Nausea subjects affected / exposed occurrences (all)	11 / 97 (11.34%) 13	32 / 350 (9.14%) 40	
Vomiting subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	14 / 350 (4.00%) 22	
Skin and subcutaneous tissue disorders			
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 350 (0.29%) 1	
Neurodermatitis subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 350 (0.29%) 1	
Pruritus subjects affected / exposed occurrences (all)	15 / 97 (15.46%) 17	88 / 350 (25.14%) 108	
Rash subjects affected / exposed occurrences (all)	4 / 97 (4.12%) 4	15 / 350 (4.29%) 18	
Rash pruritic subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	4 / 350 (1.14%) 4	
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 3	6 / 350 (1.71%) 9	
Proteinuria subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	7 / 350 (2.00%) 8	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 97 (3.09%)	8 / 350 (2.29%)	
occurrences (all)	3	9	
Back pain			
subjects affected / exposed	7 / 97 (7.22%)	14 / 350 (4.00%)	
occurrences (all)	7	15	
Musculoskeletal pain			
subjects affected / exposed	1 / 97 (1.03%)	3 / 350 (0.86%)	
occurrences (all)	1	3	
Infections and infestations			
Body tinea			
subjects affected / exposed	0 / 97 (0.00%)	3 / 350 (0.86%)	
occurrences (all)	0	3	
Bronchitis			
subjects affected / exposed	6 / 97 (6.19%)	10 / 350 (2.86%)	
occurrences (all)	7	11	
Influenza			
subjects affected / exposed	4 / 97 (4.12%)	17 / 350 (4.86%)	
occurrences (all)	4	17	
Laryngitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 350 (0.29%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	10 / 97 (10.31%)	29 / 350 (8.29%)	
occurrences (all)	11	38	
Periodontitis			
subjects affected / exposed	0 / 97 (0.00%)	2 / 350 (0.57%)	
occurrences (all)	0	2	
Rhinitis			
subjects affected / exposed	1 / 97 (1.03%)	5 / 350 (1.43%)	
occurrences (all)	1	5	
Sinusitis			
subjects affected / exposed	7 / 97 (7.22%)	11 / 350 (3.14%)	
occurrences (all)	7	11	
Tonsillitis			

subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	2 / 350 (0.57%) 2	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	10 / 97 (10.31%) 10	32 / 350 (9.14%) 35	
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 97 (3.09%) 3	14 / 350 (4.00%) 18	
Viral sinusitis subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 350 (0.29%) 1	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	9 / 350 (2.57%) 9	
Diabetes mellitus subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	7 / 350 (2.00%) 7	
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	9 / 350 (2.57%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2016	To implement recommendations from the US FDA to modify certain details of study CLJN452A2202.
07 March 2017	To ensure that the protocol text clearly outlines that a second interim analysis of Part A, to include data collected up to Week 16, would be conducted. Additionally, the eligibility criteria were updated based on the accumulating experience from ongoing Part A, other NASH studies, input from study investigators, and review of recent literature.
05 October 2017	To add Part C to the protocol to explore doses of tropifexor (LJN452) > 90 µg. Part C enrolled patients to be treated for 48 weeks with 140 µg tropifexor or 200 µg tropifexor

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No outputs were planned; and are not available for determining the effects of tropifexor on primary endpoints in the subset of patients who had historical biopsy data.

Notes: