Clinical trial results:
A multi-part, randomized, double-blind, placebo-controlled study to assess the safety, tolerability and efficacy of tropifexor (LJN452) in patients with Primary Biliary Cholangitis

Summary

EudraCT number	2015-001590-41
Trial protocol	DE PL
Global end of trial date	02 August 2018

Results information

Result version number	v1 (current)
This version publication date	22 August 2019
First version publication date	22 August 2019

Trial information

Trial identification

Sponsor protocol code	CLJN452X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02516605
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	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary Objectives:
1) To determine the effect of tropifexor on cholestatic markers in patients with PBC.
2) To determine the safety and tolerability of daily dosing of tropifexor in patients with PBC.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Canada: 7
Worldwide total number of subjects	61
EEA total number of subjects	38

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)	49
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study comprised of an escalating multiple dose design in PBC patients with incomplete biochemical response to, but still taking, ursodeoxycholic acid (UDCA).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LJN452 - 0.03 mg qd

Arm description:

Tropifexor 0.03 mg daily for 28 days

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

Dosage and administration details:

0.01 mg or 0.03 mg was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

Arm title	LJN452 - 0.06 mg qd

Arm description:

Tropifexor 0.06 mg daily for 28 days

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

Dosage and administration details:

0.01 mg or 0.03 mg was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

Arm title	LJN452 - 0.09 mg qd

Arm description:

Tropifexor 0.09 mg daily for 28 days

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

Dosage and administration details:

0.01 mg or 0.03 mg was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

Arm title	LJN452 - 0.15 mg qd

Arm description:

Tropifexor 0.15 mg daily for 28 days

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

Dosage and administration details:

0.01 mg or 0.03 mg was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

Arm title	Placebo qd

Arm description:

Tropifexor placebo daily for 28 days

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.01 mg or 0.03 mg matching placebo was prepared and supplied by Novartis as single blind patient-specific packs to be dispensed by the unblinded pharmacist at the investigator site.

Number of subjects in period 1	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd
Started	11	9	12
Completed	11	9	12
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	LJN452 - 0.15 mg qd	Placebo qd
Started	8	21
Completed	7	20
Not completed	1	1
Consent withdrawn by subject	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	LJN452 - 0.03 mg qd
Reporting group description: Tropifexor 0.03 mg daily for 28 days	
Reporting group title	LJN452 - 0.06 mg qd
Reporting group description: Tropifexor 0.06 mg daily for 28 days	
Reporting group title	LJN452 - 0.09 mg qd
Reporting group description: Tropifexor 0.09 mg daily for 28 days	
Reporting group title	LJN452 - 0.15 mg qd
Reporting group description: Tropifexor 0.15 mg daily for 28 days	
Reporting group title	Placebo qd
Reporting group description: Tropifexor placebo daily for 28 days	

Reporting group values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd
Number of subjects	11	9	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	6	11
From 65-84 years	4	3	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	58.6	57.9	53.6
standard deviation	± 12.42	± 11.21	± 7.42
Sex: Female, Male Units: Subjects			
Female	11	7	12
Male	0	2	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	10	8	12
Asian	0	0	0
Other	1	1	0

Reporting group values	LJN452 - 0.15 mg qd	Placebo qd	Total

Number of subjects	8	21	61
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	19	49
From 65-84 years	2	2	12
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	57.4	53.7	
standard deviation	± 13.81	± 10.19	-
Sex: Female, Male Units: Subjects			
Female	8	21	59
Male	0	0	2
Race/Ethnicity, Customized Units: Subjects			
Caucasian	8	19	57
Asian	0	1	1
Other	0	1	3

End points

End points reporting groups

Reporting group title	LJN452 - 0.03 mg qd
Reporting group description:	
Tropifexor 0.03 mg daily for 28 days	
Reporting group title	LJN452 - 0.06 mg qd
Reporting group description:	
Tropifexor 0.06 mg daily for 28 days	
Reporting group title	LJN452 - 0.09 mg qd
Reporting group description:	
Tropifexor 0.09 mg daily for 28 days	
Reporting group title	LJN452 - 0.15 mg qd
Reporting group description:	
Tropifexor 0.15 mg daily for 28 days	
Reporting group title	Placebo qd
Reporting group description:	
Tropifexor placebo daily for 28 days	
Subject analysis set title	LJN452 - 0.03 mg qd vs Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.03 mg daily for 28 days Tropifexor placebo daily for 28 days	
Subject analysis set title	LJN452 - 0.06 mg qd vs. Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.06 mg daily for 28 days Tropifexor placebo daily for 28 days	
Subject analysis set title	LJN452 - 0.09 mg qd vs. Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.09 mg daily for 28 days Tropifexor placebo daily for 28 days	
Subject analysis set title	LJN452 - 0.15 mg qd vs. Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.15 mg daily for 28 days Tropifexor placebo daily for 28 days	
Subject analysis set title	LJN452 - 0.03 mg qd vs Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.03 mg daily for 28 days Tropifexor placebo daily for 28 days	
Subject analysis set title	LJN452 - 0.03 mg qd vs Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.03 mg daily for 28 days Tropifexor placebo daily for 28 days	
Subject analysis set title	LJN452 - 0.06 mg qd vs. Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.06 mg daily for 28 days Tropifexor placebo daily for 28 days	

Subject analysis set title	LJN452 - 0.09 mg qd vs. Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.09 mg daily for 28 days Tropifexor placebo daily for 28 days	
Subject analysis set title	LJN452 - 0.15 mg qd vs. Placebo qd
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Tropifexor 0.15 mg daily for 28 days Tropifexor placebo daily for 28 days	

Primary: Fold change in serum gamma-glutamyl transferase (GGT)

End point title	Fold change in serum gamma-glutamyl transferase (GGT)[1][2]
End point description:	
Fold change in serum gamma-glutamyl transferase (GGT) from baseline to Day 28	
End point type	Primary
End point timeframe:	
Baseline to Day 28	

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: p-values were obtained from ANCOVA test but not shown due to system limitation.

[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: p-values were obtained from ANCOVA test but not shown due to system limitation.

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[3]	9[4]	12[5]	8[6]
Units: U/L				
number (confidence interval 90%)	0.86 (0.68 to 1.09)	0.47 (0.37 to 0.60)	0.32 (0.26 to 0.40)	0.36 (0.27 to 0.47)

Notes:

[3] - Overall Study LJN452 - 0.03 mg qd vs placebo

[4] - Overall Study LJN452 - 0.06 mg qd vs placebo

[5] - Overall Study LJN452 - 0.09 mg qd vs placebo

[6] - Overall Study LJN452 - 0.15 mg qd vs placebo

End point values	LJN452 - 0.03 mg qd vs Placebo qd	LJN452 - 0.06 mg qd vs. Placebo qd	LJN452 - 0.09 mg qd vs. Placebo qd	LJN452 - 0.15 mg qd vs. Placebo qd
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11	9	12	8
Units: U/L				
number (confidence interval 90%)	0.86 (0.68 to 1.09)	0.47 (0.37 to 0.60)	0.32 (0.26 to 0.40)	0.36 (0.27 to 0.47)

Statistical analyses

No statistical analyses for this end point

Primary: Blood pressure

End point title	Blood pressure[7]

End point description:

Vital signs - Systolic Blood pressure

End point type	Primary

End point timeframe:

Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84

Notes:

[7] - 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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	12	8
Units: mm Hg				
arithmetic mean (standard deviation)				
Screening	122.5 (± 12.21)	125.8 (± 11.79)	129.3 (± 14.42)	129.5 (± 17.42)
Baseline	124.7 (± 17.66)	128.4 (± 13.83)	122.0 (± 18.18)	132.3 (± 18.09)
Day 1	129.6 (± 20.48)	122.4 (± 20.24)	119.9 (± 11.84)	129.1 (± 25.12)
Day 7	127.2 (± 20.18)	123.7 (± 13.04)	125.6 (± 14.22)	128.0 (± 26.58)
Day 14	122.4 (± 16.30)	124.6 (± 20.67)	127.1 (± 16.45)	127.3 (± 12.45)
Day 21	121.5 (± 11.25)	126.3 (± 27.65)	123.9 (± 13.14)	124.0 (± 14.23)
Day 28	118.0 (± 11.22)	127.1 (± 28.55)	121.4 (± 12.82)	126.0 (± 7.71)
Day 56	121.4 (± 10.76)	125.4 (± 18.48)	121.5 (± 11.55)	129.1 (± 26.45)
Day 84	131.3 (± 16.04)	124.6 (± 15.77)	122.3 (± 7.70)	130.4 (± 25.51)

End point values	Placebo qd			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: mm Hg				
arithmetic mean (standard deviation)				
Screening	123.0 (± 15.40)			
Baseline	118.7 (± 12.76)			
Day 1	123.0 (± 21.84)			
Day 7	120.9 (± 19.57)			
Day 14	118.7 (± 12.88)			
Day 21	124.5 (± 19.8)			

Day 28	120.1 (± 22.38)			
Day 56	123.8 (± 19.74)			
Day 84	123.6 (± 19.09)			

Statistical analyses

No statistical analyses for this end point

Primary: Pulse rate

End point title	Pulse rate[8]

End point description:

Vital signs

End point type	Primary

End point timeframe:

Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84

Notes:

[8] - 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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	12	8
Units: bpm				
arithmetic mean (standard deviation)				
Screening	68.6 (± 10.63)	61.2 (± 7.05)	75.3 (± 8.22)	72.8 (± 8.26)
Baseline	64.3 (± 7.79)	64.1 (± 8.70)	70.8 (± 8.63)	74.4 (± 5.15)
Day 1	67.7 (± 11.93)	64.2 (± 8.07)	69.7 (± 7.50)	74.1 (± 11.62)
Day 7	65.2 (± 9.98)	66.8 (± 11.31)	70.1 (± 11.64)	73.5 (± 8.33)
Day 14	62.9 (± 10.03)	64.8 (± 8.09)	70.5 (± 14.16)	75.1 (± 6.74)
Day 21	65.5 (± 8.26)	65.8 (± 11.18)	73.2 (± 8.43)	72.5 (± 6.75)
Day 28	65.5 (± 10.83)	68.9 (± 10.60)	68.5 (± 9.01)	67.2 (± 3.42)
Day 56	66.8 (± 9.64)	67.7 (± 7.53)	69.7 (± 8.17)	69.7 (± 4.07)
Day 84	65.6 (± 10.24)	64.0 (± 9.11)	70.2 (± 8.14)	72.8 (± 8.12)

End point values	Placebo qd			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: bpm				
arithmetic mean (standard deviation)				
Screening	69.3 (± 10.69)			
Baseline	66.3 (± 9.30)			
Day 1	67.6 (± 8.35)			
Day 7	65.2 (± 8.92)			

Day 14	66.1 (± 9.61)			
Day 21	67.7 (± 10.18)			
Day 28	65.8 (± 9.29)			
Day 56	68.1 (± 10.11)			
Day 84	68.1 (± 9.82)			

Statistical analyses

No statistical analyses for this end point

Primary: Body Temperature

End point title	Body Temperature[9]

End point description:

Vital signs

End point type	Primary

End point timeframe:

Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84

Notes:

[9] - 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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	12	8
Units: Celsius				
arithmetic mean (standard deviation)				
screening	36.605 (± 0.2813)	36.567 (± 0.2000)	36.424 (± 0.3429)	36.650 (± 0.1604)
baseline	36.582 (± 0.2960)	36.644 (± 0.2128)	36.398 (± 0.3385)	36.638 (± 0.1506)
day 1	36.436 (± 0.3139)	36.537 (± 0.3076)	36.482 (± 0.2636)	36.575 (± 0.1982)
day 7	36.582 (± 0.2040)	36.533 (± 0.1323)	36.258 (± 0.3965)	36.600 (± 0.1195)
day 14	36.516 (± 0.1793)	36.444 (± 0.2007)	36.291 (± 0.4109)	36.500 (± 0.1826)
day 21	36.500 (± 0.2490)	36.267 (± 0.4637)	36.308 (± 0.3288)	36.433 (± 0.1966)
day 28	36.382 (± 0.2228)	36.444 (± 0.2128)	36.308 (± 0.3397)	36.520 (± 0.2950)
day 56	36.527 (± 0.2102)	36.500 (± 0.2179)	36.350 (± 0.4602)	36.443 (± 0.3309)
day 84	36.482 (± 0.2483)	36.500 (± 0.1500)	36.383 (± 0.2980)	36.638 (± 0.1506)

End point values	Placebo qd			
Subject group type	Reporting group			
Number of subjects analysed	21			

Units: Celsius				
arithmetic mean (standard deviation)				
screening	36.460 (± 0.4500)			
baseline	36.376 (± 0.5118)			
day 1	36.390 (± 0.4867)			
day 7	36.345 (± 0.4639)			
day 14	36.310 (± 0.4576)			
day 21	36.455 (± 0.4236)			
day 28	36.380 (± 0.4047)			
day 56	36.285 (± 0.4246)			
day 84	36.295 (± 0.4248)			

Statistical analyses

No statistical analyses for this end point

Primary: ECG - Heart Rate

End point title	ECG - Heart Rate[10]
End point description:	
Electrocardiogram (ECG)	
End point type	Primary
End point timeframe:	
Screening, Baseline, day 1, day 28	

Notes:

[10] - 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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	12	8
Units: bpm				
arithmetic mean (standard deviation)				
Screening	65.8 (± 11.32)	61.8 (± 9.97)	67.3 (± 5.58)	67.8 (± 6.54)
Baseline	60.5 (± 8.99)	61.4 (± 8.75)	64.6 (± 7.95)	67.9 (± 6.45)
Day 1	61.5 (± 11.16)	63.4 (± 11.17)	63.9 (± 8.21)	66.9 (± 11.97)
Day 28	60.5 (± 11.39)	65.2 (± 11.95)	63.5 (± 9.95)	65.8 (± 4.55)

End point values	Placebo qd			

Subject group type	Reporting group			
Number of subjects analysed	21			
Units: bpm				
arithmetic mean (standard deviation)				
Screening	63.4 (± 9.35)			
Baseline	63.8 (± 9.41)			
Day 1	63.5 (± 7.12)			
Day 28	60.8 (± 7.03)			

Statistical analyses

No statistical analyses for this end point

Primary: ECG Intervals - PR interval

End point title	ECG Intervals - PR interval[11]
End point description:	
Electrocardiogram (ECG)	
End point type	Primary
End point timeframe:	
Screening, Baseline, day 1, day 28	

Notes:

[11] - 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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	12	8
Units: msec				
arithmetic mean (standard deviation)				
Screening	159.2 (± 27.34)	158.0 (± 23.71)	172.0 (± 24.12)	159.9 (± 17.24)
Baseline	165.8 (± 20.81)	156.2 (± 18.99)	175.0 (± 34.96)	152.0 (± 22.21)
Day 1	165.5 (± 21.76)	162.9 (± 27.06)	175.7 (± 28.29)	160.0 (± 20.32)
Day 28	164.9 (± 19.75)	157.1 (± 26.70)	180.4 (± 31.63)	155.4 (± 23.51)

End point values	Placebo qd			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: msec				
arithmetic mean (standard deviation)				
Screening	162.6 (± 19.03)			
Baseline	160.3 (± 19.77)			

Day 1	161.6 (± 20.28)			
Day 28	160.2 (± 28.70)			

Statistical analyses

No statistical analyses for this end point

Primary: Haemoglobin

End point title	Haemoglobin[12]

End point description:

Hematology panel for safety laboratory assessments.

End point type	Primary

End point timeframe:

Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84

Notes:

[12] - 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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	12	8
Units: g/L				
arithmetic mean (standard deviation)				
screening	127.9 (± 9.24)	125.6 (± 11.70)	130.5 (± 9.73)	133.9 (± 12.70)
baseline	126.5 (± 8.58)	127.4 (± 11.85)	130.5 (± 11.90)	134.6 (± 13.24)
day 1	124.7 (± 8.21)	132.9 (± 10.05)	127.0 (± 9.03)	133.1 (± 11.37)
day 7	124.0 (± 8.23)	128.8 (± 16.97)	132.4 (± 10.66)	134.0 (± 8.75)
day 14	126.5 (± 9.83)	127.3 (± 12.64)	128.6 (± 7.82)	135.4 (± 13.50)
day 21	127.5 (± 8.32)	128.0 (± 13.49)	130.5 (± 10.40)	134.2 (± 9.91)
day 28	125.3 (± 9.18)	127.1 (± 14.67)	129.6 (± 10.02)	136.4 (± 13.50)
day 56	126.7 (± 6.96)	125.8 (± 11.15)	128.6 (± 10.63)	133.6 (± 12.00)
day 84	126.5 (± 8.78)	124.9 (± 9.75)	125.9 (± 11.19)	131.1 (± 10.91)

End point values	Placebo qd			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: g/L				
arithmetic mean (standard deviation)				

screening	132.2 (± 8.81)			
baseline	131.3 (± 8.02)			
day 1	126.8 (± 7.63)			
day 7	128.6 (± 9.18)			
day 14	128.7 (± 10.84)			
day 21	128.8 (± 10.79)			
day 28	125.7 (± 9.71)			
day 56	129.3 (± 11.39)			
day 84	129.3 (± 9.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma PK parameter - AUC 0-8h

End point title	Plasma PK parameter - AUC 0-8h[13]

End point description:

Tropifexor levels were determined in plasma using a validated LC-MS/MS method. AUC0-t=The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]

End point type	Secondary

End point timeframe:

Day 1, Day 28

Notes:

[13] - 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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	7	3	4
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Day 1	4.98 (± 2.87)	12.1 (± 2.68)	999 (± 999)	24.5 (± 15.9)
Day 28	7.95 (± 4.21)	17.6 (± 5.30)	23.4 (± 8.70)	44.2 (± 25.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma PK parameter - Cmax

End point title	Plasma PK parameter - Cmax[14]

End point description:

Tropifexor levels were determined in plasma using a validated LC-MS/MS method. Cmax=The observed

maximum plasma concentration following drug administration [mass /volume]

End point type	Secondary

End point timeframe:

Day 1, Day 28

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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	12	8
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	1.04 (± 0.484)	1.80 (± 0.585)	2.37 (± 1.56)	4.84 (± 2.59)
Day 28	1.25 (± 0.559)	2.55 (± 0.946)	4.30 (± 2.10)	6.37 (± 3.40)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma PK parameter - Tmax

End point title	Plasma PK parameter - Tmax[15]

End point description:

Tropifexor levels were determined in plasma using a validated LC-MS/MS method. Tmax = The time to reach the maximum concentration after drug administration [time]

End point type	Secondary

End point timeframe:

Day 1, Day 28

Notes:

[15] - 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: descriptive analysis

End point values	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	9	12	8
Units: hr				
median (inter-quartile range (Q1-Q3))				
Day 1	4.12 (2.00 to 8.00)	4.00 (3.70 to 6.00)	4.00 (0 to 7.83)	4.00 (4.00 to 4.18)
Day 28	4.08 (2.00 to 8.00)	4.00 (3.13 to 7.60)	4.00 (0 to 6.00)	5.00 (3.03 to 6.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in total PBC-40 score

End point title	Changes from baseline in total PBC-40 score

End point description:

Median difference: LJN452 vs Placebo. Baseline is defined as the latest available predose value. The PBC-40 is a paper-based patient-derived, disease specific quality of life patient reported outcome (PRO) measure which was developed and validated for use in subjects with PBC (Jacoby et al 2005). It consists of 40 questions arranged in 8 domains with between 3 and 11 questions in each domain. Each question is scored from 1 to 5 in increasing order of severity. The difference in total sum score between each treated group and placebo at Day 28 is presented.

End point type	Secondary

End point timeframe:

Baseline, Day 28, Day 56, Day 84

End point values	LJN452 - 0.03 mg qd vs Placebo qd	LJN452 - 0.06 mg qd vs. Placebo qd	LJN452 - 0.09 mg qd vs. Placebo qd	LJN452 - 0.15 mg qd vs. Placebo qd
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	9	12	8
Units: PBC-40 points				
median (confidence interval 90%)				
Day 28	1.0 (-7.0 to 6.0)	1.5 (-5.0 to 7.0)	4.0 (-3.0 to 8.0)	2.0 (-2.0 to 9.0)
Day 56	2.0 (-4.0 to 10.0)	-2.0 (-12.0 to 4.0)	-6.0 (-14.0 to 1.0)	-11.0 (-21.0 to -1.0)
Day 84	-3.0 (-11.0 to 4.0)	-1.0 (-10.0 to 8.0)	-6.5 (-15.0 to 1.0)	-3.5 (-11.0 to 3.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in itch subdomain of PBC-40 score

End point title	Change from baseline in itch subdomain of PBC-40 score

End point description:

Median difference: LJN452 vs Placebo. Baseline is defined as the latest available predose value. The domain specifically relates to cholestatic itch symptomatology. In addition to the investigation of the total PBC-40 sum score, the sum scores from the 3 question itch sub-domain of the PBC-40 questionnaire was determined and used to test for an effect of tropifexor relative to placebo.

End point type	Secondary

End point timeframe:

Baseline, Day 28, Day 56, Day 84

End point values	LJN452 - 0.06 mg qd vs. Placebo qd	LJN452 - 0.09 mg qd vs. Placebo qd	LJN452 - 0.15 mg qd vs. Placebo qd	LJN452 - 0.03 mg qd vs Placebo qd
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	12	8	9
Units: PBC-40 points				
median (confidence interval 90%)				
Day 28	1.0 (0.0 to 2.0)	2.0 (0.0 to 4.0)	2.0 (0.0 to 5.0)	1.0 (-1.0 to 2.0)
Day 56	1.0 (0.0 to 2.0)	0.0 (-1.0 to 2.0)	0.0 (-1.0 to 1.0)	0.0 (-1.0 to 2.0)
Day 84	0.0 (-2.0 to 1.0)	0.0 (-2.0 to 1.0)	0.0 (-2.0 to 1.0)	-1.0 (-3.0 to 1.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Global Itch Visual Analogue Scale (VAS)

End point title	Change from baseline in Global Itch Visual Analogue Scale (VAS)

End point description:

The Global Itch Visual Analogue Scale, a 100 mm visual analogue scale (VAS) was used to assess the severity of patients itch (ranging from 0 = none at all to 10 = the worst imaginable itch) and the 100 mm Sleep Disturbance Visual Analogue Scale was used to assess the impact of nocturnal itch on sleep (from 0 = no sleep loss to 10 = cannot sleep at all). The score (distance in mm from left) on the VAS was recorded for both parameters by the patient marking with a line and used to test for an effect of tropifexor over placebo.

End point type	Secondary

End point timeframe:

Day 7, Day 14, Day 21, Day 28, Day 56, and Day 84

End point values	LJN452 - 0.03 mg qd vs Placebo qd	LJN452 - 0.06 mg qd vs. Placebo qd	LJN452 - 0.09 mg qd vs. Placebo qd	LJN452 - 0.15 mg qd vs. Placebo qd
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	9	12	8
Units: mm				
arithmetic mean (confidence interval 90%)				
Day 7	-2.78 (-16.91 to 11.34)	11.34 (-2.78 to 25.46)	13.92 (0.58 to 27.25)	26.70 (11.97 to 41.44)
Day 14	-14.07 (-27.85 to -0.28)	7.74 (-6.05 to 21.52)	0.48 (-12.57 to 13.53)	8.17 (-6.96 to 23.29)
Day 21	7.78 (-6.81 to 22.38)	16.79 (2.20 to 31.38)	5.02 (-8.79 to 18.83)	5.90 (-10.86 to 22.66)
Day 28	7.03 (-8.36 to 22.43)	14.05 (-1.35 to 29.44)	0.19 (-14.38 to 14.77)	8.91 (-9.34 to 27.15)
Day 56	-15.25 (-27.30 to -3.19)	-1.75 (-13.80 to 10.31)	-13.82 (-25.21 to -2.43)	-11.08 (-23.95 to 1.80)
Day 84	-16.93 (-31.31 to -2.54)	-10.90 (-25.29 to 3.48)	-18.23 (-31.81 to -4.64)	-16.93 (-31.94 to -1.92)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 56 days post last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	LJN452 - 0.03 mg qd
Reporting group description:	
Tropifexor 0.03 mg daily for 28 days	
Reporting group title	Placebo qd
Reporting group description:	
Tropifexor placebo daily for 28 days	
Reporting group title	LJN452 - 0.15 mg qd
Reporting group description:	
Tropifexor 0.15 mg daily for 28 days	
Reporting group title	LJN452 - 0.06 mg qd
Reporting group description:	
Tropifexor 0.06 mg daily for 28 days	
Reporting group title	LJN452 - 0.09 mg qd
Reporting group description:	
Tropifexor 0.09 mg daily for 28 days	

Serious adverse events	LJN452 - 0.03 mg qd	Placebo qd	LJN452 - 0.15 mg qd
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	LJN452 - 0.03 mg qd	Placebo qd	LJN452 - 0.15 mg qd
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)	16 / 21 (76.19%)	8 / 8 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Non-cardiac chest pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 11 (0.00%)	2 / 21 (9.52%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Vulvovaginal discomfort			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			

subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Sleep disorder			
subjects affected / exposed	1 / 11 (9.09%)	1 / 21 (4.76%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Low density lipoprotein increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Weight increased			

subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 11 (18.18%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Muscle strain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Trifascicular block			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Dysgeusia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 11 (0.00%)	3 / 21 (14.29%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Hypoaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Optic neuritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Leukopenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			
subjects affected / exposed	2 / 11 (18.18%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 11 (9.09%)	3 / 21 (14.29%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Constipation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			

subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Epigastric discomfort			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 11 (9.09%)	3 / 21 (14.29%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Varices oesophageal			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)	2 / 21 (9.52%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 11 (27.27%)	6 / 21 (28.57%)	7 / 8 (87.50%)
occurrences (all)	3	7	7
Pruritus generalised			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Psoriasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 11 (9.09%)	1 / 21 (4.76%)	1 / 8 (12.50%)
occurrences (all)	1	1	2

Rash maculo-papular			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	2 / 11 (18.18%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Fungal infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 11 (18.18%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Overgrowth bacterial			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Rash pustular			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	1 / 11 (9.09%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 11 (0.00%)	2 / 21 (9.52%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hyperlipidaemia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 21 (4.76%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 11 (0.00%)	0 / 21 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	

Total subjects affected by non-serious adverse events subjects affected / exposed	8 / 9 (88.89%)	11 / 12 (91.67%)	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Non-cardiac chest pain subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	
Reproductive system and breast disorders Vulvovaginal discomfort subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1	

Sinus congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Blood creatinine increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Low density lipoprotein increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Weight increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Arthropod bite			

subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Trifascicular block			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Hypoaesthesia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Optic neuritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			

subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Eye pruritus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Abdominal pain lower			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Epigastric discomfort			

subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Flatulence			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Varices oesophageal			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 9 (66.67%)	5 / 12 (41.67%)	
occurrences (all)	7	5	
Pruritus generalised			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Psoriasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Proteinuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Fungal infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Overgrowth bacterial			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	

Sinusitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Tooth abscess			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Viral infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hyperlipidaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Iron deficiency			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2015	The purpose of this amendment was to address comments from a health authority. Additional inclusion criterion for Part 2 were updated.
06 November 2015	During the creation of Version No. 01 of the protocol, pregnancy testing was inadvertently removed from the Assessment Schedule. The purpose of this amendment was to re-add pregnancy testing into the protocol.
18 March 2016	The purpose of this amendment was to add a separate renal function exclusion criteria (criteria no.14). Exclusion criteria 2 and 3 were updated. In addition, other minor changes, such as the inclusion of ALP isozyme analysis, a patient dosing diary to monitor compliance, and typographical corrections were made to the protocol.
14 July 2016	The purpose of this amendment was to address feedback from a health authority. Changes have also been made to the protocol to reduce the burden on the patients participating in the study. Additional changes were made including clarification and slight modification of eligibility criteria (BMI range in the inclusion criteria 5 was updated, additional inclusion criteria for Part 1 were updated and exclusion criteria 3 and 4 were updated), addition of updated text describing the statistical analysis, addition of a higher dosage form, and addition of minor editorial updates.
22 June 2017	To enable higher dose(s) in Part 1 & 2 of the study, supported by new preclinical safety data, and to update the Part 2 study design to allow 12 wks of treatment in patients with PBC, to provide longer-term safety, tolerability and efficacy data. The additional incl criteria for Part 2 were updated to add further details. Exclusion criteria 2 & 10 were updated. Excl criteria 3, 4, 15, 16, 17 & 18 were added in this amendment.
27 November 2017	The purpose of this amendment was to address comments received from a health authority in response to protocol amendment 5. In addition, the blood volume was updated to enable the collection of additional samples for Vitamin D, biomarker and PK back-up samples. The inclusion criteria 4 was updated to included additional biochemical criteria at enrollment. The exclusion 4, 14 and 15 were updated to add additional details.

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.

Part 2 was not executed and a decision was made to terminate the study early as data revealed that Part 1 fulfilled the strategic purpose of the study.

Notes: