NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

tropifexor

Trial Indication(s)

Primary biliary cholangitis

Protocol Number

CLJN452X2201

Protocol Title

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

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: September 2015 (Actual)
Primary Completion Date: August 2018 (Actual)

Study Completion Date: August 2018 (Actual)

Reason for Termination (If applicable)

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.

Study Design/Methodology

This study was designed as a randomized, double-blind, placebo-controlled, multi-part study to assess safety, tolerability and efficacy of tropifexor in patients with PBC.
Part 1 comprised of an escalating multiple dose design in PBC patients with incomplete biochemical response to, but still taking, ursodeoxycholic acid (UDCA). Four cohorts (0.03 mg, 0.06 mg, 0.09 mg and 0.15 mg) of approximately 15 patients with PBC with incomplete biochemical response to, but still taking UDCA treatment were to be enrolled.

A second part of the study (Part 2) was designed as a parallel-group, 12-week study to assess the safety, tolerability and efficacy of two doses of tropifexor compared to placebo in PBC patients with an incomplete biochemical response to, but still taking, UDCA or those not currently taking UDCA. However, 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.

Centers

28 centers in 6 countries: United States(9), United Kingdom(5), Germany(5), Canada(2), Poland(4), Russia(3)

Objectives:

Primary Objectives:

- To determine the effect of tropifexor on cholestatic markers in patients with PBC.
- To determine the safety and tolerability of daily dosing of tropifexor in patients with PBC.

Secondary Objectives:

- To evaluate the pharmacokinetics (PK) of tropifexor in patients with PBC.
- To evaluate the change in overall disease specific quality of life.
- To determine the change in the itch domain of PBC-40 questionnaire.

- To evaluate the change in itch based on 100 mm visual analog score (VAS).

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational drug, tropifexor 0.01 mg or 0.03 mg and matching placebo, was prepared and supplied by Novartis as a single blind patient-specific pack.

Statistical Methods

Analysis of primary variables:
The primary efficacy endpoint was the fold change in serum GGT from baseline to Day 28. The serum GGT values at all time points were logarithmically transformed prior to analysis. The change from baseline was calculated as the difference between each of the log transformed post-dose serum GGT values and the log transformed baseline serum GGT value. Log-transformed changes from baseline for serum GGT were analyzed by repeated measures analysis of covariance (ANCOVA).
Analysis of secondary variables:
Efficacy/Pharmacodynamics
The secondary efficacy/PD variables included alkaline phosphatase (ALP) and patient reported variables such as the PBC-40 total score, the PBC-40 itch domain score, the visual analog scale (VAS) for itch and sleep. The change from baseline was calculated as the difference between each of the post-dose values and the baseline value. The difference between tropifexor and placebo at Day 28 was compared using Wilcoxon rank sum test for change from baseline in total PBC-40 score and PBC-40 itch subdomain score. A two-sided p value and 90% CI for a treatment difference was reported with no adjustment for multiplicity.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
• Age ≥ 18 years
• Diagnosis of PBC as demonstrated by the presence of at least 2 of the following 3 diagnostic criteria:
o History of alkaline phosphatase (ALP) elevated above upper limit of normal (ULN) for at least 6 months
o Positive antimitochondrial antibodies (AMA) titer or if AMA negative or in low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100 and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex))

o Previous liver biopsy findings consistent with PBC
• At least 1 of the following markers of disease severity:
o ALP ≥ 1.67 × ULN
o Total bilirubin > ULN but < 1.5 × ULN
• In addition, patients must meet the following biochemical criteria at enrollment:
o Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 5 × ULN
o Total bilirubin ≤ 1.5 × ULN
o INR ≤ ULN
• Taking UDCA for at least 12 months, or for at least 6 months and has reached maximal response to UDCA with a plateau in alkaline phosphatase, with no changes in dose for ≥ 3 months prior to Day 1.
• Patients must weigh at least 40 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 40 kg/m2. BMI = Body weight (kg) / [Height (m)]2

Exclusion Criteria:
• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception for 30 days before randomization, during dosing and for 30 days following the end of treatment.
• Presence of other concomitant liver diseases.
o Cirrhosis with complications, including history or presence of:
o Variceal bleed
o Uncontrolled ascites
o Encephalopathy
o Spontaneous bacterial peritonitis
• Significant hepatic impairment as defined by Child-Pugh classification of B or C, history of liver transplantation, current placement on a liver transplant list or current Model for End Stage Liver Disease (MELD) score ≥15.
• History of conditions that may cause increases in ALP (e.g., Paget's disease).
• Use of investigational drugs, or immunosuppressive drugs at the time of enrollment, or within 5 half-lives, or 30 days of randomization, whichever is longer; or longer if required by local regulations. Use of high dose oral steroids to treat co-morbid conditions (e.g., airways disease) will be allowed but must be properly documented as such in concomitant medications.
• Currently taking obeticholic acid or have taken obeticholic acid within 30 days of randomization
• Previous participation in CLJN452X2201 and received study medication within three months of randomization (or longer if required by local regulations).

Participant Flow Table

Overall Study

	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd	Placebo qd	Total
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days	
Started	11	9	12	8	21	61
Completed	11	9	12	7	20	59
Not Completed	0	0	0	1	1	2
Protocol Violation	0	0	0	0	1	1
Withdrawal by Subject	0	0	0	1	0	1

Baseline Characteristics

	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd	Placebo qd	Total
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days	
Number of Participants [units: participants]	11	9	12	8	21	61
Age Continuous (units: years) Mean ± Standard Deviation						
	58.6±12.42	57.9±11.21	53.6±7.42	57.4±13.81	53.7±10.19	55.7±10.70

Sex: Female, Male (units: participants) Count of Participants (Not Applicable)						
Female	11	7	12	8	21	59
Male	0	2	0	0	0	2
Race/Ethnicity, Customized (units: participants)						
Caucasian	10	8	12	8	19	57
Asian	0	0	0	0	1	1
Other	1	1	0	0	1	3

Summary of Efficacy

Primary Outcome Result(s)

Fold change in serum gamma-glutamyl transferase (GGT)

(Time Frame: Baseline to Day 28)

	LJN452 - 0.03 mg qd	**LJN452 - 0.06 mg qd**	**LJN452 - 0.09 mg qd**	**LJN452 - 0.15 mg qd**
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8
Fold change in serum gamma-glutamyl transferase (GGT) (units: U/L) Number (90% Confidence Interval)				

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 Analysis

Groups	LJN452 - 0.03 mg qd
P Value	0.293
Method	ANCOVA

Statistical Analysis

Groups	LJN452 - 0.06 mg qd
P Value	<0.001
Method	ANCOVA

Statistical Analysis

Groups	LJN452 - 0.09 mg qd
P Value	<.001
Method	ANCOVA

Statistical Analysis

Groups	LJN452 - 0.15 mg qd
P Value	<.001
Method	ANCOVA

Blood pressure

(Time Frame: Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84)

	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd	Placebo qd

Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8	21
Blood pressure (units: mm Hg) Mean ± Standard Deviation					
Screening	122.5 ± 12.21	125.8 ± 11.79	129.3 ± 14.42	129.5 ± 17.42	123.0 ± 15.40
Baseline	124.7 ± 17.66	128.4 ± 13.83	122.0 ± 18.18	132.3 ± 18.09	118.7 ± 12.76
Day 1	129.6 ± 20.48	122.4 ± 20.24	119.9 ± 11.84	129.1 ± 25.12	123.0 ± 21.84
Day 7	127.2 ± 20.18	123.7 ± 13.04	125.6 ± 14.22	128.0 ± 26.58	120.9 ± 19.57
Day 14	122.4 ± 16.30	124.6 ± 20.67	127.1 ± 16.45	127.3 ± 12.45	118.7 ± 12.88
Day 21	121.5 ± 11.25	126.3 ± 27.65	123.9 ± 13.14	124.0 ± 14.23	124.5 ± 19.8
Day 28	118.0 ± 11.22	127.1 ± 28.55	121.4 ± 12.82	126.0 ± 7.71	120.1 ± 22.38
Day 56	121.4 ± 10.76	125.4 ± 18.48	121.5 ± 11.55	129.1 ± 26.45	123.8 ± 19.74
Day 84	131.3 ± 16.04	124.6 ± 15.77	122.3 ± 7.70	130.4 ± 25.51	123.6 ± 19.09

Pulse rate

(Time Frame: Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84)

	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd	Placebo qd
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8	21

Pulse rate (units: bpm) Mean ± Standard Deviation					
Screening	68.6 ± 10.63	61.2 ± 7.05	75.3 ± 8.22	72.8 ± 8.26	69.3 ± 10.69
Baseline	64.3 ± 7.79	64.1 ± 8.70	70.8 ± 8.63	74.4 ± 5.15	66.3 ± 9.30
Day 1	67.7 ± 11.93	64.2 ± 8.07	69.7 ± 7.50	74.1 ± 11.62	67.6 ± 8.35
Day 7	65.2 ± 9.98	66.8 ± 11.31	70.1 ± 11.64	73.5 ± 8.33	65.2 ± 8.92
Day 14	62.9 ± 10.03	64.8 ± 8.09	70.5 ± 14.16	75.1 ± 6.74	66.1 ± 9.61
Day 21	65.5 ± 8.26	65.8 ± 11.18	73.2 ± 8.43	72.5 ± 6.75	67.7 ± 10.18
Day 28	65.5 ± 10.83	68.9 ± 10.60	68.5 ± 9.01	67.2 ± 3.42	65.8 ± 9.29
Day 56	66.8 ± 9.64	67.7 ± 7.53	69.7 ± 8.17	69.7 ± 4.07	68.1 ± 10.11
Day 84	65.6 ± 10.24	64.0 ± 9.11	70.2 ± 8.14	72.8 ± 8.12	68.1 ± 9.82

Body Temperature

(Time Frame: Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84)

	LJN452 - 0.03 mg qd	**LJN452 - 0.06 mg qd**	**LJN452 - 0.09 mg qd**	**LJN452 - 0.15 mg qd**	**Placebo qd**
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8	21
Body Temperature (units: Celsius) Mean ± Standard Deviation					
Screening	36.605 ± 0.2813	36.567 ± 0.2000	36.424 ± 0.3429	36.650 ± 0.1604	36.460 ± 0.4500
baseline	36.582 ± 0.2960	36.644 ± 0.2128	36.398 ± 0.3385	36.638 ± 0.1506	36.376 ± 0.5118

day 1	36.436 ± 0.3139	36.537 ± 0.3076	36.482 ± 0.2636	36.575 ± 0.1982	36.390 ± 0.4867
day 7	36.582 ± 0.2040	36.533 ± 0.1323	36.258 ± 0.3965	36.600 ± 0.1195	36.345 ± 0.4639
day 14	36.516 ± 0.1793	36.444 ± 0.2007	36.291 ± 0.4109	36.500 ± 0.1826	36.310 ± 0.4576
day 21	36.500 ± 0.2490	36.267 ± 0.4637	36.308 ± 0.3288	36.433 ± 0.1966	36.455 ± 0.4236
day 28	36.382 ± 0.2228	36.444 ± 0.2128	36.308 ± 0.3397	36.520 ± 0.2950	36.380 ± 0.4047
day 56	36.527 ± 0.2102	36.500 ± 0.2179	36.350 ± 0.4602	36.443 ± 0.3309	36.285 ± 0.4246
day 84	36.482 ± 0.2483	36.500 ± 0.1500	36.383 ± 0.2980	36.638 ± 0.1506	36.295 ± 0.4248

ECG - Heart Rate

(Time Frame: Screening, Baseline, day 1, day 28)

	LJN452 - 0.03 mg qd	**LJN452 - 0.06 mg qd**	**LJN452 - 0.09 mg qd**	**LJN452 - 0.15 mg qd**	**Placebo qd**
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8	21
ECG - Heart Rate (units: bpm) Mean ± Standard Deviation					
Screening	65.8 ± 11.32	61.8 ± 9.97	67.3 ± 5.58	67.8 ± 6.54	63.4 ± 9.35
Baseline	60.5 ± 8.99	61.4 ± 8.75	64.6 ± 7.95	67.9 ± 6.45	63.8 ± 9.41
Day 1	61.5 ± 11.16	63.4 ± 11.17	63.9 ± 8.21	66.9 ± 11.97	63.5 ± 7.12
Day 28	60.5 ± 11.39	65.2 ± 11.95	63.5 ± 9.95	65.8 ± 4.55	60.8 ± 7.03

ECG Intervals - PR interval

(Time Frame: Screening, Baseline, day 1, day 28)

	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd	Placebo qd
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8	21
ECG Intervals - PR interval (units: msec) Mean ± Standard Deviation					
Screening	159.2 ± 27.34	158.0 ± 23.71	172.0 ± 24.12	159.9 ± 17.24	162.6 ± 19.03
Baseline	165.8 ± 20.81	156.2 ± 18.99	175.0 ± 34.96	152.0 ± 22.21	160.3 ± 19.77
Day 1	165.5 ± 21.76	162.9 ± 27.06	175.7 ± 28.29	160.0 ± 20.32	161.6 ± 20.28
Day 28	164.9 ± 19.75	157.1 ± 26.70	180.4 ± 31.63	155.4 ± 23.51	160.2 ± 28.70

Haemoglobin

(Time Frame: Screening, Baseline, day 1, day 7, day 14, day 21, day 28, day 56, day 84)

	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd	Placebo qd
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8	21
Haemoglobin (units: g/L) Mean ± Standard Deviation					

Screening	127.9 ± 9.24	125.6 ± 11.70	130.5 ± 9.73	133.9 ± 12.70	132.2 ± 8.81
baseline	126.5 ± 8.58	127.4 ± 11.85	130.5 ± 11.90	134.6 ± 13.24	131.3 ± 8.02
day 1	124.7 ± 8.21	132.9 ± 10.05	127.0 ± 9.03	133.1 ± 11.37	126.8 ± 7.63
day 7	124.0 ± 8.23	128.8 ± 16.97	132.4 ± 10.66	134.0 ± 8.75	128.6 ± 9.18
day 14	126.5 ± 9.83	127.3 ± 12.64	128.6 ± 7.82	135.4 ± 13.50	128.7 ± 10.84
day 21	127.5 ± 8.32	128.0 ± 13.49	130.5 ± 10.40	134.2 ± 9.91	128.8 ± 10.79
day 28	125.3 ± 9.18	127.1 ± 14.67	129.6 ± 10.02	136.4 ± 13.50	125.7 ± 9.71
day 56	126.7 ± 6.96	125.8 ± 11.15	128.6 ± 10.63	133.6 ± 12.00	129.3 ± 11.39
day 84	126.5 ± 8.78	124.9 ± 9.75	125.9 ± 11.19	131.1 ± 10.91	129.3 ± 9.24

Secondary Outcome Result(s)

Plasma PK parameter - AUC 0-8h

(Time Frame: Day 1, Day 28)

	LJN452 - 0.03 mg qd	**LJN452 - 0.06 mg qd**	**LJN452 - 0.09 mg qd**	**LJN452 - 0.15 mg qd**
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days
Number of Participants Analyzed [units: participants]	9	7	3	4
Plasma PK parameter - AUC 0-8h (units: hr*ng/mL) Mean ± Standard Deviation				
Day 1	4.98 ± 2.87	12.1 ± 2.68		24.5 ± 15.9
Day 28	7.95 ± 4.21	17.6 ± 5.30	23.4 ± 8.70	44.2 ± 25.8

Plasma PK parameter - Cmax

(Time Frame: Day 1, Day 28)

	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8
Plasma PK parameter - Cmax (units: ng/mL) 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

Plasma PK parameter - Tmax

(Time Frame: Day 1, Day 28)

	LJN452 - 0.03 mg qd	LJN452 - 0.06 mg qd	LJN452 - 0.09 mg qd	LJN452 - 0.15 mg qd
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days
Number of Participants Analyzed [units: participants]	11	9	12	8
Plasma PK parameter - Tmax (units: hr) Median (Inter-Quartile Range)				
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)

Changes from baseline in total PBC-40 score

(Time Frame: Baseline, Day 28, Day 56, Day 84)

	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
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days. Tropifexor placebo daily for 28 days	Tropifexor 0.06 mg daily for 28 days. Tropifexor placebo daily for 28 days.	Tropifexor 0.09 mg daily for 28 days. Tropifexor placebo daily for 28 days.	Tropifexor 0.15 mg daily for 28 days. Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	10	9	12	8
Changes from baseline in total PBC-40 score (units: PBC-40 points) Median (90% Confidence Interval)				
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 Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.898	
Method	Other Wilcoxon rank-sum test	Day 28

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.593	
Method	Other Wilcoxon rank-sum test	Day 56

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.509	
Method	Other Wilcoxon rank-sum test	Day 84

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd	
P Value	0.591	
Method	Other Wilcoxon rank-sum test	Day 28

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd	
P Value	0.702	
Method	Other Wilcoxon rank-sum test	Day 56

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd	
P Value	0.838	
Method	Other Wilcoxon rank-sum test	Day 84

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.297	
Method	Other Wilcoxon rank-sum test	Day 28

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.236	
Method	Other Wilcoxon rank-sum test	Day 56

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.192	
Method	Other Wilcoxon rank-sum test	Day 84

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd	
P Value	0.605	
Method	Other Wilcoxon rank-sum test	Day 28

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd
P Value	0.037

Method	Other Wilcoxon rank-sum test	Day 56

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd
P Value	0.397
Method	Other Wilcoxon rank-sum test
	Day 84

Change from baseline in itch subdomain of PBC-40 score

(Time Frame: Baseline, Day 28, Day 56, Day 84)

	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**
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days. Tropifexor placebo daily for 28 days	Tropifexor 0.06 mg daily for 28 days. Tropifexor placebo daily for 28 days.	Tropifexor 0.09 mg daily for 28 days. Tropifexor placebo daily for 28 days.	Tropifexor 0.15 mg daily for 28 days. Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	9	9	12	8
Change from baseline in itch subdomain of PBC-40 score (units: PBC-40 points) Median (90% Confidence Interval)				
Day 28	1.0 (-1.0 to 2.0)	1.0 (0.0 to 2.0)	2.0 (0.0 to 4.0)	2.0 (0.0 to 5.0)
Day 56	0.0 (-1.0 to 2.0)	1.0 (0.0 to 2.0)	0.0 (-1.0 to 2.0)	0.0 (-1.0 to 1.0)
Day 84	-1.0 (-3.0 to 1.0)	0.0 (-2.0 to 1.0)	0.0 (-2.0 to 1.0)	0.0 (-2.0 to 1.0)

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.342	
Method	Other Wilcoxon rank-sum test	Day 28

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.699	
Method	Other Wilcoxon rank-sum test	Day 56

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.377	
Method	Other Wilcoxon rank-sum test	Day 84

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd	
P Value	0.132	
Method	Other Wilcoxon rank-sum test	Day 28

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd	
P Value	0.292	
Method	Other Wilcoxon rank-sum test	Day 56

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd	
P Value	0.979	
Method	Other Wilcoxon rank-sum test	Day 84

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.102	
Method	Other Wilcoxon rank-sum test	Day 28

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.717	
Method	Other Wilcoxon rank-sum test	Day 56

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	1.000	
Method	Other Wilcoxon rank-sum test	Day 84

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd	
P Value	0.142	

Method	Other Wilcoxon rank-sum test	Day 28

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd
P Value	0.975
Method	Other Wilcoxon rank-sum test
Time	Day 56

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd
P Value	0.602
Method	Other Wilcoxon rank-sum test
Time	Day 84

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

(Time Frame: Day 7, Day 14, Day 21, Day 28, Day 56, and Day 84)

	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**
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days. Tropifexor placebo daily for 28 days.	Tropifexor 0.06 mg daily for 28 days Tropifexor placebo daily for 28 days	Tropifexor 0.09 mg daily for 28 days Tropifexor placebo daily for 28 days	Tropifexor 0.15 mg daily for 28 days Tropifexor placebo daily for 28 days
Number of Participants Analyzed [units: participants]	10	9	12	8

Change from baseline in Global Itch Visual Analogue Scale (VAS)
(units: mm)
Mean (90% Confidence Interval)

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 Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.743	
Method	ANCOVA	Day 7

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.093	
Method	ANCOVA	Day 14

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.376	
Method	ANCOVA	Day 21

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.448	
Method	ANCOVA	Day 28

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.039	
Method	ANCOVA	Day 56

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd	
P Value	0.054	
Method	ANCOVA	Day 84

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd
P Value	0.185

Method	ANCOVA	Day 7

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd
P Value	0.351
Method	ANCOVA

Method	ANCOVA	Day 14

Statistical Analysis

Groups	LJN452 - 0.03 mg qd vs Placebo qd
P Value	0.059
Method	ANCOVA

Method	ANCOVA	day 21

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd
P Value	0.132
Method	ANCOVA

Method	ANCOVA	Day 28

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd
P Value	0.809
Method	ANCOVA

Method	ANCOVA	Day 56

Statistical Analysis

Groups	LJN452 - 0.06 mg qd vs. Placebo qd	
P Value	0.210	
Method	ANCOVA	Day 84

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.086	
Method	ANCOVA	day 7

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.951	
Method	ANCOVA	Day 14

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.545	
Method	ANCOVA	day 21

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd	
P Value	0.982	

Method	ANCOVA	Day 28

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd
P Value	0.047
Method	ANCOVA

day 56

Statistical Analysis

Groups	LJN452 - 0.09 mg qd vs. Placebo qd
P Value	0.029
Method	ANCOVA

Day 84

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd
P Value	0.004
Method	ANCOVA

Day 7

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd
P Value	0.370
Method	ANCOVA

Day 14

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd	
P Value	0.558	
Method	ANCOVA	Day 21

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd	
P Value	0.418	
Method	ANCOVA	Day 28

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd	
P Value	0.156	
Method	ANCOVA	Day 56

Statistical Analysis

Groups	LJN452 - 0.15 mg qd vs. Placebo qd	
P Value	0.064	
Method	ANCOVA	Day 84

Summary of Safety

Safety Results

All-Cause Mortality

	LJN452 - 0.03 mg qd N = 11	LJN452 - 0.06 mg qd N = 9	LJN452 - 0.09 mg qd N = 12	LJN452 - 0.15 mg qd N = 8	Placebo qd N = 21
Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	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.
Source Vocabulary for Table Default	MedDRA (21.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

LJN452 - 0.03 mg qd N = 11	LJN452 - 0.06 mg qd N = 9	LJN452 - 0.09 mg qd N = 12	LJN452 - 0.15 mg qd N = 8	Placebo qd N = 21

Arm/Group Description	Tropifexor 0.03 mg daily for 28 days	Tropifexor 0.06 mg daily for 28 days	Tropifexor 0.09 mg daily for 28 days	Tropifexor 0.15 mg daily for 28 days	Tropifexor placebo daily for 28 days
Total participants affected	9 (81.82%)	8 (88.89%)	11 (91.67%)	8 (100.00%)	16 (76.19%)
Blood and lymphatic system disorders					
Anaemia	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Leukopenia	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thrombocytopenia	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders					
Trifascicular block	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders					
Dry eye	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Eye pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Gastrointestinal disorders					
Abdominal discomfort	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal distension	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain lower	2 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain upper	1 (9.09%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	3 (14.29%)
Constipation	0 (0.00%)	1 (11.11%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Diarrhoea	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Dry mouth	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Dyspepsia	1 (9.09%)	2 (22.22%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Epigastric discomfort	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Flatulence	1 (9.09%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)

Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Haemorrhoidal haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Nausea	1 (9.09%)	1 (11.11%)	2 (16.67%)	0 (0.00%)	3 (14.29%)
Varices oesophageal	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vomiting	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)
General disorders and administration site conditions					
Fatigue	0 (0.00%)	0 (0.00%)	1 (8.33%)	1 (12.50%)	1 (4.76%)
Non-cardiac chest pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (9.52%)
Infections and infestations					
Fungal infection	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasopharyngitis	2 (18.18%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	1 (4.76%)
Overgrowth bacterial	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Pneumonia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Rash pustular	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sinusitis	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tooth abscess	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	2 (16.67%)	0 (0.00%)	0 (0.00%)
Viral infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Viral upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)

Injury, poisoning and procedural complications					
Arthropod bite	2 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle strain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Investigations					
Alanine aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (25.00%)	0 (0.00%)
Aspartate aminotransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Blood creatinine increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Low density lipoprotein increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Weight increased	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders					
Decreased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	2 (9.52%)
Hypercholesterolaemia	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Hyperlipidaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Iron deficiency	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders					
Costochondritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Muscle spasms	2 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Pain in extremity	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders					
Aphasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Dizziness	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Dysgeusia	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Headache	0 (0.00%)	0 (0.00%)	2 (16.67%)	1 (12.50%)	3 (14.29%)
Hypoaesthesia	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Optic neuritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Psychiatric disorders					
Initial insomnia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Insomnia	1 (9.09%)	0 (0.00%)	1 (8.33%)	1 (12.50%)	0 (0.00%)
Sleep disorder	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (4.76%)
Renal and urinary disorders					
Dysuria	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Pollakiuria	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Proteinuria	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Reproductive system and breast disorders					
Vulvovaginal discomfort	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders					
Cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.76%)
Nasal congestion	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)

Oropharyngeal pain	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Productive cough	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Sinus congestion	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders					
Pruritus	3 (27.27%)	6 (66.67%)	5 (41.67%)	7 (87.50%)	6 (28.57%)
Pruritus generalised	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Psoriasis	0 (0.00%)	1 (11.11%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash	1 (9.09%)	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (4.76%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	1 (8.33%)	0 (0.00%)	0 (0.00%)
Vascular disorders					
Hypertension	1 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Relevant Findings

Conclusion:

Tropifexor was generally safe and well tolerated in patients with PBC at daily doses of 0.03 mg, 0.06 mg, and 0.09 mg. At doses of 0.150 mg, increased itch was reported by VAS and led either to dose reduction in two patients or to discontinuation of study drug in one patient. Exposure to tropifexor in patients with PBC was greater than in healthy volunteers, most likely due to increased absorption, in the absence of obvious differences in distribution, metabolism or elimination in these patients with chronic liver disease. There was an improvement in cholestatic markers GGT and ALP and markers of hepatocellular injury ALT; improvement in GGT showed a clear dose dependent effect. These data support the future development of tropifexor for treatment of primary biliary cholangitis.

Date of Clinical Trial Report

20 May 2019