NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Tropifexor

Trial Indication(s)

Non-alcoholic steatohepatitis (NASH)

Protocol Number

CLJN452A2113

Protocol Title

A randomized, investigator and subject blinded, multicenter, parallel-arm study to determine the safety and tolerability of tropifexor.

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: 29 May 2020 (Actual)
Primary Completion Date: 4 November 2020 (Actual)
Study Completion Date: 4 November 2020 (Actual)

Study Design/Methodology

This was a randomized, subject and investigator blinded, multicenter, parallel-arm study to assess the safety and tolerability of tropifexor dosed in the evening as compared to dosing in the morning in subjects with non-alcoholic steatohepatitis (NASH). Subjects whose eligibility was confirmed were randomized with stratification by domicile status at Day 1 of the treatment period into tropifexor (200 µg) morning (AM) dose group (hereafter referred to as AM dose group) or tropifexor (200 µg) evening (PM) dose group (hereafter referred to as PM dose group) in a 1:1 ratio. Subjects in the AM dose group took tropifexor in the morning and placebo in the evening while subjects in the PM dose group took placebo in the morning and tropifexor in the evening for 4 weeks in a blinded manner.

Centers

United States(10)

Objectives:

The primary objective was to determine the effect of tropifexor dosed AM or PM on fasting low-density lipoprotein-cholesterol (LDL-C) levels after 2 weeks of treatment.

The secondary objectives were:

- To determine the effects of tropifexor dosed AM or PM on fasting LDL-C and high-density lipoprotein cholesterol (HDL-C) after 4 weeks of treatment
- To determine the effect of tropifexor dosed AM or PM on safety and tolerability during 4 weeks of treatment
- To determine the effects of tropifexor dosed AM or PM on liver tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and gamma-glutamyltransferase [GGT])
- To determine the concentration of tropifexor dosed AM or PM after 4 weeks of treatment

- To determine the 24-hour pharmacokinetic (PK) profile of tropifexor dosed AM or PM after 4 weeks of treatment (optional)

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

Tropifexor as a dry blend in hard gelatin capsules at dose strength of 100 µg and placebo capsules were supplied by Novartis and administered orally in the 2 dose groups as follows:

- Tropifexor 200 µg (AM) and Placebo (PM) once daily each
- Tropifexor 200 µg (PM) and Placebo (AM) once daily each

Statistical Methods

The primary endpoint was change from baseline in fasting direct Low density lipoprotein-cholesterol (LDL-C) in the log domain after 2 weeks of tropifexor treatment on pharmacodynamics (PD) analysis set. Log transformed ratio to baseline fasting direct LDL-C was analyzed using analysis of covariance (ANCOVA). The model included effects for treatment, visit, treatment by visit, interaction, stratification factor (domiciled or not), log(baseline) and log(baseline) by visit interaction. An unstructured variance-covariance matrix was used to account for variance heterogeneity and correlation among multiple measurements from the same subject.

The secondary endpoints of changes in fasting direct LDL-C and fasting direct High density lipoprotein-cholesterol (HDL-C) after 4 weeks of tropifexor treatment were analyzed on PD analysis set using the same approach as that for the primary endpoint.

All subjects in the safety analysis set were included in the safety data analysis. Summary statistics were provided for domiciled and non-domiciled subjects separately and pooled.

All subjects within the pharmacokinetics (PK) analysis set were included in the PK data analysis. For domiciled subjects, PK parameters of maximum plasma concentration (Cmax), time to Cmax (Tmax), the AUC calculated to the end of a

dosing interval (tau) at steady-state (AUCtau) and the area under concentration-time profile (AUC) from time zero to the last measurable concentration sampling time (AUClast) and tropifexor concentration were to be determined. For non-domiciled subjects, only pre-AM dose concentration was determined. Tropifexor plasma concentration data were listed. Descriptive summary statistics were provided for domiciled and non-domiciled subjects separately and for pre-AM dose concentrations pooled.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

-Presence of non-alcoholic steatohepatitis (NASH) based on histologic evidence (liver biopsy obtained 2 years or less prior to screening) with a diagnosis consistent with NASH, fibrosis levels F0, F1, F2, or F3, and no diagnosis of alternative chronic liver disease, OR phenotypic diagnosis based on elevated alanine aminotransferase (ALT), elevated Body Mass Index (BMI), diagnosis of Type 2 diabetes mellitus, and elevated liver fat

Exclusion Criteria:

-Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations
-Subjects taking the certain prohibited medicines UNLESS on a stable dose (within 25% of baseline dose) for at least 3 months before randomization
-Type 1 diabetes and Uncontrolled Type 2 diabetes defined as HbAlc ≥ 9.5% at screening
-Calculated eGFR ≤ 60 mL/min/1.73m2 (using the MDRD formula)
-New use of GLP-1 agonists such as liraglutide, exenatide, lixisenatide, albiglutide, or dulaglutide within 3 months of screening
-Subjects with contraindications to Magnetic Resonance Imaging

Participant Flow Table

Overall Study

	tropifexor AM 200 micrograms	tropifexor PM 200 micrograms	Total

	and Placebo (PM)	and Placebo (AM)	
Arm/Group Description	Tropifexor 200 µg (AM) and Placebo (PM) once daily each	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	
Started	42	45	87
Completed	39	37	76
Not Completed	3	8	11
Adverse Event	2	7	9
Withdrawal by Subject	0	1	1
Lost to Follow-up	1	0	1

Baseline Characteristics

	tropifexor AM 200 micrograms and Placebo (PM)	tropifexor PM 200 micrograms and Placebo (AM)	Total
Arm/Group Description	Tropifexor 200 µg (AM) and Placebo (PM) once daily each	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	
Number of Participants [units: participants]	42	45	87

Age Continuous (units: Years) Mean ± Standard Deviation			
	55.9±11.01	53.4±11.27	54.6±11.15
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	32	28	60
Male	10	17	27
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)			
White	38	42	80
Black or African American	3	0	3
Asian	1	2	3
American Indian or Alaska Native	0	1	1

Primary Outcome Result(s)

Change from baseline in fasting circulating LDL-C levels after 2 weeks of tropifexor treatment

(Time Frame: week 2)

	tropifexor PM 200 micrograms and Placebo (AM)	**tropifexor AM 200 micrograms and Placebo (PM)**

Arm/Group Description	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	Tropifexor 200 µg (AM) and Placebo (PM) once daily each
Number of Participants Analyzed [units: participants]	38	41
Change from baseline in fasting circulating LDL-C levels after 2 weeks of tropifexor treatment (units: mmol/L) Geometric Mean (90% Confidence Interval)		
Day 15	118.4 (110.7 to 126.6)	116.4 (109.2 to 124.2)

Statistical Analysis

Groups	tropifexor PM 200 micrograms and Placebo (AM), tropifexor AM 200 micrograms and Placebo (PM)
P Value	0.616
Method	ANCOVA
Other % Ratio	101.7
90 % Confidence Interval 2-Sided	92.68 to 111.53

Secondary Outcome Result(s)

Change from baseline in fasting circulating LDL-C levels after 4 weeks of tropifexor treatment

(Time Frame: week 4)

	tropifexor PM 200 micrograms and Placebo (AM)	tropifexor AM 200 micrograms and Placebo (PM)
Arm/Group Description	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	Tropifexor 200 µg (AM) and Placebo (PM) once daily each
Number of Participants Analyzed [units: participants]	36	39
Change from baseline in fasting circulating LDL-C levels after 4 weeks of tropifexor treatment (units: mmol/L) Geometric Mean (90% Confidence Interval)		
Day 29	120.0 (112.1 to 128.5)	117.9 (110.4 to 125.9)

Statistical Analysis

Groups	tropifexor PM 200 micrograms and Placebo (AM), tropifexor AM 200

	micrograms and Placebo (PM)
P Value	0.624
Method	ANCOVA
Other % Ratio	101.8
90 % Confidence Interval 2-Sided	92.64 to 111.90

Change in fasting circulating High density lipoprotein cholesterol (HDL-C) levels over 4 weeks of treatment

(Time Frame: week 4)

	tropifexor PM 200 micrograms and Placebo (AM)	**tropifexor AM 200 micrograms and Placebo (PM)**
Arm/Group Description	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	Tropifexor 200 µg (AM) and Placebo (PM) once daily each
Number of Participants Analyzed [units: participants]	36	39
Change in fasting circulating High density lipoprotein cholesterol (HDL-C) levels over 4 weeks of treatment (units: mmol/L) Mean (90% Confidence Interval)		

HDL-C	-0.27 (-0.3259 to -0.2205)	-0.24 (-0.2896 to -0.1880)

Statistical Analysis

Groups	tropifexor PM 200 micrograms and Placebo (AM), tropifexor AM 200 micrograms and Placebo (PM)
P Value	0.219
Method	ANCOVA
Other Difference	-0.03
90 % Confidence Interval 2-Sided	-0.1078 to 0.0391

Change from baseline in ALT, AST and GGT at Week 4

(Time Frame: Week 4)

	tropifexor PM 200 micrograms and Placebo (AM)	**tropifexor AM 200 micrograms and Placebo (PM)**
Arm/Group Description	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	Tropifexor 200 µg (AM) and Placebo (PM) once daily each
Number of Participants Analyzed [units: participants]	36	39

Change from baseline in ALT, AST and GGT at Week 4 (units: U/L) Mean (90% Confidence Interval)		
ALT (U/L) (n=36,38)	-5.74 (-11.423 to -0.0625)	-14.0 (-19.571 to -8.4953)
AST (U/L) (n=36,37)	10.38 (2.8640 to 17.8934)	-0.63 (-8.0951 to 6.8287)
GGT (U/L) (n=36,39)	-24.1 (-26.238 to -21.920)	-24.0 (-26.138 to -21.885)

Statistical Analysis

Groups	tropifexor PM 200 micrograms and Placebo (AM), tropifexor AM 200 micrograms and Placebo (PM)	ALT
P Value	0.957	
Method	ANCOVA	
Other Difference	8.29	
90 % Confidence Interval 2-Sided	-0.3669 to 16.2134	

Statistical Analysis

Groups	tropifexor PM 200 micrograms and Placebo (AM), tropifexor AM 200	AST

	micrograms and Placebo (PM)
P Value	0.956
Method	ANCOVA
Other Difference	11.01
90 % Confidence Interval 2-Sided	0.4248 to 21.5989

Statistical Analysis

Groups	tropifexor PM 200 micrograms and Placebo (AM), tropifexor AM 200 micrograms and Placebo (PM)	GGT
P Value	0.485	
Method	ANCOVA	
Other Difference	-0.07	
90 % Confidence Interval 2-Sided	-3.0888 to 2.9544	

Plasma Pharmacokinetics trough concentration for analyte LJN452

(Time Frame: week 4)

	tropifexor PM 200 micrograms and Placebo (AM)	**tropifexor AM 200 micrograms and Placebo (PM)**

Arm/Group Description	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	Tropifexor 200 µg (AM) and Placebo (PM) once daily each
Number of Participants Analyzed [units: participants]	39	36
Plasma Pharmacokinetics trough concentration for analyte LJN452 (units: ng/mL) Mean ± Standard Deviation		
	1.99 ± 1.44	4.48 ± 2.13

Plasma pharmacokinetics parameter - Cmax - domiciled subjects only

(Time Frame: 4 weeks)

	tropifexor AM 200 micrograms and Placebo (PM)	**tropifexor PM 200 micrograms and Placebo (AM)**
Arm/Group Description	Tropifexor 200 µg (AM) and Placebo (PM) once daily each	Tropifexor 200 µg (PM) and Placebo (AM) once daily each
Number of Participants Analyzed [units: participants]	15	9
Plasma pharmacokinetics parameter - Cmax - domiciled subjects only		

(units: ng/mL) Mean ± Standard Deviation		
	4.31 ± 1.82	6.52 ± 1.74

Plasma pharmacokinetics parameter - AUCtau - domiciled subjects only

(Time Frame: 4 weeks)

	tropifexor AM 200 micrograms and Placebo (PM)	**tropifexor PM 200 micrograms and Placebo (AM)**
Arm/Group Description	Tropifexor 200 µg (AM) and Placebo (PM) once daily each	Tropifexor 200 µg (PM) and Placebo (AM) once daily each
Number of Participants Analyzed [units: participants]	15	9
Plasma pharmacokinetics parameter - AUCtau - domiciled subjects only (units: h·ng/mL) Mean ± Standard Deviation		
	68.8 ± 35.0	101 ± 34.2

Plasma pharmacokinetics parameter -Tmax - domiciled subjects only

(Time Frame: 4 weeks)

	tropifexor AM 200 micrograms	**tropifexor PM 200 micrograms**

	and Placebo (PM)	and Placebo (AM)
Arm/Group Description	Tropifexor 200 µg (AM) and Placebo (PM) once daily each	Tropifexor 200 µg (PM) and Placebo (AM) once daily each
Number of Participants Analyzed [units: participants]	15	9
Plasma pharmacokinetics parameter -Tmax - domiciled subjects only (units: h) Median (Full Range)		
	4.00 (4.00 to 8.00)	11.9 (11.9 to 12.4)

Safety Results

All-Cause Mortality

	tropifexor AM 200 micrograms and Placebo (PM) N = 42	tropifexor PM 200 micrograms and Placebo (AM) N = 45	Total N = 87

Arm/Group Description	Tropifexor 200 µg (AM) and Placebo (PM) once daily each	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	Total
Total participants affected	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 are reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 60 days.
Source Vocabulary for Table Default	MedDRA (23.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	tropifexor AM 200 micrograms and Placebo (PM) N = 42	**tropifexor PM 200 micrograms and Placebo (AM) N = 45**	**Total N = 87**
Arm/Group Description	Tropifexor 200 µg (AM) and Placebo (PM) once daily each	Tropifexor 200 µg (PM) and Placebo (AM) once daily each	Total
Total participants affected	26 (61.90%)	30 (66.67%)	56 (64.37%)

Gastrointestinal disorders			
Constipation	4 (9.52%)	6 (13.33%)	10 (11.49%)
Dry mouth	1 (2.38%)	3 (6.67%)	4 (4.60%)
Nausea	5 (11.90%)	5 (11.11%)	10 (11.49%)
Vomiting	1 (2.38%)	4 (8.89%)	5 (5.75%)
Metabolism and nutrition disorders			
Decreased appetite	3 (7.14%)	1 (2.22%)	4 (4.60%)
Skin and subcutaneous tissue disorders			
Pruritus	20 (47.62%)	25 (55.56%)	45 (51.72%)

Conclusion:

After 2 weeks treatment of tropifexor, there was no statistically significant difference in change from baseline in fasting direct Low-density lipoprotein-cholesterol (LDL-C) concentration between the morning and evening doses.

Treatment with tropifexor in the evening for 4 weeks did not show statistically significant differences in change from baseline in fasting direct LDL-C, fasting direct High density lipoprotein-cholesterol (HDL-C), or liver test parameters concentration as compared to dosing in the morning.

Dosing tropifexor in the evening resulted in delayed median time to Cmax (Tmax), increased mean area under concentration-time profile (AUC) calculated to the end of a dosing interval (tau) at steady-state (AUCtau) and increased mean maximum plasma concentration (Cmax) as compared to dosing in the morning.

While the incidences of pruritus, severe pruritus, and treatment-related pruritus were numerically higher in the evening (PM) dose group than those in the morning (AM) dose group, the safety profile of tropifexor when dosed in the evening was generally similar with that when dosed in the morning.

Tropifexor was generally safe in subjects with Non-alcoholic steatohepatitis (NASH) at the dose of 200 µg after 4 weeks of treatment in this study.

Date of Clinical Trial Report

4 Oct 2021