



Clinical trial results:

A randomized, double-blind, multicenter study to assess the safety, tolerability, and efficacy of a combination treatment of tropifexor (LJN452) and cenicriviroc (CVC) in adult patients with nonalcoholic steatohepatitis (NASH) and liver fibrosis (TANDEM)

Summary

EudraCT number	2017-004208-24
Trial protocol	GB CZ DE BE FR PT ES LV IT
Global end of trial date	15 October 2020

Results information

Result version number	v1 (current)
This version publication date	30 October 2021
First version publication date	30 October 2021

Trial information

Trial identification

Sponsor protocol code	CLJC242A2201J
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03517540
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma AG, 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	15 June 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and tolerability of tropifexor + CVC in patients with NASH and fibrosis (stage 2 or 3 as per NASH CRN histological score, F2/F3) by monitoring adverse events, vital signs and laboratory values during 48 weeks of treatment as compared to monotherapy with each of tropifexor and CVC.

The endpoint for the primary objective was to evaluate the occurrence of AEs, SAEs, AEs resulting in discontinuation of study treatment, AESIs, and changes in vital signs and laboratory values over 48 weeks of treatment.

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:

Cenicriviroc (CVC) is a C-C chemokine receptors type 2 and 5 dual antagonist under evaluation for treating liver fibrosis in adults with nonalcoholic steatohepatitis (NASH)

Evidence for comparator: -

Actual start date of recruitment	06 September 2018
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	Argentina: 8
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Egypt: 1
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	India: 7
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Russian Federation: 4

Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	United States: 101
Worldwide total number of subjects	193
EEA total number of subjects	37

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)	149
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

193 participants enrolled at 65 sites in 17 countries

Pre-assignment

Screening details:

450 of 643 subjects discontinued during screening phase

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	LJN452 140 mcg
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Arm description:

tropifexor 140 mcg, once daily

Arm type	Experimental
Investigational medicinal product name	Arm A: tropifexor 140 mcg, once daily
Investigational medicinal product code	LJN452
Other name	tropifexor
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants in this arm received tropifexor 140 mcg capsule once daily

Arm title	CVC 150 mg
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Arm description:

Cenicriviroc (CVC) 150 mg, once daily

Arm type	Experimental
Investigational medicinal product name	Arm B: CVC 150 mg, once daily
Investigational medicinal product code	CVC
Other name	cenicriviroc
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants in this arm received CVC 150 mg capsule once daily

Arm title	LJN452 140 mcg + CVC 150 mg
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Arm description:

tropifexor 140 mcg + CVC 150 mg, once daily

Arm type	Experimental
Investigational medicinal product name	Arm C: tropifexor 140 mcg + CVC 150 mg, once daily
Investigational medicinal product code	LJN452 + CVC
Other name	tropifexor and cenicriviroc
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants in this group received tropifexor 140 mcg capsule + CVC 150 mg capsule once daily

Arm title	LJN452 90 mcg + CVC 150 mg
Arm description: tropifexor 90 mcg + CVC 150 mg, once daily	
Arm type	Experimental
Investigational medicinal product name	Arm D: tropifexor 90 mcg + CVC 150 mg, once daily.
Investigational medicinal product code	LJN452 + CVC
Other name	tropifexor and cenicriviroc
Pharmaceutical forms	Capsule
Routes of administration	Intratumoral use, Oral use

Dosage and administration details:

Participants in this group received tropifexor 90 mcg capsule + CVC 150 mg capsule once daily

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: This was a double-blind study: patients, Investigator staff, persons performing the assessments, and Novartis clinical trial team (or delegates) remained blinded to the identity of study treatments from the time of randomization (until final database lock).

Number of subjects in period 1	LJN452 140 mcg	CVC 150 mg	LJN452 140 mcg + CVC 150 mg
Started	50	48	47
Completed	36	41	38
Not completed	14	7	9
Consent withdrawn by subject	3	4	1
Adverse event, non-fatal	9	3	8
Protocol deviation	2	-	-

Number of subjects in period 1	LJN452 90 mcg + CVC 150 mg
Started	48
Completed	43
Not completed	5
Consent withdrawn by subject	3
Adverse event, non-fatal	1
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	LJN452 140 mcg
Reporting group description:	tropifexor 140 mcg, once daily
Reporting group title	CVC 150 mg
Reporting group description:	Cenicriviroc (CVC) 150 mg, once daily
Reporting group title	LJN452 140 mcg + CVC 150 mg
Reporting group description:	tropifexor 140 mcg + CVC 150 mg, once daily
Reporting group title	LJN452 90 mcg + CVC 150 mg
Reporting group description:	tropifexor 90 mcg + CVC 150 mg, once daily

Reporting group values	LJN452 140 mcg	CVC 150 mg	LJN452 140 mcg + CVC 150 mg
Number of subjects	50	48	47
Age Categorical Units: participants			
<65	35	39	37
>=65	15	9	10
Age Continuous Units: years			
arithmetic mean	54.8	53.7	54.7
standard deviation	± 13.35	± 11.79	± 12.65
Sex/Gender, Customized Units: participants			
Male	20	17	18
Female	30	31	29
Race/Ethnicity, Customized Units: Subjects			
White	41	44	40
Asian	7	4	5
Black	1	0	2
Unknown	1	0	0

Reporting group values	LJN452 90 mcg + CVC 150 mg	Total	
Number of subjects	48	193	
Age Categorical Units: participants			
<65	38	149	
>=65	10	44	
Age Continuous Units: years			
arithmetic mean	54.9	-	
standard deviation	± 12.29	-	

Sex/Gender, Customized Units: participants			
Male	25	80	
Female	23	113	
Race/Ethnicity, Customized Units: Subjects			
White	43	168	
Asian	5	21	
Black	0	3	
Unknown	0	1	

End points

End points reporting groups

Reporting group title	LJN452 140 mcg
Reporting group description: tropifexor 140 mcg, once daily	
Reporting group title	CVC 150 mg
Reporting group description: Cenicriviroc (CVC) 150 mg, once daily	
Reporting group title	LJN452 140 mcg + CVC 150 mg
Reporting group description: tropifexor 140 mcg + CVC 150 mg, once daily	
Reporting group title	LJN452 90 mcg + CVC 150 mg
Reporting group description: tropifexor 90 mcg + CVC 150 mg, once daily	

Primary: Number of participants with Adverse Events

End point title	Number of participants with Adverse Events ^[1]
End point description: Occurrence of adverse events and serious adverse events	
Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment and then up to 66 weeks	
End point type	Primary
End point timeframe: AEs and SAEs were collected from first dose of study treatment until end of study treatment at week 48 and then up to maximum duration of 66 weeks	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical Analysis was planned for this outcome	

End point values	LJN452 140 mcg	CVC 150 mg	LJN452 140 mcg + CVC 150 mg	LJN452 90 mcg + CVC 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	48	47	48
Units: participants				
Number of participants with at least one AE	42	41	40	42
Number of participants with at least one SAE	5	3	4	10
Deaths	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants who have at least a one point improvement in fibrosis

End point title	Proportion of participants who have at least a one point improvement in fibrosis
End point description: Efficacy of tropifexor + CVC in patients with Nonalcoholic steatohepatitis (NASH) with fibrosis stage F2/F3 as assessed by histological improvement after 48 weeks of treatment compared to monotherapies (tropifexor and CVC) compared to baseline biopsy	
End point type	Secondary
End point timeframe: baseline to 48 Weeks	

End point values	LJN452 140 mcg	CVC 150 mg	LJN452 140 mcg + CVC 150 mg	LJN452 90 mcg + CVC 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	38	37	40
Units: participants	10	12	11	13

Statistical analyses

Statistical analysis title	At least 1 point improvement in fibrosis
Statistical analysis description: Proportion of participants with at least one improvement point in fibrosis	
Comparison groups	LJN452 140 mcg + CVC 150 mg v LJN452 140 mcg
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.688
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	2.63

Statistical analysis title	At least 1 point improvement in fibrosis
Statistical analysis description: Proportion of participants with at least one improvement point in fibrosis	
Comparison groups	LJN452 140 mcg v LJN452 90 mcg + CVC 150 mg

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.985
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.99

Statistical analysis title	At least 1 point improvement in fibrosis
Statistical analysis description:	
Proportion of participants with at least one improvement point in fibrosis	
Comparison groups	LJN452 140 mcg + CVC 150 mg v LJN452 90 mcg + CVC 150 mg
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.84

Statistical analysis title	At least 1 point improvement in fibrosis
Statistical analysis description:	
Proportion of participants with at least one improvement point in fibrosis	
Comparison groups	CVC 150 mg v LJN452 90 mcg + CVC 150 mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	3.61

Secondary: Proportion of participants with resolution of steatohepatitis

End point title	Proportion of participants with resolution of steatohepatitis
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End point description:

Efficacy of tropifexor + CVC in patients with Nonalcoholic steatohepatitis (NASH) with fibrosis stage F2/F3 as assessed by histological improvement after 48 weeks of treatment compared to monotherapies (tropifexor and CVC) compared to baseline biopsy

End point type	Secondary
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End point timeframe:

baseline to 48 weeks

End point values	LJN452 140 mcg	CVC 150 mg	LJN452 140 mcg + CVC 150 mg	LJN452 90 mcg + CVC 150 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	38	37	40
Units: participants	8	8	5	9

Statistical analyses

Statistical analysis title	Participants with resolution of Steatohepatitis
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Statistical analysis description:

Proportion of participants with resolution of Steatohepatitis

Comparison groups	LJN452 140 mcg v LJN452 140 mcg + CVC 150 mg
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Number of subjects included in analysis	68
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.136
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Method	Cochran-Mantel-Haenszel
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Parameter estimate	Odds ratio (OR)
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Point estimate	0.37
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.08
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upper limit	1.61
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Statistical analysis title	Participants with resolution of Steatohepatitis
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Statistical analysis description:

Proportion of participants with resolution of Steatohepatitis

Comparison groups	LJN452 140 mcg v LJN452 90 mcg + CVC 150 mg
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Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.747
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	2.9

Statistical analysis title	Participants with resolution of Steatohepatitis
Statistical analysis description:	
Proportion of participants with resolution of Steatohepatitis	
Comparison groups	CVC 150 mg v LJN452 140 mcg + CVC 150 mg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.784
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	3.63

Statistical analysis title	Participants with resolution of Steatohepatitis
Statistical analysis description:	
Proportion of participants with resolution of Steatohepatitis	
Comparison groups	CVC 150 mg v LJN452 90 mcg + CVC 150 mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.521
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	5.69

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Tropifexor 140mcg
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Reporting group description:

Tropifexor 140mcg

Reporting group title	CVC 150mg
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Reporting group description:

CVC 150mg

Reporting group title	Tropifexor 140mg + CVC 150mg
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Reporting group description:

Tropifexor 140mg + CVC 150mg

Reporting group title	Tropifexor 90mg + CVC 150mg
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Reporting group description:

Tropifexor 90mg + CVC 150mg

Serious adverse events	Tropifexor 140mcg	CVC 150mg	Tropifexor 140mg + CVC 150mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 50 (10.00%)	3 / 48 (6.25%)	4 / 47 (8.51%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			

Cataract operation			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression suicidal			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anaesthetic complication			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			

subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oesophageal ulcer			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder polyp			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spondylitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	1 / 50 (2.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Euglycaemic diabetic ketoacidosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 48 (2.08%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tropifexor 90mg + CVC 150mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 48 (20.83%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression suicidal			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anaesthetic complication			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal ulcer			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pancreatitis acute			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gallbladder polyp			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spondylitis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Euglycaemic diabetic ketoacidosis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tropifexor 140mcg	CVC 150mg	Tropifexor 140mg + CVC 150mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 50 (78.00%)	30 / 48 (62.50%)	33 / 47 (70.21%)
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 50 (6.00%)	0 / 48 (0.00%)	1 / 47 (2.13%)
occurrences (all)	3	0	1
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	2 / 50 (4.00%)	0 / 48 (0.00%)	0 / 47 (0.00%)
occurrences (all)	3	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 50 (4.00%)	3 / 48 (6.25%)	2 / 47 (4.26%)
occurrences (all)	2	3	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 50 (8.00%)	2 / 48 (4.17%)	5 / 47 (10.64%)
occurrences (all)	4	2	5
Fatigue			
subjects affected / exposed	7 / 50 (14.00%)	4 / 48 (8.33%)	5 / 47 (10.64%)
occurrences (all)	7	4	5
Oedema peripheral			

subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 48 (0.00%) 0	0 / 47 (0.00%) 0
Eye disorders			
Cataract			
subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	3 / 48 (6.25%) 3	0 / 47 (0.00%) 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	3 / 48 (6.25%) 3	1 / 47 (2.13%) 1
Abdominal pain			
subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5	3 / 48 (6.25%) 5	5 / 47 (10.64%) 5
Abdominal pain upper			
subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4	2 / 48 (4.17%) 2	5 / 47 (10.64%) 6
Constipation			
subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5	2 / 48 (4.17%) 3	6 / 47 (12.77%) 6
Diarrhoea			
subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	7 / 48 (14.58%) 9	4 / 47 (8.51%) 4
Dyspepsia			
subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 48 (0.00%) 0	3 / 47 (6.38%) 3
Flatulence			
subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	1 / 48 (2.08%) 1	3 / 47 (6.38%) 3
Nausea			
subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	6 / 48 (12.50%) 6	7 / 47 (14.89%) 9
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed occurrences (all)	20 / 50 (40.00%) 23	10 / 48 (20.83%) 10	15 / 47 (31.91%) 21
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	1 / 48 (2.08%) 1	3 / 47 (6.38%) 3
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 6	3 / 48 (6.25%) 3	6 / 47 (12.77%) 7
Back pain subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	3 / 48 (6.25%) 3	5 / 47 (10.64%) 5
Muscle spasms subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	2 / 48 (4.17%) 2	3 / 47 (6.38%) 3
Osteoarthritis subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	0 / 48 (0.00%) 0	3 / 47 (6.38%) 3
Pain in extremity subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	3 / 48 (6.25%) 3	0 / 47 (0.00%) 0
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 2	0 / 48 (0.00%) 0	3 / 47 (6.38%) 4
Ear infection subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0	0 / 48 (0.00%) 0	3 / 47 (6.38%) 3
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1	1 / 48 (2.08%) 1	3 / 47 (6.38%) 3
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 3	3 / 48 (6.25%) 3	2 / 47 (4.26%) 2
Sinusitis subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2	1 / 48 (2.08%) 1	4 / 47 (8.51%) 4
Upper respiratory tract infection			

subjects affected / exposed	3 / 50 (6.00%)	2 / 48 (4.17%)	5 / 47 (10.64%)
occurrences (all)	3	3	6
Urinary tract infection			
subjects affected / exposed	7 / 50 (14.00%)	3 / 48 (6.25%)	2 / 47 (4.26%)
occurrences (all)	7	5	2

Non-serious adverse events	Tropifexor 90mg + CVC 150mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 48 (66.67%)		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			

Abdominal distension subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4		
Abdominal pain subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2		
Constipation subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Dyspepsia subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 4		
Flatulence subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2		
Nausea subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 6		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	10 / 48 (20.83%) 12		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		

Back pain			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	6		
Muscle spasms			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2018	<ul style="list-style-type: none">Revision to information fortropifexor, cenicriviroc and the combination, including non-clinical data, clinical pharmacology data, toxicology data, combination safety considerations, drug-drug interaction data for the combination and the rationale for use of the combination in this studyExclusion criteria 14: Revised cut-off values for total bilirubin and alkaline phosphatase. The units were consistently stated in mg/dL. Exclusion criteria 25: Revised platelets limit.Section 5.5.8.1: Revised dose limit for rosuvastatin and simvastatin to 10 mg daily, since CVC co-administration may increase their exposure and added the caution to monitor closely.Section 9.5.4: Added additional details on population PK analysisOther clarifications and corrections
11 December 2018	<ul style="list-style-type: none">Included occurrence of sleep disturbances in the exploratory objectives for Patient Reported Outcomes (PROs)Section 6, Table 6-1: The footnotes were revised to clarify the instructions for liver biopsy and FibroScan®Section 6.5.6 and Table 6-1: Monthly pregnancy test was required during the study and updated to specify the instructions for urine pregnancy test.Other clarifications and corrections
07 May 2020	<p>At the time of amendment (V03) release, enrollment was completed with 193 patients randomized. This amendment provides the option to extend the study treatment for patients who are unable to come to site for the week 48 visit as scheduled due to COVID-19 pandemic restrictions.</p> <ul style="list-style-type: none">Section 3.6: Updated to clarify the possible benefits and risks of longer study treatmentSection 5.5.2: updated to include the stepwise approach to extend study treatment for patients who were unable to come to the study site for their Week-48, End of treatment (EOT) visit as scheduled per study protocol due to COVID-19 pandemic related restrictionsSection 6 and table 6.1: updated to include remote consultation for patients who were unable to come to the study site for their study visits (except Week-48, End-of-treatment visit) as scheduled per study protocol due to COVID-19 pandemic-related restrictions. The footnotes were revised to clarify the instructions for urine pregnancy test and study treatment extension.Section 9.5.1: updated to clarify analysis plan for the delayed Week 48, End-of-Treatment (EOT) visits due to COVID-19 pandemic related restrictions

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported