Clinical trial results:
A randomized, double-blind, placebo-controlled, multicenter, dose-range, proof-of-concept, 24-week treatment study of IVA337 in adult subjects with nonalcoholic steatohepatitis (NASH)

Summary

EudraCT number	2016-001979-70
Trial protocol	BE GB CZ AT PT ES NL PL FR BG SI IT
Global end of trial date	16 March 2020

Results information

Result version number	v1 (current)
This version publication date	01 April 2021
First version publication date	01 April 2021

Trial information

Trial identification

Sponsor protocol code	IVA_01_337_HNAS_16_002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03008070
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inventiva S.A.
Sponsor organisation address	50 rue de Dijon, Daix, France, 21121
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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	16 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2020
Global end of trial reached?	Yes
Global end of trial date	16 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study main objective was to assess the safety and the efficacy (based on the activity part of the Steatosis Activity Fibrosis [SAF-A] histological score [inflammation and ballooning]) of a 24-week treatment with 2 doses of lanifibranor (800 mg/day and 1200 mg/day) in NASH adult patients.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 2017
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	Poland: 6
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Bulgaria: 55
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Mauritius: 7
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	247
EEA total number of subjects	179

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)	199
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment of patients started in January 2017, and last patient was recruited on March 2019. A total of 868 patients were screened for the study.

Pre-assignment

Screening details:

Patients were invited to participate into the study by their referent doctor according to the patient's medical records. Patients had to fulfil all the inclusion and none of the exclusion criteria to be eligible. A total of 247 patients were randomised. Main reason for non randomization was inclusion/exclusion criteria not met (470 - 76%).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LAN800

Arm description:

Patients who received lanifibranor 800mg daily: 2 tablets of lanifibranor and 1 tablet of placebo.

Arm type	Experimental
Investigational medicinal product name	Lanifibranor
Investigational medicinal product code	IVA337
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

White to off-white, bi-convex tablet of 400mg to be taken orally. Each tablet contained 400 mg of the active ingredient in an immediate release formulation.

Arm title	LAN1200

Arm description:

Patients who received lanifibranor 1200mg daily: 3 tablets of lanifibranor

Arm type	Experimental
Investigational medicinal product name	Lanifibranor
Investigational medicinal product code	IVA337
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

White to off-white, bi-convex tablet of 400mg to be taken orally. Each tablet contained 400 mg of the active ingredient in an immediate release formulation.

Arm title	Placebo

Arm description:

Patients who received placebo: 3 tablets of placebo daily

Arm type	Placebo

Investigational medicinal product name	Placebo to match lanifibranor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated tablets containing a mixture of lactose monohydrate, microcrystalline cellulose, sodium starch and magnesium stearate served as placebo. 3 tablets to be taken orally.

Number of subjects in period 1	LAN800	LAN1200	Placebo
Started	83	83	81
Completed	77	77	74
Not completed	6	6	7
Consent withdrawn by subject	-	2	1
Adverse event, non-fatal	3	3	3
Non compliance	-	-	1
Non-compliance	1	-	-
Withdrawal by patient + Adverse event non fatal	1	-	-
Lost to follow-up	1	1	-
Use of prohibited drug	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	LAN800
Reporting group description:	
Patients who received lanifibranor 800mg daily: 2 tablets of lanifibranor and 1 tablet of placebo.	
Reporting group title	LAN1200
Reporting group description:	
Patients who received lanifibranor 1200mg daily: 3 tablets of lanifibranor	
Reporting group title	Placebo
Reporting group description:	
Patients who received placebo: 3 tablets of placebo daily	

Reporting group values	LAN800	LAN1200	Placebo
Number of subjects	83	83	81
Age categorical Units: Subjects			
Adults (18-64 years)	69	67	63
From 65-84 years	14	16	18
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.0	52.2	53.4
standard deviation	± 10.4	± 13.8	± 13.1
Gender categorical Units: Subjects			
Female	54	49	41
Male	29	34	40

Reporting group values	Total		
Number of subjects	247		
Age categorical Units: Subjects			
Adults (18-64 years)	199		
From 65-84 years	48		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	144		
Male	103		

End points

End points reporting groups

Reporting group title	LAN800
Reporting group description:	
Patients who received lanifibranor 800mg daily: 2 tablets of lanifibranor and 1 tablet of placebo.	
Reporting group title	LAN1200
Reporting group description:	
Patients who received lanifibranor 1200mg daily: 3 tablets of lanifibranor	
Reporting group title	Placebo
Reporting group description:	
Patients who received placebo: 3 tablets of placebo daily	

Primary: SAF Activity score (SAF-A) decrease of at least 2 points with no worsening of the CRN Fibrosis score (CRN-F)

End point title	SAF Activity score (SAF-A) decrease of at least 2 points with no worsening of the CRN Fibrosis score (CRN-F)
End point description:	
SAF-A is the activity part of the Steatosis Activity Fibrosis [SAF] histological score, calculated as the sum of lobular inflamation score and balloning score. No worsening of fibrosis means that the CRN fibrosis score (CRN-F) remains stable or decreases.	
End point type	Primary
End point timeframe:	
From baseline to Week 24.	

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number of patients				
Yes	34	41	22	
No	49	42	59	

Statistical analyses

Statistical analysis title	Comparison of LAN800 vs Placebo
Statistical analysis description:	
The primary endpoint was a binary outcome (Yes/No). Responders rates were compared between the placebo and lanifibranor 800 mg at the end of the treatment period (week 24) using a Cochran Mantel Haenzel test stratified on diabetic status at baseline (that was the stratified factors in the randomisation). The CMH risk ratio is used to estimate the effect size. Patients with missing data are considered as non-responders.	
Comparison groups	Placebo v LAN800

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	2.12

Statistical analysis title	Comparison of LAN1200 vs Placebo

Statistical analysis description:

The primary endpoint was a binary outcome (Yes/No). Responders rates were compared between the placebo and lanifibranor 1200 mg at the end of the treatment period (week 24) using a Cochran Mantel Haenzel test stratified on diabetic status at baseline (that was the stratified factors in the randomisation).
The CMH risk ratio is used to estimate the effect size.
Patients with missing data are considered as non-responders.

Comparison groups	LAN1200 v Placebo
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	2.4

Secondary: NASH improvement

End point title	NASH improvement

End point description:

NASH improvement is defined as a decrease of at least 2 points in NAS score (sum of CRN Steatosis, Inflammation and Ballooning scores) without worsening of CRN Fibrosis score.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	43	53	26	
No	40	30	55	

Statistical analyses

No statistical analyses for this end point

Secondary: NASH resolution and no worsening of fibrosis

End point title	NASH resolution and no worsening of fibrosis

End point description:

Resolution of NASH is defined as a CRN Inflammation score equal to 0 or 1, and a CRN Ballooning score equal to 0.
No worsening of fibrosis means that the CRN fibrosis score remains stable or decreases.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	27	37	15	
No	56	46	66	

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement of fibrosis by at least 1 stage and no worsening of NASH

End point title	Improvement of fibrosis by at least 1 stage and no worsening of NASH

End point description:

Improvement of fibrosis is defined as a decrease of at least one stage in CRN Fibrosis score. No worsening of NASH is defined as no increase of CRN Steatosis score, no increase of CRN Inflammation score ans no increase of CRN Ballooning score.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	23	35	19	
No	60	48	62	

Statistical analyses

No statistical analyses for this end point

Secondary: Activity (SAF-A) improvement

End point title	Activity (SAF-A) improvement

End point description:

SAF-A is the activity part of the Steatosis Activity Fibrosis [SAF] histological score, calculated as the sum of lobular inflamation score and balloning score. Improvement of SAF-A is defined as a decrease of at least 1 point

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	54	62	40	
No	29	21	41	

Statistical analyses

No statistical analyses for this end point

Secondary: Steatosis (CRN-S) improvement

End point title	Steatosis (CRN-S) improvement

End point description:

Improvement of CRN Steatosis score (CRN-S) is defined as a decrease of at least 1 point.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	46	54	21	
No	37	29	60	

Statistical analyses

No statistical analyses for this end point

Secondary: Lobular inflammation (CRN-I) improvement

End point title	Lobular inflammation (CRN-I) improvement

End point description:

Improvement of CRN Lobular inflammation score (CRN-I) is defined as a decrease of at least 1 point.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	34	43	30	
No	49	40	51	

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatocyte balooning (CRN-B) improvement

End point title	Hepatocyte balooning (CRN-B) improvement

End point description:

Improvement of CRN Ballooning (CRN-B) is defined as a decrease of at least 1 point.

End point type	Secondary

End point timeframe:

From basline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	54	60	37	
No	29	23	44	

Statistical analyses

No statistical analyses for this end point

Secondary: Fibrosis (CRN-F) improvement

End point title	Fibrosis (CRN-F) improvement
End point description:	
Improvement of CRN Fibrosis score (CRN-F) is defined as a decrease of at least 1 point.	
End point type	Secondary
End point timeframe:	
From baseline to Week 24.	

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	28	36	22	
No	55	47	59	

Statistical analyses

No statistical analyses for this end point

Secondary: Modified ISHAK Fibrosis (ISHAK-F) improvement

End point title	Modified ISHAK Fibrosis (ISHAK-F) improvement
End point description:	
Improvement of Modified ISHAK Fibrosis (ISHAK-F) is defined as a decrease of at least 1 point.	
End point type	Secondary
End point timeframe:	
From baseline to Week 24.	

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	32	41	25	
No	51	42	56	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in ALT

End point title	Absolute change in ALT

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	72	
Units: U/L				
arithmetic mean (standard error)	-26.08 (± 3.85)	-24.54 (± 3.82)	-1.4 (± 3.88)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in AST

End point title	Absolute change in AST

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	72	
Units: U/L				
arithmetic mean (standard error)	-15.11 (± 3.2)	-12.04 (± 3.17)	-0.08 (± 3.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in GGT

End point title	Absolute change in GGT

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	72	
Units: U/L				
arithmetic mean (standard error)	-43.38 (± 5.61)	-27.87 (± 5.57)	4.41 (± 5.65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Fibrinogen

End point title	Absolute change in Fibrinogen

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	73	73	
Units: g/L				
arithmetic mean (standard error)	-0.17 (± 0.08)	-0.1 (± 0.07)	0.02 (± 0.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Hs-CRP

End point title	Absolute change in Hs-CRP

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	72	
Units: mg/L				
arithmetic mean (standard error)	-2.05 (± 0.47)	-1.37 (± 0.46)	0.11 (± 0.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Alpha2 macroglobulin

End point title	Absolute change in Alpha2 macroglobulin

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	72	71	
Units: gram(s)/litre				
arithmetic mean (standard error)	0.15 (± 0.40)	0.13 (± 0.38)	0.05 (± 0.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Haptoglobulin

End point title	Absolute change in Haptoglobulin

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	72	
Units: g/L				
arithmetic mean (standard deviation)	-0.053 (± 0.256)	-0.099 (± 0.378)	0.074 (± 0.291)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of Fasting Plasma Glucose

End point title	Absolute change of Fasting Plasma Glucose

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	73	72	
Units: mmol/L				
arithmetic mean (standard error)	-0.78 (± 0.12)	-0.6 (± 0.12)	0.24 (± 0.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Insulin

End point title	Absolute change in Insulin

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	65	66	
Units: pmol/L				
arithmetic mean (standard error)	-118.66 (± 11.66)	-114.91 (± 11.75)	-35.7 (± 11.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in HOMA index

End point title	Absolute change in HOMA index

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	64	63	65	
Units: NA				
arithmetic mean (standard error)	-5.79 (± 0.58)	-5.46 (± 0.58)	-1.47 (± 0.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in HbA1c

End point title	Absolute change in HbA1c

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	72	
Units: percentage				
arithmetic mean (standard error)	-0.38 (± 0.05)	-0.41 (± 0.05)	0.07 (± 0.05)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Total Cholesterol

End point title	Absolute change in Total Cholesterol

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	74	73	
Units: mmol/L				
arithmetic mean (standard error)	-0.02 (± 0.08)	-0.07 (± 0.07)	0.01 (± 0.08)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of HDL-Cholesterol

End point title	Absolute change of HDL-Cholesterol

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	74	73	
Units: mmol/L				
arithmetic mean (standard error)	0.16 (± 0.02)	0.11 (± 0.02)	0.01 (± 0.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of LDL-Cholesterol

End point title	Absolute change of LDL-Cholesterol

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	73	69	
Units: mmol/L				
arithmetic mean (standard error)	0.03 (± 0.07)	0.03 (± 0.07)	0.01 (± 0.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Triglycerides

End point title	Absolute change in Triglycerides

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	74	72	
Units: mmol/L				
arithmetic mean (standard error)	-0.49 (± 0.09)	-0.44 (± 0.09)	0.06 (± 0.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Apo A1

End point title	Absolute change in Apo A1

End point description:

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	73	72	
Units: mg/dL				
arithmetic mean (standard error)	-0.29 (± 2.19)	-4.39 (± 2.16)	0.03 (± 2.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Adiponectin

End point title	Absolute change in Adiponectin

End point description:

Absolute change is defined as Week 24 value - baseline value. Baseline value was defined as the last available non-missing data before or equal to the treatment start. Only fasting values were considered.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	66	73	72	
Units: microgram(s)/millilitre				
arithmetic mean (standard error)	11.95 (± 1.51)	17.12 (± 1.44)	-0.35 (± 1.44)	

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of NASH and improvement of fibrosis by at least 1 stage

End point title	Resolution of NASH and improvement of fibrosis by at least 1 stage

End point description:

Resolution of NASH is defined as a CRN Inflammation score equal to 0 or 1, and a CRN Ballooning score equal to 0.
Improvement of fibrosis is defined as a decrease of at least one stage in CRN Fibrosis score.

End point type	Secondary

End point timeframe:

From baseline to Week 24.

End point values	LAN800	LAN1200	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	83	83	81	
Units: number				
Yes	17	26	6	
No	66	57	75	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
On or after the first dose of treatment up to 30 days post last dose.	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	LAN800
Reporting group description:	
Patients who received lanifibranor 800mg daily: 2 tablets of lanifibranor and 1 tablet of placebo.	
Reporting group title	LAN1200
Reporting group description:	
Patients who received lanifibranor 1200mg daily: 3 tablets of lanifibranor	
Reporting group title	Placebo
Reporting group description:	
Patients who received placebo: 3 tablets of placebo daily	

Serious adverse events	LAN800	LAN1200	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 83 (3.61%)	7 / 83 (8.43%)	3 / 81 (3.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	1 / 83 (1.20%)	0 / 83 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	1 / 83 (1.20%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 83 (1.20%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			

subjects affected / exposed	0 / 83 (0.00%)	0 / 83 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 83 (0.00%)	1 / 83 (1.20%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 83 (0.00%)	0 / 83 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Foot operation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 83 (1.20%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 83 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Pneumobilia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 83 (1.20%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 83 (0.00%)	0 / 83 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Undifferentiated connective tissue disease			

subjects affected / exposed	1 / 83 (1.20%)	0 / 83 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 83 (1.20%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 83 (1.20%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LAN800	LAN1200	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 83 (30.12%)	23 / 83 (27.71%)	19 / 81 (23.46%)
Investigations			
Weight increased			
subjects affected / exposed	8 / 83 (9.64%)	7 / 83 (8.43%)	0 / 81 (0.00%)
occurrences (all)	8	7	0
Transaminases increased			
subjects affected / exposed	5 / 83 (6.02%)	2 / 83 (2.41%)	0 / 81 (0.00%)
occurrences (all)	5	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 83 (4.82%)	7 / 83 (8.43%)	4 / 81 (4.94%)
occurrences (all)	6	7	5
Dizziness			
subjects affected / exposed	2 / 83 (2.41%)	6 / 83 (7.23%)	3 / 81 (3.70%)
occurrences (all)	3	6	3
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	2 / 83 (2.41%)	10 / 83 (12.05%)	6 / 81 (7.41%)
occurrences (all)	2	10	6
Oedema peripheral			
subjects affected / exposed	5 / 83 (6.02%)	7 / 83 (8.43%)	2 / 81 (2.47%)
occurrences (all)	5	7	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 83 (9.64%)	10 / 83 (12.05%)	1 / 81 (1.23%)
occurrences (all)	8	11	2
Nausea			
subjects affected / exposed	8 / 83 (9.64%)	7 / 83 (8.43%)	3 / 81 (3.70%)
occurrences (all)	8	7	3
Constipation			
subjects affected / exposed	3 / 83 (3.61%)	5 / 83 (6.02%)	6 / 81 (7.41%)
occurrences (all)	3	5	6
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 83 (3.61%)	3 / 83 (3.61%)	5 / 81 (6.17%)
occurrences (all)	4	5	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2017	• Inclusion/exclusion criteria were updated: o The contraceptive method was to be followed for at least one menstruation cycle after the end of the study. o Patients with type 2 diabetes on insulin, patients with any clinically significant ECG abnormality reported by central ECG reading, patients with CPK >5xULN and patients with osteopenia or any other well documented bone disease with the exception of patients treated with vitamin D and/or calcium based supplements for preventive reasons, were to be excluded from the study. Also, details of the excipients were added to the criterion excluding patients with hypersensitivity to IMP excipients. • Prohibited and allowed medications update: i) specification of the prohibited anticoagulants medications (warfarin, dabigatran, rivaroxaban and apixaban); ii) addition of some medications allowed during the study (antiplatelet agents, aspirin, ticlopidine, clopidogrel, prasugrel and ticagrelor).
03 August 2017	• The initial study enrolment period of 6 months was extended to 16 months. Consequently, the expected study completion date was extended to Q1 2019, • Regarding laboratory assays, beta human chorionic gonadotropin (βHCG) was added at screening as biological parameter to collect to assess pregnancy, INR was added to specify the measure used to express the prothrombin time and the laboratory category for plasma iron, transferrin and ferritin was updated to chemistry to be consistent with the Clinical Data Interchange Standards Consortium (CDISC). • Number of kits to be dispensed at each visit was clarified as well as the process for accountability. • Upon request of DSMB members, the frequency of the DSMB meeting was updated: the formal analysis meeting to review data was to be held every 50 patients for the entire duration of the study.
02 November 2017	• A liver biopsy was added as screening tests procedures when a liver biopsy was not performed within 6 months from screening. For these patients, the screening phase was organised in 3 successive and detailed steps to avoid unnecessary biopsy and the screening period was extended to 8 weeks. • Two (2) exclusion criteria were added for patients undergoing an MRI/LMS in the selected centres: patients suffering from claustrophobia to a degree to not tolerate MRI scanning procedure and patients with metallic implant of any sort preventing MRI examination were to be excluded from the study. • A FibroScan® was to be performed at screening and at the end of the treatment period, if available, to evaluate TE and CAP. FibroScan® at screening was mandatory only if a liver biopsy within the 6 months prior screening was not available. • In selected centres (Bulgaria), a LMS was set for patient's liver examination at screening, to propose to undergo a liver biopsy only for the patients who would have had a higher probability of fulfilling the histological inclusion criteria.

09 July 2019	• Minor modifications of anti-diabetic treatments or dosages were allowed if done in a context of stable type 2 diabetes (HbA1c <8.5% in the previous 6 months). • Exclusion criteria were clarified: o Patients with a history of sustained excess alcohol ingestion in the year before the pre-study treatment biopsy were to be excluded. o Details on dosages of drugs known to produce hepatic steatosis were given as exclusion criteria. Similarly, the route of administration (oral) was specified for corticosteroids as prohibited concomitant medication. • The percent of patients with at least one-point improvement of fibrosis score on a 4-point scale (SAF) without worsening of NASH, defined as no increase for ballooning, or inflammation, or steatosis, using the SAF scoring system, from baseline to end of treatment (Week 24) was added as secondary endpoint. • The following exploratory endpoints were added: TE and CAP changes from baseline to the end of treatment and if deemed necessary, the change in the semi-quantitative score of ballooning and stellate cell activation from baseline to end of treatment. • P3NP was added as central laboratory test for efficacy assessment to be performed before and at the end of the treatment period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported