Clinical trial results:
Investigation of efficacy and safety of semaglutide s.c. once-weekly versus placebo in subjects with non-alcoholic steatohepatitis and compensated liver cirrhosis

Summary

EudraCT number	2018-004484-31
Trial protocol	GB DE FR ES
Global end of trial date	10 June 2021

Results information

Result version number	v1 (current)
This version publication date	22 June 2022
First version publication date	22 June 2022

Trial information

Trial identification

Sponsor protocol code	NN9931-4492

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03987451
WHO universal trial number (UTN)	U1111-1224-4062

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.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	21 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2021
Global end of trial reached?	Yes
Global end of trial date	10 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of semaglutide subcutaneous (s.c.) 2.4 mg once-weekly on liver fibrosis compared with placebo in subjects with Non-alcoholic Steatohepatitis (NASH) and compensated fibrosis stage 4

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents, (2016) and 21 US Code of Federal Regulations (CFR) 312.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	18 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 51
Worldwide total number of subjects	71
EEA total number of subjects	15

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	55
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 38 sites in 5 countries as follows (number of sites that screened subjects/ number of sites that randomised subjects): United States (24/19); United Kingdom (4/3); Germany (3/2); France (5/3); Spain (2/2).

Pre-assignment

Screening details:

Subjects were randomised in a 2:1 ratio to receive once-weekly either semaglutide or placebo subcutaneously as an adjunct to a reduced-calorie diet and increased physical activity.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 2.4 mg

Arm description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of semaglutide for 48 weeks. Subjects initially received 0.24 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 2.4 mg was reached: 0.24 mg (week 1 to week 4), 0.5 mg (week 5 to week 8), 1.0 mg (week 9 to week 12), 1.7 mg (week 13 to week 16), 2.4 mg (week 16 to week 48).

Arm type	Experimental
Investigational medicinal product name	Semaglutide B 3.0 mg/ml PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive once weekly subcutaneous (s.c.) injection of semaglutide for 48 weeks. Subjects initially received 0.24 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 2.4 mg was reached: 0.24 mg (week 1 to week 4), 0.5 mg (week 5 to week 8), 1.0 mg (week 9 to week 12), 1.7 mg (week 13 to week 16), 2.4 mg (week 16 to week 48).

Arm title	Placebo

Arm description:

Subjects were to receive once weekly s.c. injection of placebo matched to semaglutide (0.24 mg, 0.5 mg, 1.0 mg, 1.7 mg or 2.4 mg) for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive once weekly s.c. injection of placebo matched to semaglutide (0.24 mg, 0.5 mg, 1.0 mg, 1.7 mg or 2.4 mg) for 48 weeks.

Number of subjects in period 1	Semaglutide 2.4 mg	Placebo
Started	47	24
Completed	45	23
Not completed	2	1
Consent withdrawn by subject	1	1
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 2.4 mg
Reporting group description:	
Subjects were to receive once weekly subcutaneous (s.c.) injection of semaglutide for 48 weeks. Subjects initially received 0.24 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 2.4 mg was reached: 0.24 mg (week 1 to week 4), 0.5 mg (week 5 to week 8), 1.0 mg (week 9 to week 12), 1.7 mg (week 13 to week 16), 2.4 mg (week 16 to week 48).	
Reporting group title	Placebo
Reporting group description:	
Subjects were to receive once weekly s.c. injection of placebo matched to semaglutide (0.24 mg, 0.5 mg, 1.0 mg, 1.7 mg or 2.4 mg) for 48 weeks.	

Reporting group values	Semaglutide 2.4 mg	Placebo	Total
Number of subjects	47	24	71
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
<65 years	37	18	55
65<= to <75 years	10	6	16
Age Continuous Units: years			
arithmetic mean	59.9	58.7	
standard deviation	± 7.1	± 9.7	-
Gender Categorical Units: Subjects			
Female	31	18	49
Male	16	6	22

End points

End points reporting groups

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of semaglutide for 48 weeks. Subjects initially received 0.24 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 2.4 mg was reached: 0.24 mg (week 1 to week 4), 0.5 mg (week 5 to week 8), 1.0 mg (week 9 to week 12), 1.7 mg (week 13 to week 16), 2.4 mg (week 16 to week 48).

Reporting group title	Placebo

Reporting group description:

Subjects were to receive once weekly s.c. injection of placebo matched to semaglutide (0.24 mg, 0.5 mg, 1.0 mg, 1.7 mg or 2.4 mg) for 48 weeks.

Primary: At Least One Stage of Liver Fibrosis Improvement With No Worsening of NASH (Yes/No) (worsening defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or steatosis according to the NASH CRN criteria)

End point title	At Least One Stage of Liver Fibrosis Improvement With No Worsening of NASH (Yes/No) (worsening defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or steatosis according to the NASH CRN criteria)

End point description:

NASH resolution defined by NASH clinical research network (CRN) as lobular inflammation of 0 or 1; hepatocellular ballooning reduced to 0; both criteria were necessary conditions. Hepatocellular ballooning ranges from 0-2; lobular inflammation ranges from 0-3, higher scores indicate more severe hepatocellular ballooning/lobular inflammation. Worsening of NASH defined by increase of at least 1 stage of either lobular inflammation, hepatocyte ballooning or steatosis. Worsening of fibrosis defined by increase in fibrosis at least 1 stage of Kleiner fibrosis classification: fibrosis stages range from 0-4, higher scores indicate greater fibrosis (0=None, 4=Cirrhosis). Endpoint evaluated based on data from in-trial period which started on date of randomisation visit and ended on first of following dates (both inclusive): follow-up visit (week 55); withdrawal of consent; last contact with participant (for participants lost to follow-up); death. Full analysis set: all randomised subjects.

End point type	Primary

End point timeframe:

From baseline (week 0) to visit 12 (week 48)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	24		
Units: Percentage of subjects				
number (not applicable)	10.6	29.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The common odds ratio between semaglutide and placebo adjusting for baseline diabetes was estimated

along with exact 95% confidence interval based on conditioning on the marginal 2×2 tables.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0867
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.24

Secondary: Relative Change in Liver Fat Content (%) Measured by MRI-PDFF

End point title	Relative Change in Liver Fat Content (%) Measured by MRI-PDFF

End point description:

Relative change in liver fat content (measured in %) is presented as ratio to baseline. It was assessed by Magnetic Resonance Imaging–Proton Density Fat Fraction (MRI-PDFF) that utilized a gradient echo sequence with low flip angle to minimize T1 bias, corrected T2* decay (due to iron overload) via modeling of fat signal as a superposition of multiple frequency components from 5 different lipid types, was applied in each of 9 Couinaud segments. Technique improved fat quantification accuracy for entire liver permitting quantification of small changes following pharmacological intervention. Endpoint evaluated based on data from in-trial period which started on date of randomisation visit and ended on first of following dates (both inclusive): follow-up visit (week 55); withdrawal of consent; last contact with subject (for subjects lost to follow-up); death. Full analysis set (FAS): all randomised subjects. Number of subjects analysed = Number of subjects who contributed to the analysis

End point type	Secondary

End point timeframe:

From baseline (week 0) to visit 12 (week 48)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	18		
Units: Ratio of liver fat content				
geometric mean (geometric coefficient of variation)	0.62 (± 63.38)	1.01 (± 34.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: NASH Resolution (Yes/No) (defined by the NASH CRN as lobular inflammation 0 – 1 and ballooning 0)

End point title	NASH Resolution (Yes/No) (defined by the NASH CRN as lobular inflammation 0 – 1 and ballooning 0)

End point description:

NASH resolution defined by NASH clinical research network as lobular inflammation of 0 or 1 and hepatocellular ballooning reduced to 0; both criteria were necessary conditions. Hepatocellular ballooning ranges from 0-2; lobular inflammation ranges from 0-3, with higher scores indicating more severe hepatocellular ballooning or lobular inflammation. Worsening of fibrosis defined by an increase in fibrosis at least one stage of Kleiner fibrosis classification: fibrosis stages range from 0-4, with higher scores indicating greater fibrosis (0=None, 4=Cirrhosis). Endpoint was evaluated based on data from in-trial period which started on date of randomisation visit and ended on first of following dates (both inclusive):1) follow-up visit (week 55); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. FAS included all randomised subjects.

End point type	Secondary

End point timeframe:

From baseline (week 0) to visit 12 (week 48)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	24		
Units: Percentage of subjects				
number (not applicable)	34.0	20.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Stage of Fibrosis According to the NASH CRN Fibrosis Score

End point title	Change in Stage of Fibrosis According to the NASH CRN Fibrosis Score

End point description:

Percentage of subjects who had improved, worsened, had no change in fibrosis stage from baseline to week 48 or missing data is presented. Degree of fibrosis defined by Kleiner fibrosis staging system, range from 0-4: F0 (absence of fibrosis), F1 (portal/perisinusoidal fibrosis), F2 (perisinusoidal & portal/periportal fibrosis), F3 (septal/bridging fibrosis) through F4 (cirrhosis); higher scores indicate greater fibrosis. Improvement defined as at least 1 stage decrease; Worsening by at least 1 stage increase; No change is no change in fibrosis stage and missing refers to subjects with missing outcomes. Endpoint evaluated based on data from in-trial period which started on date of randomisation visit and ended on first of following dates (both inclusive): follow-up visit (week 55); withdrawal of consent; last contact with subject (subjects lost to follow-up); death. FAS: all randomised subjects. Number of subjects analysed = Number of subjects who contributed to the analysis

End point type	Secondary

End point timeframe:

From baseline (week 0) to visit 12 (week 48)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	24		
Units: Percentage of subjects				
number (not applicable)				
Improvement	12.8	33.3		
Worsening	0.0	0.0		
No change	72.3	62.5		
Missing	14.9	4.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Change in Liver Stiffness Measured by MRE

End point title	Relative Change in Liver Stiffness Measured by MRE

End point description:

Relative change in Liver Stiffness from baseline to week 48 is presented as ratio to baseline. Liver stiffness was measured by MRI using a Magnetic Resonance Elastography (MRE) technique and measured in kilopascal. MRE is a technology that uses MRI imaging with low-frequency vibrations to create a visual map (elastogram) that shows stiffness of the liver. Endpoint was evaluated based on data from in-trial period which started on date of randomisation visit and ended on first of following dates (both inclusive):1) follow-up visit (week 55); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. FAS included all randomised subjects. Number of subjects analysed = Number of subjects who contributed to the analysis

End point type	Secondary

End point timeframe:

From baseline (week 0) to visit 12 (week 48)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	21		
Units: Ratio of liver stiffness				
geometric mean (geometric coefficient of variation)	0.87 (± 22.24)	0.98 (± 28.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NAFLD Activity Score (NAS) According to the NASH CRN Criteria

End point title	Change in NAFLD Activity Score (NAS) According to the NASH CRN Criteria

End point description:

Percentage of subjects who had worsened, improved or had no change in total Non-Alcoholic Fatty Liver Disease (NAFLD) activity score from baseline to week 48 or missing data is presented. Worsening defined as an increase of at least 1 in the NAS; Improvement was defined as a decrease of at least 1 in the NAS; while no change corresponds to no change in NAS and missing refers to subjects with missing outcomes for NAS from baseline to week 48. NAS was calculated as the sum of scores for steatosis (0 to 3), lobular inflammation (0 to 3), and hepatocyte ballooning (0 to 2). Therefore, it is assessed on a scale of 0-8, with higher scores indicating more severe disease. Endpoint was evaluated based on data from in-trial period which started on date of randomisation visit and ended on first of following dates (both inclusive):1) follow-up visit (week 55); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. FAS included all randomised subjects.

End point type	Secondary

End point timeframe:

From baseline (week 0) to visit 12 (week 48)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	24		
Units: Percentage of subjects				
number (not applicable)				
Improvement	61.7	58.3		
Worsening	2.1	16.7		
No change	21.3	20.8		
Missing	14.9	4.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treatment Emergent Adverse Events

End point title	Number of Treatment Emergent Adverse Events

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical trial subject administered or using a medicinal product, whether or not considered related to the medicinal product or usage. All AEs reported here are Treatment Emergent Adverse Events (TEAEs). TEAE is defined as an event that had onset date during the on-treatment period. Endpoint was evaluated based on data from on-treatment period which started on the date of first administration of trial product and ended on the date of whatever comes first of: a) last dose of trial product + 49 days (7 half-lives of semaglutide), b) follow-up visit (week 55), or c) end of the in-trial period. Safety analysis set included all subjects receiving at least one dose of randomised treatment.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 55

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	24		
Units: Events				
number (not applicable)	290	85		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From week 0 to week 55. Results are based on the safety analysis set which included all subjects who received at least one dose of randomised treatment.

Adverse event reporting additional description:

All AEs here are TEAEs, defined as an event that had onset date during on-treatment period. On-treatment period started on the date of first administration of trial product and ended on the date of whatever comes first of: last dose of trial product + 49 days (7 half-lives of semaglutide); follow-up visit (week 55), or end of the in-trial period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects were to receive once weekly s.c. injection of placebo matched to semaglutide (0.24 mg, 0.5 mg, 1.0 mg, 1.7 mg or 2.4 mg) for 48 weeks.

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of semaglutide for 48 weeks. Subjects initially received 0.24 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 2.4 mg was reached: 0.24 mg (week 1 to week 4), 0.5 mg (week 5 to week 8), 1.0 mg (week 9 to week 12), 1.7 mg (week 13 to week 16), 2.4 mg (week 16 to week 48).

Serious adverse events	Placebo	Semaglutide 2.4 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	6 / 47 (12.77%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Spinal claudication			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous detachment			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 24 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 24 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Semaglutide 2.4 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 24 (62.50%)	38 / 47 (80.85%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)	2 / 47 (4.26%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	2 / 24 (8.33%)	4 / 47 (8.51%)	
occurrences (all)	2	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 24 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	7	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 24 (8.33%)	5 / 47 (10.64%)	
occurrences (all)	2	8	
Abdominal pain			
subjects affected / exposed	0 / 24 (0.00%)	6 / 47 (12.77%)	
occurrences (all)	0	6	
Abdominal distension			
subjects affected / exposed	1 / 24 (4.17%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	2 / 24 (8.33%)	9 / 47 (19.15%)	
occurrences (all)	3	13	
Dyspepsia			
subjects affected / exposed	0 / 24 (0.00%)	5 / 47 (10.64%)	
occurrences (all)	0	5	
Constipation			
subjects affected / exposed	2 / 24 (8.33%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
Dysphagia			

subjects affected / exposed	0 / 24 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 24 (4.17%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Eructation			
subjects affected / exposed	0 / 24 (0.00%)	6 / 47 (12.77%)	
occurrences (all)	0	19	
Nausea			
subjects affected / exposed	4 / 24 (16.67%)	21 / 47 (44.68%)	
occurrences (all)	6	34	
Vomiting			
subjects affected / exposed	0 / 24 (0.00%)	8 / 47 (17.02%)	
occurrences (all)	0	10	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 24 (4.17%)	4 / 47 (8.51%)	
occurrences (all)	1	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 24 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 24 (12.50%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Arthralgia			
subjects affected / exposed	1 / 24 (4.17%)	3 / 47 (6.38%)	
occurrences (all)	1	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 24 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	4	
Urinary tract infection			
subjects affected / exposed	4 / 24 (16.67%)	3 / 47 (6.38%)	
occurrences (all)	4	3	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	2 / 47 (4.26%) 2	
Metabolism and nutrition disorders Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 47 (0.00%) 0	
Decreased appetite subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	6 / 47 (12.77%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2020	Following changes were made in this amendment: • To align with requirements as per regulatory guidance regarding primary endpoint in NASH trials, the former secondary endpoint was changed to the primary endpoint: "At least one stage of liver fibrosis improvement with no worsening of NASH after 48 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or steatosis according to the NASH CRN criteria)." • As a consequence of the above, the former primary endpoint was changed to the secondary endpoint: "Relative change from baseline (week 0) to week 48 in liver stiffness measured by MRE." • To ensure complete follow-up of primary endpoint assessment, liver biopsies were needed at week 48 for subjects who discontinued treatment during the trial (visit 12 A). • To reflect the change in primary endpoint, the primary estimand was changed accordingly. • Clarification of various procedures and assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported