Clinical trial results:
A Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Non-Alcoholic Steatohepatitis (NASH) and Fibrosis.

Summary

EudraCT number	2015-005385-38
Trial protocol	BE GB DE CZ SE IT PT NL DK FI
Global end of trial date	28 October 2020

Results information

Result version number	v2 (current)
This version publication date	06 June 2022
First version publication date	12 February 2022
Version creation reason	• Correction of full data set Updated to align with results posted to clincialtrials.gov

Trial information

Trial identification

Sponsor protocol code	GFT505-315-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02704403
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 115028

Notes:

Sponsors

Sponsor organisation name	Genfit
Sponsor organisation address	Parc Eurasanté, 885, Avenue Eugène Avinée, LOOS, France, 59120
Public contact	GENFIT, Genfit, +33 3 20 16 40 00, clinicaltrial@genfit.com
Scientific contact	Carol Addy, MD MMSc, Genfit, +33 6179536469 ,

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 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2020
Global end of trial reached?	Yes
Global end of trial date	28 October 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to evaluate the effect of Elafibranor treatment compared to placebo on:
1) histological improvement and
2) all-cause mortality and liver-related outcomes in patients with nonalcoholic steatohepatitis (NASH) and fibrosis.

Protection of trial subjects:

An independent Data and Safety Monitoring Board (DSMB) was established in order to review the progress of the study and to perform a safety data review (as defined by the DSMB Charter) on a regular basis during the trial to protect patient welfare and preserve study integrity.

Knowing the risks associated with NASH the Clinical Events Committee focused on potential hepatotoxicity, liver-related and cardiovascular events.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2016
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	Netherlands: 10
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Spain: 67
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 66
Country: Number of subjects enrolled	Belgium: 65
Country: Number of subjects enrolled	Czechia: 23
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	France: 172
Country: Number of subjects enrolled	Germany: 80
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Puerto Rico: 8
Country: Number of subjects enrolled	Australia: 84
Country: Number of subjects enrolled	Argentina: 18

Country: Number of subjects enrolled	Canada: 57
Country: Number of subjects enrolled	Colombia: 32
Country: Number of subjects enrolled	Turkey: 102
Country: Number of subjects enrolled	Chile: 50
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Mexico: 102
Country: Number of subjects enrolled	South Africa: 35
Country: Number of subjects enrolled	Switzerland: 30
Country: Number of subjects enrolled	United States: 1045
Worldwide total number of subjects	2157
EEA total number of subjects	515

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)	1725
From 65 to 84 years	432
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The enrollment cut-off date of 04 December 2019, the date of randomization of the 1070th patient, was used as the date for which the ITT Set for the Surrogate endpoint analysis (resolution of NASH without worsening of fibrosis after 72 weeks of treatment) took place.

Pre-assignment

Screening details:

A total of 5460 patients were screened, of whom 2157 (38.8%) patients were randomized. Seven (7 [0.1%]) patients were randomized but not treated. A total of 3403 (61.2%) patients failed screening, with the most common reason being not meeting inclusion criteria (2260 [40.6%]).

Period 1

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

Blinding implementation details:

A quadruple blind (Participant, Care Provider, Investigator, Outcomes Assessor). Elafibranor 120 mg and placebo tablets were supplied in identical blisters/wallets and were similar in physical appearance, thereby enabling double-blind conditions. The subjects who successfully passed screening were assigned an individual randomization code and randomly allocated to one of the two treatment groups in a ratio 2:1 for elafibranor 120mg versus placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	120 mg Elafibranor

Arm description:

Elafibranor 120 mg one tablet per day.
Intent-to-treat Set: a cohort of randomized fibrosis stage 2 (F2) to fibrosis stage 3 (F3) participants who completed the Week 72 treatment period or discontinued the study treatment early.

Arm type	Experimental
Investigational medicinal product name	Elafibranor
Investigational medicinal product code	
Other name	GFT505
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Elafibranor 120 mg coated tablets
Drug administration - one tablet per day before breakfast with a glass of water

Arm title	Placebo

Arm description:

Matched placebo one tablet per day.
Intent-to-treat Set: a cohort of randomized F2 to F3 participants who completed the Week 72 treatment period or discontinued the study treatment early.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match elafibranor 120 mg was provided as a coated tablet.
Administration - one tablet per day before breakfast with a glass of water.

Number of subjects in period 1	120 mg Elafibranor	Placebo
Started	1437	720
Full Safety Population	1433	717
Completed	0	0
Not completed	1437	720
Consent withdrawn by subject	85	45
Death	4	3
Other	4	3
Endpoint event	52	24
Lost to follow-up	22	11
Administrative reasons by sponsor	1251	616
Randomized, not treated (protocol noncompliance)	4	3
Protocol deviation	15	15

Baseline characteristics

Reporting groups	
Reporting group title	120 mg Elafibranor
Reporting group description:	
Elafibranor 120 mg one tablet per day. Intent-to-treat Set: a cohort of randomized fibrosis stage 2 (F2) to fibrosis stage 3 (F3) participants who completed the Week 72 treatment period or discontinued the study treatment early.	
Reporting group title	Placebo
Reporting group description:	
Matched placebo one tablet per day. Intent-to-treat Set: a cohort of randomized F2 to F3 participants who completed the Week 72 treatment period or discontinued the study treatment early.	

Reporting group values	120 mg Elafibranor	Placebo	Total
Number of subjects	1437	720	2157
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	54.0	54.4	
standard deviation	± 11.78	± 11.63	-
Gender categorical Units: Subjects			
Female	622	308	930
Male	815	412	1227
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	336	177	513
Not Hispanic or Latino	1089	532	1621
Unknown or Not Reported	12	11	23
Race (NIH/OMB) Units: Subjects			
American Indian or or Alaska Native	8	1	9
Asian	53	27	80
Black or African American	28	10	38
Native Hawaiian or Other Pacific Islander	3	3	6
White	1234	614	1848
Other	93	49	142

Not Reported	18	16	34
Child Bearing Potential Units: Subjects			
Yes	105	46	151
No	516	262	778
Not applicable	815	412	1227
Missing	1	0	1
Type 2 Diabetes Units: Subjects			
Yes	699	351	1050
No	738	369	1107
Fibrosis stage			
There are five stages of fibrosis with F0: no scarring (no fibrosis); F1: minimal scarring; F2: scarring has occurred and extends outside the liver area (significant fibrosis); F3: fibrosis spreading and forming bridges with other fibrotic liver areas (severe fibrosis); F4: cirrhosis or advanced scarring			
Units: Subjects			
F1	135	69	204
F2	603	302	905
F3	699	349	1048
Non-alcoholic fatty liver disease activity score grouped severity score			
Non-alcoholic fatty liver disease Activity Score Severity Score (NAS score) is a measure of grade and is the sum of numerical scores applied to steatosis (0-3), hepatocellular ballooning (0-2), and lobular inflammation (0-3). Accordingly, the NAS ranges from 0 to 8. NAS scores of 0-2 are considered not diagnostic of NASH, NAS scores of 3-4 are considered as NASH diagnostic, borderline, or positive for NASH. NAS Scores of 5-8 occurred in cases that are largely considered diagnostic of NASH			
Units: Subjects			
Moderate (4-5)	663	317	980
Severe (>=6)	774	402	1176
Missing	0	1	1
Non-alcoholic fatty liver disease activity score severity score			
Non-alcoholic fatty liver disease Activity Score Severity Score (NAS score) is a measure of grade and is the sum of numerical scores applied to steatosis (0-3), hepatocellular ballooning (0-2), and lobular inflammation (0-3). Accordingly, the NAS ranges from 0 to 8. NAS scores of 0-2 are considered not diagnostic of NASH, NAS scores of 3-4 are considered as NASH diagnostic, borderline, or positive for NASH. NAS Scores of 5-8 occurred in cases that are largely considered diagnostic of NASH			
Units: Subjects			
four (4)	193	94	287
five (5)	470	223	693
six (6)	453	225	678
seven (7)	271	154	425
eight (8)	50	23	73
Missing	0	1	1
Model For End-Stage Liver Disease (MELD) Score			
The Model for End-Stage Liver Disease (MELD) is a scoring system for assessing the severity of chronic liver disease. the score is useful both in predicting short-term survival in groups of patients on the waiting list for liver transplantation as well as the risk of postoperative mortality. Patients are assigned a score from 6 to 40, with 40 representing the greatest severity of liver disease, and a high risk of death in the ensuing three months without transplantation. Patients with score < 15 are deferred of liver transplantation.			
Units: Subjects			
<15	1426	715	2141
>=15	11	5	16

Weight (kg)			
Units: kg			
arithmetic mean	98.0	96.3	
standard deviation	± 21.90	± 20.84	-
Height (cm)			
All participants with data available are presented (1436 / 718)			
Units: cm			
arithmetic mean	169.1	168.8	
standard deviation	± 10.48	± 10.23	-
BMI (kg/m2)			
All participants with data available are presented (1436/ 718)			
Units: kg/m^2			
arithmetic mean	34.1	33.6	
standard deviation	± 6.13	± 5.77	-
Waist Circumference (cm)			
All participants with data available are presented (1431 / 719)			
Units: cm			
arithmetic mean	111.9	110.4	
standard deviation	± 14.19	± 13.48	-

End points

End points reporting groups

Reporting group title	120 mg Elafibranor

Reporting group description:

Elafibranor 120 mg one tablet per day.
Intent-to-treat Set: a cohort of randomized fibrosis stage 2 (F2) to fibrosis stage 3 (F3) participants who completed the Week 72 treatment period or discontinued the study treatment early.

Reporting group title	Placebo

Reporting group description:

Matched placebo one tablet per day.
Intent-to-treat Set: a cohort of randomized F2 to F3 participants who completed the Week 72 treatment period or discontinued the study treatment early.

Primary: Number of Elafibranor-treated Participants Relative to Placebo Achieving Resolution of Nonalcoholic Steatohepatitis Without Worsening of Fibrosis

End point title	Number of Elafibranor-treated Participants Relative to Placebo Achieving Resolution of Nonalcoholic Steatohepatitis Without Worsening of Fibrosis

End point description:

To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis stage 2 (F2) and fibrosis stage 3 (F3).
Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

End point type	Primary

End point timeframe:

Measurement at 72 weeks

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	717	353		
Units: Count of participants	138	52		

Statistical analyses

Statistical analysis title	Primary Outcome Analysis

Statistical analysis description:

To evaluate the effect of Elafibranor compared to placebo on liver histology in nonalcoholic steatohepatitis (NASH) participants with fibrosis by assessing the following endpoint: The number of Elafibranor-treated participants relative to placebo achieving NASH resolution without worsening of fibrosis. This outcome measure is for the surrogate endpoint analysis.

Comparison groups	120 mg Elafibranor v Placebo

Number of subjects included in analysis	1070
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0659
Method	Regression, Logistic
Parameter estimate	Median difference (net)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.09

Notes:

[1] - The null hypothesis was that there was no difference in response rates between the elafibranor and placebo treatment groups. The alternative hypothesis was that there was a difference in the response rates between the elafibranor and placebo treatment groups.

Primary: Time to Long-term Outcome Composed of All-cause Mortality, Cirrhosis, and Liver-related Clinical Outcomes

End point title	Time to Long-term Outcome Composed of All-cause Mortality, Cirrhosis, and Liver-related Clinical Outcomes

End point description:

Composite long-term outcome measured by the number of participants with the onset of any of the adjudicated events, composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events as follows: liver transplantation; model for end stage liver disease (MELD) score greater than or equal to 15 for participants with baseline score less than or equal to 12, and onset of variceal bleeding requiring hospitalization, hepatic encephalopathy with West Haven/Conn score greater than or equal to 2 and requiring hospitalization, spontaneous bacterial peritonitis, and ascites requiring treatment. The MELD scale ranges from 6 to 40, showing how much a participant needs a liver transplant: higher number is more urgent. The West Haven/Conn scale is 5-point (0 to 4) grading severity of hepatic encephalopathy: higher score means worse hepatic encephalopathy. This outcome measure is for the long-term endpoint analysis.

End point type	Primary

End point timeframe:

From first randomization up to early termination of the study corresponding to 54 months (54 months being the longest duration for any given participant)

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1437	720		
Units: subjects				
Baseline- Events	0	0		
Baseline- Censored	0	0		
Baseline- No events or not censored	1437	720		
6 months- Events	1	1		
6 months- Censored	48	26		
6 months- No events or not censored	1388	693		
12 months- Events	1	1		
12 months- Censored	159	82		
12 months- No events or not censored	1277	637		
18 months- Events	53	28		
18 months- Censored	374	195		

18 months- No events or not censored	1010	497		
24 months- Events	56	31		
24 months- Censored	609	301		
24 months- No events or not censored	772	388		
30 months- Events	57	31		
30 months- Censored	778	393		
30 months- No events or not censored	602	296		
36 months- Events	60	32		
36 months- Censored	1049	531		
36 months- No events or not censored	328	157		
42 months- Events	61	32		
42 months- Censored	1293	652		
42 months- No events or not censored	83	36		
48 months- Events	61	32		
48 months- Censored	1374	687		
48 months- No events or not censored	2	1		
54 months- Events	61	32		
54 months- Censored	1376	688		
54 months- No events or not censored	0	0		

Statistical analyses

Statistical analysis title	Long Term Endpoint Analysis
Statistical analysis description:	
Statistical Analysis 1 for Time to Long-term Outcome Composed of All-cause Mortality, Cirrhosis, and Liver-related Clinical Outcomes.	
Comparison groups	120 mg Elafibranor v Placebo
Number of subjects included in analysis	2157
Analysis specification	Pre-specified
Analysis type	superiority[2]
Parameter estimate	Cox proportional hazard
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.619
upper limit	1.457

Notes:

[2] - Long-term outcome is measured by the number of participants with the onset of any of the adjudicated events, composed of death due to any cause,histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events. The MELD scale ranges from 6 to 40,showing how much a participant needs a liver transplant: higher number is more urgent.The West Haven/Conn scale is 5-point (0 to 4) grading severity of hepatic encephalopathy: higher score means worse hepatic encephalopathy

Secondary: Number of Elafibranor-treated Participants Relative to Placebo Achieving Improvement of Fibrosis of at Least 1 Stage

End point title	Number of Elafibranor-treated Participants Relative to Placebo Achieving Improvement of Fibrosis of at Least 1 Stage

End point description:

To evaluate the effect of Elafibranor compared to placebo on liver histology in nonalcoholic steatohepatitis (NASH) participants by assessing the following endpoint: The number of Elafibranor-

treated participants relative to placebo achieving improvement of liver fibrosis of at least 1 stage according to NASH Clinical Research Network (CRN) Scoring.

As the primary efficacy objective was not met, no formal statistical analysis performed on the secondary efficacy endpoints. This outcome measure is for the surrogate endpoint analysis.

End point type	Secondary

End point timeframe:

Measurements at 72 weeks

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	717	353		
Units: Count of participants	176	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Hemoglobin A1c (HbA1c) in Diabetic Participants After 72 Weeks of Treatment with Elafibranor

End point title	Change From Baseline of Hemoglobin A1c (HbA1c) in Diabetic Participants After 72 Weeks of Treatment with Elafibranor

End point description:

Hemoglobin A1c (HbA1c) were tested at Week 72. Changes from baseline in HbA1c at Week 72 were evaluated. As the primary efficacy objective was not met, no formal statistical analysis performed on the secondary efficacy endpoints. This outcome measure is for the surrogate endpoint analysis.

End point type	Secondary

End point timeframe:

Measurements after 72 weeks of treatment and up to study termination.

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318	150		
Units: mmol/L				
least squares mean (confidence interval 95%)	0.03 (-0.19 to 0.25)	-0.01 (-0.24 to 0.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of High-density Lipoprotein (HDL) Cholesterol

After 72 Weeks of Treatment with Elafibranor

End point title	Change From Baseline of High-density Lipoprotein (HDL) Cholesterol After 72 Weeks of Treatment with Elafibranor

End point description:

High-density lipoprotein (HDL) cholesterol was tested at Week 72. Changes from baseline in HDL cholesterol were evaluated at Week 72. As the primary efficacy objective was not met, no formal statistical analysis performed on the secondary efficacy endpoints. This outcome measure is for the surrogate endpoint analysis.
Analysis Population Description:
Intent-to-Treat Set - a cohort of randomized F2 to F3 participants who completed the Week 72 treatment period or discontinued the study treatment early.

End point type	Secondary

End point timeframe:

Measurements after 72 weeks of treatment and up to study termination.

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	629	303		
Units: mmol/L				
least squares mean (confidence interval 95%)	-0.036 (-0.050 to -0.021)	-0.052 (-0.073 to -0.032)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Low-density Lipoprotein (LDL) Cholesterol After 72 Weeks of Treatment with Elafibranor

End point title	Change From Baseline of Low-density Lipoprotein (LDL) Cholesterol After 72 Weeks of Treatment with Elafibranor

End point description:

Low-density lipoprotein (LDL) cholesterol was tested at Week 72. Changes from baseline in LDL cholesterol were evaluated at Week 72. As the primary efficacy objective was not met, no formal statistical analysis performed on the secondary efficacy endpoints. This outcome measure is for the surrogate endpoint analysis.
Analysis Population Description:
Intent-to-Treat Set - a cohort of randomized F2 to F3 participants who completed the Week 72 treatment period or discontinued the study treatment early.

End point type	Secondary

End point timeframe:

Measurements after 72 weeks of treatment and up to study termination.

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	600	283		
Units: mmol/L				
least squares mean (confidence interval 95%)	-0.250 (-0.295 to -0.204)	-0.217 (-0.282 to -0.151)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Homeostatic Model Assessment-IR After 72 Weeks of Treatment with Elafibranor in Non-diabetic Participants

End point title	Change From Baseline of Homeostatic Model Assessment-IR After 72 Weeks of Treatment with Elafibranor in Non-diabetic Participants

End point description:

Homeostatic model assessment-IR (HOMA-IR) was tested at Week 72. Changes from baseline in HOMA-IR were evaluated at Week 72.As the primary efficacy objective was not met, no formal statistical analysis performed on the secondary efficacy endpoints. This outcome measure is for the surrogate endpoint analysis.
Analysis Population Description:
Intent-to-Treat Set - a cohort of randomized F2 to F3 participants who completed the Week 72 treatment period or discontinued the study treatment early.

End point type	Secondary

End point timeframe:

Measurements after 72 weeks of treatment and up to study termination.

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	311	152		
Units: index				
least squares mean (confidence interval 95%)	-0.789 (-2.979 to 1.402)	-0.930 (-3.347 to 1.486)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Non-high Density Lipoprotein Cholesterol After 72 Weeks of Treatment with Elafibranor

End point title	Change From Baseline of Non-high Density Lipoprotein Cholesterol After 72 Weeks of Treatment with Elafibranor

End point description:

Non-high density lipoprotein (HDL) cholesterol was tested at Week 72. Changes from baseline in non-HDL cholesterol were evaluated at Week 72. As the primary efficacy objective was not met, no formal statistical analysis performed on the secondary efficacy endpoints. This outcome measure is for the

surrogate endpoint analysis.
Analysis Population Description:
Intent-to-Treat Set - a cohort of randomized F2 to F3 participants who completed the Week 72 treatment period or discontinued the study treatment early.

End point type	Secondary

End point timeframe:

Measurements after 72 weeks of treatment and up to study termination.

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	609	302		
Units: mmol/L				
least squares mean (confidence interval 95%)	-0.445 (-0.499 to -0.392)	-0.271 (-0.348 to -0.195)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Triglycerides After 72 Weeks of Treatment in Elafibranor-treated Participants Relative to Placebo

End point title	Change From Baseline of Triglycerides After 72 Weeks of Treatment in Elafibranor-treated Participants Relative to Placebo

End point description:

As the primary efficacy objective was not met, no formal statistical analysis performed on the secondary efficacy endpoints.
Analysis Population Description:
Intent-to-Treat Set - a cohort of randomized F2 to F3 participants who completed the Week 72 treatment period or discontinued the study treatment early.

End point type	Secondary

End point timeframe:

Measurements after 72 weeks of treatment and up to study termination.

End point values	120 mg Elafibranor	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	636	307		
Units: mmol/L				
least squares mean (confidence interval 95%)	-0.466 (-0.537 to -0.395)	-0.148 (-0.249 to -0.046)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event information was collected at every study visit from screening up to early termination of the study corresponding to 54 months (54 months being the longest duration for any given participant) plus 30 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	120 mg Elafibranor
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	120 mg Elafibranor	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	190 / 1433 (13.26%)	95 / 717 (13.25%)	
number of deaths (all causes)	6	2	
number of deaths resulting from adverse events	6	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma stage IV			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct adenocarcinoma			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			

subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholesteatoma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroid melanoma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal metastasis			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	3 / 1433 (0.21%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobular breast carcinoma in situ			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant peritoneal neoplasm			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian endometrioid carcinoma			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary renal cell carcinoma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostatic adenoma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour of ampulla of Vater			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 1433 (0.07%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	5 / 1433 (0.35%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 1433 (0.21%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
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			
Acute respiratory failure			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	2 / 1433 (0.14%)	3 / 717 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal discomfort			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pickwickian syndrome			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1433 (0.07%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Behaviour disorder			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dependence			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder injury			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest crushing			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 1433 (0.00%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	2 / 1433 (0.14%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	5 / 1433 (0.35%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 1433 (0.14%)	5 / 717 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac asthma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical radiculopathy			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningocele acquired			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyramidal tract syndrome			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 1433 (0.14%)	3 / 717 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	4 / 1433 (0.28%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral artery dissection			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wernicke-Korsakoff syndrome			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochromic anaemia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diplopia			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 1433 (0.07%)	3 / 717 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	3 / 1433 (0.21%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal mucocoele			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac artery stenosis			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 1433 (0.14%)	3 / 717 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 1433 (0.07%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 1433 (0.07%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 1433 (0.14%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	4 / 1433 (0.28%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder necrosis			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haematoma			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 1433 (0.21%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder prolapse			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	3 / 1433 (0.21%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital fistula			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Primary hypothyroidism			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1433 (0.00%)	5 / 717 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	4 / 1433 (0.28%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb discomfort			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	5 / 1433 (0.35%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacroiliitis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (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 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon disorder			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral lateral recess stenosis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 1433 (0.21%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	5 / 1433 (0.35%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis intestinal perforated			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis shigella			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes ophthalmic			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bite			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 1433 (0.42%)	3 / 717 (0.42%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 1433 (0.07%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 1433 (0.14%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Shigella sepsis			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection bacterial			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 1433 (0.14%)	3 / 717 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (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			
Dehydration			

subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 1433 (0.07%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folate deficiency			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 1433 (0.07%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 1433 (0.14%)	0 / 717 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 1433 (0.00%)	1 / 717 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 1433 (0.00%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 1433 (0.14%)	2 / 717 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	120 mg Elafibranor	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1227 / 1433 (85.62%)	601 / 717 (83.82%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	86 / 1433 (6.00%)	39 / 717 (5.44%)	
occurrences (all)	99	42	
Nervous system disorders			
Headache			
subjects affected / exposed	98 / 1433 (6.84%)	43 / 717 (6.00%)	
occurrences (all)	114	46	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	79 / 1433 (5.51%)	49 / 717 (6.83%)	
occurrences (all)	94	57	
Abdominal pain upper			
subjects affected / exposed	83 / 1433 (5.79%)	47 / 717 (6.56%)	
occurrences (all)	105	49	
Diarrhoea			
subjects affected / exposed	148 / 1433 (10.33%)	68 / 717 (9.48%)	
occurrences (all)	171	82	
Nausea			
subjects affected / exposed	140 / 1433 (9.77%)	50 / 717 (6.97%)	
occurrences (all)	158	51	
Fatigue			
subjects affected / exposed	103 / 1433 (7.19%)	49 / 717 (6.83%)	
occurrences (all)	111	54	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	85 / 1433 (5.93%)	40 / 717 (5.58%)	
occurrences (all)	99	47	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	160 / 1433 (11.17%)	81 / 717 (11.30%)	
occurrences (all)	202	110	
Back pain			
subjects affected / exposed	120 / 1433 (8.37%)	60 / 717 (8.37%)	
occurrences (all)	144	62	
Pain in extremity			
subjects affected / exposed	71 / 1433 (4.95%)	25 / 717 (3.49%)	
occurrences (all)	77	27	
Infections and infestations			
Bronchitis			
subjects affected / exposed	93 / 1433 (6.49%)	33 / 717 (4.60%)	
occurrences (all)	111	36	
Influenza			

subjects affected / exposed	115 / 1433 (8.03%)	54 / 717 (7.53%)	
occurrences (all)	127	68	
Nasopharyngitis			
subjects affected / exposed	134 / 1433 (9.35%)	52 / 717 (7.25%)	
occurrences (all)	186	61	
Sinusitis			
subjects affected / exposed	72 / 1433 (5.02%)	43 / 717 (6.00%)	
occurrences (all)	96	53	
Upper respiratory tract infection			
subjects affected / exposed	107 / 1433 (7.47%)	46 / 717 (6.42%)	
occurrences (all)	132	55	
Urinary tract infection			
subjects affected / exposed	145 / 1433 (10.12%)	77 / 717 (10.74%)	
occurrences (all)	236	134	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	102 / 1433 (7.12%)	58 / 717 (8.09%)	
occurrences (all)	109	62	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2017	Amendment 1 addressed inconsistencies in the original protocol and increases clarity. It also detailed the statistical analyses to be consistent with the statistical analysis plan. Revisions were made to protocol sections as well as to the study synopsis, the study general assessment schedule, study biological assessment schedule, study duration and visit schedule, and throughout the protocol text as required.
03 April 2017	Amendment 2 was a non-substantial change to clarify the collection of 2 baseline values of liver enzymes before study treatment initiation. This remains in line with the FDA request to obtain 2 baseline values of liver transaminase, total bilirubin, and INR at least 8 weeks apart, in order to be able to have 2 baseline values in case of DILI adjudication.
20 November 2017	Amendment 1 (PK sub-study): Amendment 1 for the PK sub-study was a non-substantial change to revise the protocol ID and title to clarify this is a sub-study for GFT505-315-1.
08 June 2018	Amendment 2 (PK sub-study): a non-substantial change to remove text specifying involved countries to allow the involvement of further sites from more than 4 countries.
03 January 2020	Amendment 3 was a substantial change to address the addition of a key secondary objective at the Surrogate Endpoint Analysis (SEA). Some metabolic endpoints (triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c [in diabetic patients], HOMA-IR [in non diabetic patients]) were upgraded as key secondary endpoints that resulted in addition of a gatekeeping procedure to control the overall type I error rate at a two-sided alpha level of 0.01. Furthermore, some updates and clarifications were made in the "Statistical Methods and Data Analysis" section to be consistent with the SAP. Other updates to clarify the FibroScan assessments and the rules of discontinuation related to the liver function monitoring were added. The summary of the safety data was also updated to reflect the update of the effective Investigator's Brochure with no changes to the benefit/risk assessment to the medicinal product.
20 April 2020	Amendment 4 was a substantial change to address the change in definition of the primary clinical benefit endpoint and associated adjudication process. In addition, updates were made to clarify the criteria to be used to identify patients with potential DILIs. A list of AEs of special interest was also added and clarification was made on the required follow-up of the potential treatment related AEs. An additional section was added to address the optional solutions put in place in case a patient participating in the RESOLVE-IT study cannot attend a site visit during the COVID-19 crisis or future crisis situation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely terminated based upon limited efficacy at time of the interim analysis, not due to safety concerns. Therefore, the results for efficacy endpoints other than the primary and key secondary endpoints are not presented here.

Notes: