Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib in Subjects with Nonalcoholic Steatohepatitis (NASH) and Bridging (F3) Fibrosis.

Summary

EudraCT number	2016-004374-18
Trial protocol	AT BE GB DE PT PL NL ES IT
Global end of trial date	19 June 2019

Results information

Result version number	v1 (current)
This version publication date	26 June 2020
First version publication date	26 June 2020

Trial information

Trial identification

Sponsor protocol code	GS-US-384-1943

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03053050
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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	19 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate whether selonsertib (SEL; GS-4997) can cause fibrosis regression and reduce progression to cirrhosis and associated complications in adults with nonalcoholic steatohepatitis (NASH) and bridging (F3) fibrosis.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 417
Country: Number of subjects enrolled	Japan: 80
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Hong Kong: 24
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	India: 15
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Singapore: 11
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Belgium: 8

Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Puerto Rico: 3
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Switzerland: 3
Worldwide total number of subjects	808
EEA total number of subjects	110

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)	616
From 65 to 84 years	192
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Asia, Europe, Australia, South America, Puerto Rico, and New Zealand. The first participant was screened on 13 February 2017. The last study visit occurred on 19 June 2019.

Pre-assignment

Screening details:

2250 participants were screened. No participants completed the study. In the Subject Disposition, the number of participants reported in the Randomised Phase arms for "Completed" is the number of participants with a confirmed clinical event who discontinued the randomized phase per protocol.

Period 1

Period 1 title	Randomized Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	SEL 18 mg

Arm description:

Randomized Phase: SEL 18 mg tablet orally once daily + placebo to match SEL 6 mg tablet orally once daily for 240 weeks.

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

18 mg administered once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets administered once daily

Arm title	SEL 6 mg

Arm description:

Randomized Phase: SEL 6 mg tablet orally once daily + placebo to match SEL 18 mg tablet orally once daily for 240 weeks.

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details: 6 mg administered once daily	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Tablets administered once daily	
Arm title	Placebo
Arm description: Randomized Phase: Placebo to match SEL 6 mg tablet orally once daily + placebo to match SEL 18 mg tablet orally once daily for 240 weeks.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Tablets administered once daily	

Number of subjects in period 1[1]	SEL 18 mg	SEL 6 mg	Placebo
Started	322	321	159
Completed	36	45	18
Not completed	286	276	141
Withdrew Consent	16	8	9
Adverse Event	-	1	-
Investigator's Discretion	6	6	3
Study Terminated by Sponsor	259	260	128
Lost to follow-up	5	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 6 participants (2 in SEL 18 mg arm, 2 in SEL 6 mg arm, and 2 in Placebo arm) were randomized but did not receive study treatment.

Period 2

Period 2 title	Open-Label Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-Label SEL 18 mg

Arm description:

Open-Label (OL) Phase: Participants who experienced a hepatic clinical event or have biopsy confirmed progression to cirrhosis during the randomized phase, prior to completing the Week 240 visit, were offered the option to roll over into an OL phase to receive OL SEL 18 mg daily for a total treatment duration of 240 weeks inclusive of the randomized phase.

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

18 mg administered once daily

Number of subjects in period 2	Open-Label SEL 18 mg
Started	99
Completed	0
Not completed	99
Withdrew Consent	6
Investigator's Discretion	4
Study Terminated by Sponsor	89

Baseline characteristics

Reporting groups	
Reporting group title	SEL 18 mg
Reporting group description:	
Randomized Phase: SEL 18 mg tablet orally once daily + placebo to match SEL 6 mg tablet orally once daily for 240 weeks.	
Reporting group title	SEL 6 mg
Reporting group description:	
Randomized Phase: SEL 6 mg tablet orally once daily + placebo to match SEL 18 mg tablet orally once daily for 240 weeks.	
Reporting group title	Placebo
Reporting group description:	
Randomized Phase: Placebo to match SEL 6 mg tablet orally once daily + placebo to match SEL 18 mg tablet orally once daily for 240 weeks.	

Reporting group values	SEL 18 mg	SEL 6 mg	Placebo
Number of subjects	322	321	159
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57	57	57
standard deviation	± 9.1	± 9.2	± 9.0
Gender categorical Units: Subjects			
Female	181	196	76
Male	141	125	83
Race			
Not Permitted = Local regulators did not allow collection of race or ethnicity information.			
Units: Subjects			
American Indian or Alaska Native	5	1	2
Asian	88	84	41
Black	8	5	2
White	219	227	113
Other	2	3	1
Not Permitted	0	1	0
Ethnicity			
Not Permitted = Local regulators did not allow collection of race or ethnicity information.			
Units: Subjects			
Not Hispanic or Latino	269	269	137
Hispanic or Latino	52	48	22
Not Permitted	1	4	0

Reporting group values	Total		
Number of subjects	802		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	453		
Male	349		
Race			
Not Permitted = Local regulators did not allow collection of race or ethnicity information.			
Units: Subjects			
American Indian or Alaska Native	8		
Asian	213		
Black	15		
White	559		
Other	6		
Not Permitted	1		
Ethnicity			
Not Permitted = Local regulators did not allow collection of race or ethnicity information.			
Units: Subjects			
Not Hispanic or Latino	675		
Hispanic or Latino	122		
Not Permitted	5		

End points

End points reporting groups

Reporting group title	SEL 18 mg
Reporting group description:	
Randomized Phase: SEL 18 mg tablet orally once daily + placebo to match SEL 6 mg tablet orally once daily for 240 weeks.	
Reporting group title	SEL 6 mg
Reporting group description:	
Randomized Phase: SEL 6 mg tablet orally once daily + placebo to match SEL 18 mg tablet orally once daily for 240 weeks.	
Reporting group title	Placebo
Reporting group description:	
Randomized Phase: Placebo to match SEL 6 mg tablet orally once daily + placebo to match SEL 18 mg tablet orally once daily for 240 weeks.	
Reporting group title	Open-Label SEL 18 mg
Reporting group description:	
Open-Label (OL) Phase: Participants who experienced a hepatic clinical event or have biopsy confirmed progression to cirrhosis during the randomized phase, prior to completing the Week 240 visit, were offered the option to roll over into an OL phase to receive OL SEL 18 mg daily for a total treatment duration of 240 weeks inclusive of the randomized phase.	

Primary: Percentage of Participants Who Achieved a ≥ 1-Stage Improvement in Fibrosis According to the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network (CRN) Classification Without Worsening of NASH at Week 48

End point title	Percentage of Participants Who Achieved a ≥ 1-Stage Improvement in Fibrosis According to the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network (CRN) Classification Without Worsening of NASH at Week 48
End point description:	
Fibrosis improvement was defined as ≥ 1-stage decrease from baseline in fibrosis according to the NASH CRN classification. NASH CRN fibrosis stages range from 0 to 4, with higher scores indicating greater fibrosis (0=None, 4=Cirrhosis). Worsening of NASH was defined as ≥ 1 point increase from baseline in hepatocellular ballooning or lobular inflammation according to the Non-Alcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) criteria. As defined by NAS, hepatocellular ballooning ranges from 0-2 and lobular inflammation ranges from 0-3, with higher scores indicating more severe hepatocellular ballooning or lobular inflammation. The Full Analysis Set included all participants who were randomized into the study and received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Week 48	

End point values	SEL 18 mg	SEL 6 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	322	321	159	
Units: percentage of participants				
number (confidence interval 95%)	9.6 (6.6 to 13.4)	12.1 (8.8 to 16.2)	13.2 (8.4 to 19.5)	

Statistical analyses

Statistical analysis title	SEL 18 mg vs Placebo
Comparison groups	SEL 18 mg v Placebo
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4941 [1]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	4

Notes:

[1] - Difference between SEL 18 mg and Placebo, 95% confidence interval (CI) and p-value were obtained by stratum-adjusted Mantel-Haenszel method with baseline diabetes mellitus status and Enhanced Liver Fibrosis (ELF) test score as stratification factors.

Statistical analysis title	SEL 6 mg vs Placebo
Comparison groups	SEL 6 mg v Placebo
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9321 [2]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	6

Notes:

[2] - Difference between SEL 6 mg and Placebo, 95% CI and p-value were obtained by stratum-adjusted Mantel-Haenszel method with baseline diabetes mellitus status and ELF test score as stratification factors.

Primary: Event-Free Survival (EFS) at Week 240 as Assessed by Time to First Clinical Event

End point title	Event-Free Survival (EFS) at Week 240 as Assessed by Time to First Clinical Event[3]

End point description:

EFS was assessed by the time to the first clinical event, including progression to cirrhosis on liver biopsy, liver decompensation events, liver transplantation, and all-cause mortality.

End point type	Primary

End point timeframe:

Week 240

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.

End point values	SEL 18 mg	SEL 6 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[4]	0[5]	0[6]	
Units: months				
median (inter-quartile range (Q1-Q3))	(to)	(to)	(to)	

Notes:

[4] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.
[5] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.
[6] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Had Progression to Cirrhosis at Week 48

End point title	Percentage of Participants Who Had Progression to Cirrhosis at Week 48

End point description:

Progression to cirrhosis was defined as a change in NASH CRN fibrosis stage from < 4 at baseline to 4 at Week 48. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 48

End point values	SEL 18 mg	SEL 6 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	322	321	159	
Units: percentage of participants				
number (confidence interval 95%)	13.0 (9.6 to 17.2)	15.6 (11.8 to 20.0)	15.7 (10.4 to 22.3)	

Statistical analyses

Statistical analysis title	SEL 18 mg vs Placebo
Comparison groups	SEL 18 mg v Placebo

Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2593 [7]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	2.9

Notes:

[7] - Difference between SEL 18 mg and Placebo, 95% CI and p-value were obtained by stratum-adjusted Mantel-Haenszel method with baseline diabetes mellitus status and ELF test score as stratification factors.

Statistical analysis title	SEL 6 mg vs Placebo
Comparison groups	SEL 6 mg v Placebo
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.808 [8]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	6.1

Notes:

[8] - Difference between SEL 6 mg vs Placebo, 95% CI and p-value were obtained by stratum-adjusted Mantel-Haenszel method with baseline diabetes mellitus status and ELF test score as stratification factors.

Secondary: Percentage of Participants Who Had a ≥ 1-Stage Improvement in Fibrosis Without Worsening of NASH at Week 240

End point title	Percentage of Participants Who Had a ≥ 1-Stage Improvement in Fibrosis Without Worsening of NASH at Week 240

End point description:

Fibrosis improvement was defined as ≥ 1-stage decrease from baseline in fibrosis according to the NASH CRN classification. NASH CRN fibrosis stages range from 0 to 4, with higher scores indicating greater fibrosis (0=None, 4=Cirrhosis). Worsening of NASH was defined as ≥ 1 point increase from baseline in hepatocellular ballooning or lobular inflammation according to the NAS criteria. As defined by NAS, hepatocellular ballooning ranges from 0-2 and lobular inflammation ranges from 0-3, with higher scores indicating more severe hepatocellular ballooning or lobular inflammation.

End point type	Secondary

End point timeframe:

Week 240

End point values	SEL 18 mg	SEL 6 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[9]	0[10]	0[11]	
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[9] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.
[10] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.
[11] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Had a ≥ 1-Stage Improvement in Fibrosis at Week 48

End point title	Percentage of Participants Who Had a ≥ 1-Stage Improvement in Fibrosis at Week 48

End point description:

Fibrosis improvement was defined as ≥ 1-stage decrease from baseline in fibrosis according to the NASH CRN classification. NASH CRN fibrosis stages range from 0 to 4, with higher scores indicating greater fibrosis (0=None, 4=Cirrhosis). Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 48

End point values	SEL 18 mg	SEL 6 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	322	321	159	
Units: percentage of participants				
number (confidence interval 95%)	12.7 (9.3 to 16.9)	13.7 (10.1 to 18.0)	16.4 (11.0 to 23.0)	

Statistical analyses

Statistical analysis title	SEL 18 mg vs Placebo
Comparison groups	SEL 18 mg v Placebo
Number of subjects included in analysis	481
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5636 [12]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	4.8

Notes:

[12] - Difference between SEL 18 mg and Placebo, 95% CI and p-value were obtained by stratum-adjusted Mantel-Haenszel method with baseline diabetes mellitus status and ELF test score as stratification factors.

Statistical analysis title	SEL 6 mg vs Placebo
Comparison groups	Placebo v SEL 6 mg
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5915 [13]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	4.9

Notes:

[13] - Difference between SEL 6 mg and Placebo, 95% CI and p-value were obtained by stratum-adjusted Mantel-Haenszel method with baseline diabetes mellitus status and ELF test score as stratification factors.

Secondary: Percentage of Participants Who Had a ≥ 1-Stage Improvement in Fibrosis at Week 240

End point title	Percentage of Participants Who Had a ≥ 1-Stage Improvement in Fibrosis at Week 240

End point description:

Fibrosis improvement was defined as ≥ 1-stage decrease from baseline in fibrosis according to the NASH CRN classification. NASH CRN fibrosis stages range from 0 to 4, with higher scores indicating greater fibrosis (0=None, 4=Cirrhosis).

End point type	Secondary

End point timeframe:

Week 240

End point values	SEL 18 mg	SEL 6 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	0[15]	0[16]	
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[14] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint

[15] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint

[16] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Had NASH Resolution Without Worsening of Fibrosis at Week 48

End point title	Percentage of Participants Who Had NASH Resolution Without Worsening of Fibrosis at Week 48

End point description:

NASH resolution was defined as lobular inflammation of 0 or 1 from ≥ 1 at baseline and hepatocellular ballooning of 1 from a value ≥ 1 at baseline; both criteria were necessary conditions. Evaluable participants had baseline lobular inflammation and hepatocellular ballooning ≥ 1. Worsening of Fibrosis was defined by an increase in Fibrosis stage from 3 to 4 as defined by NASH CRN. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Week 48

End point values	SEL 18 mg	SEL 6 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	322	321	158	
Units: percentage of participants				
number (confidence interval 95%)	5.0 (2.9 to 7.9)	4.4 (2.4 to 7.2)	8.9 (4.9 to 14.4)	

Statistical analyses

Statistical analysis title	SEL 18 mg vs Placebo
Comparison groups	SEL 18 mg v Placebo
Number of subjects included in analysis	480
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2455 [17]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	2.2

Notes:

[17] - Difference between SEL 18 mg and Placebo, 95% CI and p-value were obtained by stratum-adjusted Mantel-Haenszel method with baseline diabetes mellitus status and ELF test score as stratification factors.

Statistical analysis title	SEL 6 mg vs Placebo
Comparison groups	SEL 6 mg v Placebo
Number of subjects included in analysis	479
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1371 [18]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	1.3

Notes:

[18] - Difference between SEL 6 mg and Placebo, 95% CI and p-value were obtained by stratum-adjusted Mantel-Haenszel method with baseline diabetes mellitus status and ELF test score as stratification factors.

Secondary: Percentage of Participants Who Had NASH Resolution Without Worsening of Fibrosis at Week 240

End point title	Percentage of Participants Who Had NASH Resolution Without Worsening of Fibrosis at Week 240

End point description:

NASH resolution was defined as lobular inflammation of 0 or 1 from ≥ 1 at baseline and hepatocellular ballooning of 1 from a value ≥ 1 at baseline; both criteria were necessary conditions. Evaluable participants had baseline lobular inflammation and hepatocellular ballooning ≥ 1. Worsening of Fibrosis was defined by an increase in Fibrosis stage from 3 to 4 as defined by NASH CRN.

End point type	Secondary

End point timeframe:

Week 240

End point values	SEL 18 mg	SEL 6 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[19]	0[20]	0[21]	
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[19] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.
[20] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.
[21] - No data was analyzed as the study was terminated and no participants reached the Week 240 timepoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
First dose date up to last dose (maximum: 111.4 weeks) plus 30 days	
Adverse event reporting additional description:	
The Safety Analysis Set included all participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	SEL 18 mg
Reporting group description:	
Randomized Phase: Selonsertib (SEL) 18 mg tablet orally once daily + placebo to match SEL 6 mg tablet orally once daily for 240 weeks.	
Reporting group title	SEL 6 mg
Reporting group description:	
Randomized Phase: SEL 6 mg tablet orally once daily + placebo to match SEL 18 mg tablet orally once daily for 240 weeks.	
Reporting group title	Placebo
Reporting group description:	
Randomized Phase: Placebo to match SEL 6 mg tablet orally once daily + placebo to match SEL 18 mg tablet orally once daily for 240 weeks.	
Reporting group title	Open-Label SEL 18 mg
Reporting group description:	
Open-Label (OL) Phase: Participants who experienced a hepatic clinical event or have biopsy confirmed progression to cirrhosis during the randomized phase, prior to completing the Week 240 visit, were offered the option to roll over into an OL phase to receive OL SEL 18 mg daily for a total treatment duration of 240 weeks inclusive of the randomized phase.	

Serious adverse events	SEL 18 mg	SEL 6 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 322 (14.60%)	36 / 321 (11.21%)	17 / 159 (10.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 322 (0.31%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer recurrent			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoid tumour pulmonary			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma of skin			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic lymphoma			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			

subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the vulva			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 322 (0.31%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular necrosis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic hydrothorax			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar I disorder			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizoaffective disorder			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ammonia increased			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			

subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	1 / 322 (0.31%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			

subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic leak			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 322 (0.93%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			

subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular disorder			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 322 (0.31%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			

subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 322 (0.31%)	2 / 321 (0.62%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Retinal detachment			
subjects affected / exposed	1 / 322 (0.31%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 322 (0.62%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Internal hernia			

subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis relapsing			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			

subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic lesion			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 322 (0.31%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis interstitial			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 322 (0.31%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthralgia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 322 (0.93%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 322 (0.00%)	2 / 321 (0.62%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 322 (0.00%)	2 / 321 (0.62%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis of male external genital organ			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis externa			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative abscess			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 322 (0.00%)	0 / 321 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 322 (0.31%)	0 / 321 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 322 (0.00%)	1 / 321 (0.31%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-Label SEL 18 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 99 (6.06%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			

subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatocellular carcinoma				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast cancer recurrent				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carcinoid tumour pulmonary				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemangioma of skin				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to liver				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic lymphoma				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				

subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of the vulva				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Orthostatic hypotension				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral artery thrombosis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Testicular necrosis			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic hydrothorax			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			

subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bipolar I disorder				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Insomnia				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Schizoaffective disorder				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Ammonia increased				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood glucose increased				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Body temperature increased				

subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oxygen saturation decreased				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Post procedural complication				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clavicle fracture				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				

subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic leak				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Patella fracture				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				

subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis coronary artery				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiovascular disorder				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Syncope				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ataxia				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				

subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic encephalopathy				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic anaemia				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				

Retinal detachment				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Pancreatitis acute				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Internal hernia				

subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Irritable bowel syndrome				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis chronic				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis relapsing				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritoneal haemorrhage				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varices oesophageal				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis acute				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic haemorrhage				

subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic lesion			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis interstitial			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Arthralgia				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscle spasms				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				

subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis of male external genital organ				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis externa				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative abscess				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	1 / 99 (1.01%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 99 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SEL 18 mg	SEL 6 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	248 / 322 (77.02%)	254 / 321 (79.13%)	130 / 159 (81.76%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	10 / 322 (3.11%)	5 / 321 (1.56%)	8 / 159 (5.03%)
occurrences (all)	10	5	9
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 322 (11.18%)	38 / 321 (11.84%)	18 / 159 (11.32%)
occurrences (all)	50	47	19
Dizziness			

subjects affected / exposed	16 / 322 (4.97%)	30 / 321 (9.35%)	2 / 159 (1.26%)
occurrences (all)	17	32	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	35 / 322 (10.87%)	33 / 321 (10.28%)	12 / 159 (7.55%)
occurrences (all)	39	35	12
Oedema peripheral			
subjects affected / exposed	18 / 322 (5.59%)	9 / 321 (2.80%)	4 / 159 (2.52%)
occurrences (all)	18	9	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	52 / 322 (16.15%)	47 / 321 (14.64%)	30 / 159 (18.87%)
occurrences (all)	64	59	43
Constipation			
subjects affected / exposed	40 / 322 (12.42%)	43 / 321 (13.40%)	19 / 159 (11.95%)
occurrences (all)	43	49	19
Nausea			
subjects affected / exposed	32 / 322 (9.94%)	39 / 321 (12.15%)	14 / 159 (8.81%)
occurrences (all)	37	46	20
Abdominal pain upper			
subjects affected / exposed	33 / 322 (10.25%)	26 / 321 (8.10%)	16 / 159 (10.06%)
occurrences (all)	33	28	17
Abdominal pain			
subjects affected / exposed	22 / 322 (6.83%)	27 / 321 (8.41%)	15 / 159 (9.43%)
occurrences (all)	25	34	15
Vomiting			
subjects affected / exposed	19 / 322 (5.90%)	18 / 321 (5.61%)	8 / 159 (5.03%)
occurrences (all)	24	22	12
Abdominal distension			
subjects affected / exposed	13 / 322 (4.04%)	12 / 321 (3.74%)	8 / 159 (5.03%)
occurrences (all)	14	12	9
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	42 / 322 (13.04%)	50 / 321 (15.58%)	25 / 159 (15.72%)
occurrences (all)	42	50	25
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	28 / 322 (8.70%)	18 / 321 (5.61%)	14 / 159 (8.81%)
occurrences (all)	31	21	14
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	23 / 322 (7.14%)	20 / 321 (6.23%)	11 / 159 (6.92%)
occurrences (all)	24	21	11
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	33 / 322 (10.25%)	30 / 321 (9.35%)	18 / 159 (11.32%)
occurrences (all)	35	31	20
Back pain			
subjects affected / exposed	33 / 322 (10.25%)	27 / 321 (8.41%)	11 / 159 (6.92%)
occurrences (all)	37	27	11
Pain in extremity			
subjects affected / exposed	20 / 322 (6.21%)	15 / 321 (4.67%)	11 / 159 (6.92%)
occurrences (all)	22	15	11
Muscle spasms			
subjects affected / exposed	16 / 322 (4.97%)	17 / 321 (5.30%)	7 / 159 (4.40%)
occurrences (all)	17	18	7
Musculoskeletal pain			
subjects affected / exposed	14 / 322 (4.35%)	18 / 321 (5.61%)	8 / 159 (5.03%)
occurrences (all)	14	19	10
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	41 / 322 (12.73%)	46 / 321 (14.33%)	21 / 159 (13.21%)
occurrences (all)	54	53	27
Nasopharyngitis			
subjects affected / exposed	46 / 322 (14.29%)	40 / 321 (12.46%)	21 / 159 (13.21%)
occurrences (all)	71	64	23
Sinusitis			
subjects affected / exposed	21 / 322 (6.52%)	21 / 321 (6.54%)	12 / 159 (7.55%)
occurrences (all)	30	29	14
Influenza			
subjects affected / exposed	19 / 322 (5.90%)	20 / 321 (6.23%)	14 / 159 (8.81%)
occurrences (all)	20	21	16

Urinary tract infection			
subjects affected / exposed	14 / 322 (4.35%)	27 / 321 (8.41%)	13 / 159 (8.18%)
occurrences (all)	20	32	21
Bronchitis			
subjects affected / exposed	23 / 322 (7.14%)	21 / 321 (6.54%)	6 / 159 (3.77%)
occurrences (all)	25	26	7

Non-serious adverse events	Open-Label SEL 18 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 99 (48.48%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 99 (5.05%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	2 / 99 (2.02%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 99 (3.03%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	3 / 99 (3.03%)		
occurrences (all)	3		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 99 (8.08%)		
occurrences (all)	8		
Constipation			
subjects affected / exposed	4 / 99 (4.04%)		
occurrences (all)	6		
Nausea			

subjects affected / exposed occurrences (all)	6 / 99 (6.06%) 6		
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 99 (5.05%) 5		
Abdominal pain subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3		
Vomiting subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 1		
Abdominal distension subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2		
Hepatobiliary disorders Hepatic cirrhosis subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3		
Back pain subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	5 / 99 (5.05%) 5		

Muscle spasms subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 99 (6.06%) 7		
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0		
Sinusitis subjects affected / exposed occurrences (all)	5 / 99 (5.05%) 5		
Influenza subjects affected / exposed occurrences (all)	4 / 99 (4.04%) 4		
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 99 (3.03%) 3		
Bronchitis subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2017	1. Clarified that events of hepatic decompensation included portal hypertension-related bleeding that required endoscopy, hospitalization and would be adjudicated by the Hepatic Events/Drug-Induced Liver Injury Adjudication Committee. 2. Hepatocellular carcinoma (HCC) was removed as a component of primary clinical efficacy endpoint. 3. The outcome of "death" was changed to "all-cause mortality" to clarify that all deaths would be included in EFS analysis. 4. References to a HepQuant substudy were removed. Only subjects enrolled at participating US sites could participate. 5. Laboratory parameters and assessments at screening were clarified; INR ≤ 1.4 and platelet count ≥100,000/µL were added as inclusion criteria. 6. Stool frequency assessment was added to the study procedures at all visits, beginning with baseline/Day 1. 7. EFS assessed as time to the first clinical event, including HCC, as well as progression to cirrhosis, liver decompensation events, liver transplantation, and all-cause mortality, was added as an exploratory efficacy endpoint. 8. Clarified that a sensitivity analysis of EFS that included hepatic clinical events and liver-related death would be performed. 9. Clarified that all clinical events except all-cause mortality and liver transplantation required confirmation by the Hepatic Events Adjudication Committee. 10. A stratified log-rank test was added to the exploratory endpoint analysis to compare between-group differences (SEL 18 mg, SEL 6 mg, Placebo) in time to the first clinical events, including HCC. 11. Estimated glomerular filtration rate (eGFR) calculation was included at all visits. 12. Specified that single PK sampling would be performed who entered OL phase and had severe hepatic impairment (Child-Pugh [CP] Class C) and renal impairment (eGFR < 30 mL/min). 13. Clarified that subjects in OL phase who completed study treatment should complete the Week 240/EOT visit. 14. A telephone follow-up visit to occur 12 weeks after Week 240 visit.
31 May 2018	1. Added abdominal ultrasound to be performed for HCC surveillance in the OL phase. 2. An early termination (ET) visit that was to be completed within 30 days after the last dose of study drug and the list of assessments to be performed at the visit was clarified for subjects who prematurely discontinued the study. 3. Clarified that hepatic clinical events would be adjudicated and deaths would be reviewed by the Hepatic Events/DILI Adjudication Committee during the randomized phase of the study; DILI events and cardiovascular events, including deaths, were to be adjudicated in the OL phase of the study by the hepatic events/DILI and cardiovascular Adjudication Committees, as appropriate. 4. Clinical trial information was updated, based on updates to the SEL Investigator's Brochure, including the numbers of SEL studies conducted and subjects dosed, updated safety data, final study data, and completion of studies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 June 2019	Based on the results of the Week 48 analysis, the study was terminated early for lack of efficacy as prespecified in the clinical study protocol.	-

Notes:

Limitations and caveats

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

Based on the results of the Week 48 analysis, the study was terminated early for lack of efficacy as prespecified in the clinical study protocol.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31271665

http://www.ncbi.nlm.nih.gov/pubmed/30779990