Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis (NASH)

Summary

EudraCT number	2016-004148-13
Trial protocol	AT BE GB PT PL NL ES FR IT
Global end of trial date	06 May 2019

Results information

Result version number	v1 (current)
This version publication date	10 May 2020
First version publication date	10 May 2020

Trial information

Trial identification

Sponsor protocol code	GS-US-384-1944

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03053063
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	06 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 May 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 associated complications in subjects with cirrhosis due to NASH.

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	30 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	United States: 525
Country: Number of subjects enrolled	Japan: 58
Country: Number of subjects enrolled	Canada: 37
Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	India: 31
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Hong Kong: 15
Country: Number of subjects enrolled	Taiwan: 9

Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Puerto Rico: 7
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	883
EEA total number of subjects	108

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)	636
From 65 to 84 years	247
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Asia, Australia, New Zealand, Europe and Puerto Rico. The first participant was screened on 30 January 2017. The last study visit occurred on 06 May 2019.

Pre-assignment

Screening details:

2154 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 who had confirmed clinical event therefore discontinued randomised phase per protocol.

Period 1

Period 1 title	Randomised 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:

Randomised Phase: SEL 18 mg tablet orally once daily + placebo for up to 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:

Randomised Phase : SEL 6 mg tablet orally once daily + placebo for up to 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:

Randomised Phase: Placebo to match SEL 18 mg and 6 mg orally once daily for up to 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:

Placebo to match SEL 18 mg and 6 mg administered once daily

Number of subjects in period 1[1]	SEL 18 mg	SEL 6 mg	Placebo
Started	354	351	172
Completed	9	11	3
Not completed	345	340	169
Study terminated by sponsor	326	317	161
Adverse event	-	1	-
Withdrew consent	8	11	5
Investigator's discretion	8	6	2
Lost to follow-up	3	5	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 (1 in SEL 18 mg arm, 3 in SEL 6 mg arm, and 2 in Placebo arm) were randomised 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 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, including the treatment duration in 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	23
Completed	0
Not completed	23
Death	2
Study terminated by sponsor	19
Investigator's discretion	2

Baseline characteristics

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

Reporting group values	SEL 18 mg	SEL 6 mg	Placebo
Number of subjects	354	351	172
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58	57	60
standard deviation	± 8.5	± 8.7	± 8.4
Gender categorical Units: Subjects			
Female	216	230	101
Male	138	121	71
Race Units: Subjects			
American Indian or Alaska Native	3	3	0
Asian	73	59	33
Black	5	4	1
Native Hawaiian or Pacific Islander	1	0	0
White	261	279	136
Other	7	6	1
Not Permitted	4	0	1
Ethnicity Units: Subjects			
Not Hispanic or Latino	300	297	149
Hispanic or Latino	49	51	22
Not Permitted	5	3	1

Reporting group values	Total		
Number of subjects	877		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	547		
Male	330		
Race Units: Subjects			
American Indian or Alaska Native	6		
Asian	165		
Black	10		
Native Hawaiian or Pacific Islander	1		
White	676		
Other	14		
Not Permitted	5		
Ethnicity Units: Subjects			
Not Hispanic or Latino	746		
Hispanic or Latino	122		
Not Permitted	9		

End points

End points reporting groups

Reporting group title	SEL 18 mg
Reporting group description:	
Randomised Phase: SEL 18 mg tablet orally once daily + placebo for up to 240 weeks.	
Reporting group title	SEL 6 mg
Reporting group description:	
Randomised Phase : SEL 6 mg tablet orally once daily + placebo for up to 240 weeks.	
Reporting group title	Placebo
Reporting group description:	
Randomised Phase: Placebo to match SEL 18 mg and 6 mg orally once daily for up to 240 weeks.	
Reporting group title	Open-Label SEL 18 mg
Reporting group description:	
Open-Label (OL) Phase: Participants who experienced a hepatic clinical event 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, including the treatment duration in the randomized phase.	

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

End point title	Percentage of Participants Who Achieve a ≥ 1-Stage Improvement in Fibrosis According to the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network (CRN) Classification Without Worsening of NASH
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 randomised 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	354	351	172	
Units: percentage of participants				
number (confidence interval 95%)	14.4 (10.9 to 18.5)	12.8 (9.5 to 16.8)	12.8 (8.2 to 18.7)	

Statistical analyses

Statistical analysis title	SEL 18 mg vs Placebo
Comparison groups	SEL 18 mg v Placebo
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5572 [1]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	8.2

Notes:

[1] - Difference between SEL 18 mg vs Placebo, 95% confidence interval (CI) and p-value were obtained by stratified Mantel-Haenszel method adjusting for baseline (BL) diabetes mellitus status and BL Enhanced Liver Fibrosis (ELF) score (<11.27 vs ≥11.27).

Statistical analysis title	SEL 6 mg vs Placebo
Comparison groups	SEL 6 mg v Placebo
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9272 [2]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	6.5

Notes:

[2] - Difference between SEL 6 mg vs Placebo, 95% CI and p-value were obtained by stratified Mantel-Haenszel method adjusting for BL diabetes mellitus status and BL ELF score (<11.27 vs ≥11.27).

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 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 analysed 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 analysed as the study was terminated and no participants reached the Week 240 timepoint.
[5] - No data was analysed as the study was terminated and no participants reached the Week 240 timepoint.
[6] - No data was analysed 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 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[7]	0[8]	0[9]	
Units: percentage of participants				
number (not applicable)				

Notes:

[7] - No data was analysed as the study was terminated and no participants reached the Week 240 timepoint.
[8] - No data was analysed as the study was terminated and no participants reached the Week 240 timepoint.
[9] - No data was analysed 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 analysed.

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	354	351	172	
Units: percentage of participants				
number (confidence interval 95%)	18.9 (15.0 to 23.4)	16.8 (13.0 to 21.1)	15.7 (10.6 to 22.0)	

Statistical analyses

Statistical analysis title	SEL 18 mg vs Placebo
Comparison groups	SEL 18 mg v Placebo
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.285 [10]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	10.6

Notes:

[10] - Difference between SEL 18 mg vs Placebo, 95% CI and p-value were obtained by stratified Mantel-Haenszel method adjusting for BL diabetes mellitus status and ELF score (<11.27 vs ≥11.27).

Statistical analysis title	SEL 6 mg vs Placebo
Comparison groups	SEL 6 mg v Placebo
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6731 [11]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	8.2

Notes:

[11] - Difference between SEL 6 mg vs Placebo, 95% CI and p-value were obtained by stratified Mantel-Haenszel method adjusting for BL diabetes mellitus status and BL ELF score (<11.27 vs ≥11.2.

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[12]	0[13]	0[14]	
Units: percentage of participants				
number (not applicable)				

Notes:

[12] - No data was analysed as the study was terminated and no participants reached the Week 240 timepoint.
[13] - No data was analysed as the study was terminated and no participants reached the Week 240 timepoint.
[14] - No data was analysed 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 at Week 48

End point title	Percentage of Participants Who Had NASH Resolution at Week 48

End point description:

NASH resolution was defined as lobular inflammation of 0 or 1 from ≥ 1 at baseline and hepatocellular ballooning reduced to 0 from a value ≥ 1 at baseline; both criteria were necessary conditions. 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. Evaluable participants had baseline lobular inflammation and hepatocellular ballooning ≥ 1. Participants in the Full Analysis Set were analysed.

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	353	351	172	
Units: percentage of participants				
number (confidence interval 95%)	2.3 (1.0 to 4.4)	3.7 (2.0 to 6.3)	4.1 (1.7 to 8.2)	

Statistical analyses

Statistical analysis title	SEL 18 mg vs Placebo
Comparison groups	SEL 18 mg v Placebo
Number of subjects included in analysis	525
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.365 [15]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	2

Notes:

[15] - Difference between SEL 18 mg vs Placebo, 95% CI and p-value were obtained by stratified Mantel-Haenszel method adjusting for BL diabetes mellitus status and BL ELF score (<11.27 vs ≥11.27).

Statistical analysis title	SEL 6 mg vs Placebo
Comparison groups	SEL 6 mg v Placebo
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8557 [16]
Method	Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	3.6

Notes:

[16] - Difference between SEL 6 mg vs Placebo, 95% CI and p-value were obtained by stratified Mantel-Haenszel method adjusting for BL diabetes mellitus status and BL ELF score (<11.27 vs ≥11.27).

Secondary: Percentage of Participants Who Had NASH Resolution at Week 240

End point title	Percentage of Participants Who Had NASH Resolution at Week 240

End point description:

NASH resolution was defined as lobular inflammation of 0 or 1 from ≥ 1 at baseline and hepatocellular ballooning reduced to 0 from a value ≥ 1 at baseline; both criteria were necessary conditions. 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. Evaluable participants had baseline lobular inflammation and hepatocellular ballooning ≥ 1.

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[17]	0[18]	0[19]	
Units: percentage of participants				
number (not applicable)				

Notes:

[17] - No data was analysed as the study was terminated and no participants reached the Week 240 timepoint.
[18] - No data was analysed as the study was terminated and no participants reached the Week 240 timepoint.
[19] - No data was analysed 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 date (maximum: 108.7 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: SEL 18 mg tablet orally once daily + placebo for up to 240 weeks.	
Reporting group title	SEL 6 mg
Reporting group description:	
Randomized Phase: SEL 6 mg tablet orally once daily + placebo for up to 240 weeks.	
Reporting group title	Placebo
Reporting group description:	
Randomized Phase: Placebo tablet orally once daily for up to 240 weeks.	
Reporting group title	Open-Label SEL 18 mg
Reporting group description:	
Participants who experienced a hepatic clinical event 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, including the treatment duration in the randomized phase, of 240 weeks.	

Serious adverse events	SEL 18 mg	SEL 6 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	60 / 354 (16.95%)	53 / 351 (15.10%)	22 / 172 (12.79%)
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)			
Hepatocellular carcinoma			
subjects affected / exposed	2 / 354 (0.56%)	1 / 351 (0.28%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	0 / 172 (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

Colon adenoma			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Colon cancer			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Nasal cavity cancer			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian adenoma			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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			
Haematoma			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Shock haemorrhagic			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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			
Non-cardiac chest pain			
subjects affected / exposed	2 / 354 (0.56%)	2 / 351 (0.57%)	3 / 172 (1.74%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chest pain			
subjects affected / exposed	3 / 354 (0.85%)	0 / 351 (0.00%)	2 / 172 (1.16%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Drug hypersensitivity			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcoidosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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			
Endometrial hyperplasia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Endometrial hypertrophy			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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

Endometrial thickening			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Hydrosalpinx			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Ovarian cyst			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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	1 / 354 (0.28%)	1 / 351 (0.28%)	0 / 172 (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
Cough			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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 hydrothorax			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	0 / 172 (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 mass			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Bipolar disorder			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Suicidal ideation			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Suicide attempt			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Model for end stage liver disease score increased			

subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	0 / 172 (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
Rib fracture			
subjects affected / exposed	1 / 354 (0.28%)	1 / 351 (0.28%)	0 / 172 (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
Toxicity to various agents			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Lower limb fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Perirenal haematoma			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Wound secretion			

subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Wrist fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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			
Acute myocardial infarction			
subjects affected / exposed	3 / 354 (0.85%)	0 / 351 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 354 (0.28%)	1 / 351 (0.28%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 354 (0.00%)	2 / 351 (0.57%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	0 / 172 (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
Coronary artery disease			
subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	0 / 172 (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
Bradycardia			

subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prinzmetal angina			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 354 (0.28%)	2 / 351 (0.57%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 354 (0.28%)	1 / 351 (0.28%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 354 (0.00%)	2 / 351 (0.57%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	1 / 354 (0.28%)	1 / 351 (0.28%)	0 / 172 (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
Cervical radiculopathy			

subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Diabetic hyperosmolar coma			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Dizziness			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Facial paralysis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Loss of consciousness			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Metabolic encephalopathy			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Nervous system disorder			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Toxic encephalopathy			

subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 354 (0.85%)	3 / 351 (0.85%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 354 (1.13%)	2 / 351 (0.57%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 354 (0.28%)	2 / 351 (0.57%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	2 / 354 (0.56%)	1 / 351 (0.28%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	0 / 172 (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
Ascites			
subjects affected / exposed	1 / 354 (0.28%)	1 / 351 (0.28%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	0 / 172 (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
Melaena			
subjects affected / exposed	1 / 354 (0.28%)	1 / 351 (0.28%)	0 / 172 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Appendiceal mucocoele			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Constipation			

subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	0 / 172 (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
Duodenitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Enterocolitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Gastric polyps			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Gastric ulcer			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Gastric ulcer perforation			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Gastritis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal wall thickening			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			

subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Large intestine polyp			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Mesenteric panniculitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Nausea			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	0 / 172 (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
Oesophagitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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 acute			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Rectal haemorrhage			

subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Visceral venous thrombosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Vomiting			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 354 (0.00%)	3 / 351 (0.85%)	0 / 172 (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
Cholecystitis acute			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic hepatic failure			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Cholangitis acute			

subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Cholelithiasis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Drug-induced liver injury			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemobilia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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 cirrhosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Hepatorenal syndrome			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	0 / 172 (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
Intrahepatic portal hepatic venous fistula			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Jaundice			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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 and urinary disorders			
Acute kidney injury			

subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	0 / 172 (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
Chronic kidney disease			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	0 / 172 (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
Ureterolithiasis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Myalgia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Osteoarthritis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Cellulitis			
subjects affected / exposed	3 / 354 (0.85%)	3 / 351 (0.85%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 354 (0.85%)	1 / 351 (0.28%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	2 / 172 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Bacteraemia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Bronchitis			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
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	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Enterocolitis infectious			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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 pyelonephritis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Genital herpes			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Meningitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Nasal abscess			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perineal abscess			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Pulmonary tuberculosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Septic shock			
subjects affected / exposed	0 / 354 (0.00%)	1 / 351 (0.28%)	0 / 172 (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
Tonsillitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 354 (0.00%)	2 / 351 (0.57%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	2 / 354 (0.56%)	0 / 351 (0.00%)	0 / 172 (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
Fluid overload			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Hyperkalaemia			

subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 354 (0.00%)	0 / 351 (0.00%)	1 / 172 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	1 / 354 (0.28%)	0 / 351 (0.00%)	0 / 172 (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

Serious adverse events	Open-Label SEL 18 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 23 (30.43%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
B-cell lymphoma			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon adenoma			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nasal cavity cancer				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian adenoma				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Haematoma				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Non-cardiac chest pain				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Peripheral swelling				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Contrast media allergy				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug hypersensitivity				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sarcoidosis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Endometrial hyperplasia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endometrial hypertrophy				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endometrial thickening				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydrosalpinx				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Ovarian cyst				
subjects affected / exposed	0 / 23 (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	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic hydrothorax				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary mass				
subjects affected / exposed	0 / 23 (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	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Bipolar disorder				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood pressure increased				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Model for end stage liver disease score increased				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Procedural pain				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perirenal haematoma				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound secretion				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Angina unstable				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prinzmetal angina				

subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar radiculopathy			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical radiculopathy			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic hyperosmolar coma			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial paralysis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Toxic encephalopathy				
subjects affected / exposed	0 / 23 (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 / 23 (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 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic anaemia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune thrombocytopenic purpura				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Iron deficiency anaemia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendiceal mucocoele				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric polyps				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer perforation				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal wall thickening				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mallory-Weiss syndrome				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mesenteric panniculitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstructive pancreatitis				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Visceral venous thrombosis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic hepatic failure				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis acute				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemobilia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatorenal syndrome				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intrahepatic portal hepatic venous fistula				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				

subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 23 (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 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Gastroenteritis				
subjects affected / exposed	0 / 23 (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 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 23 (4.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 23 (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 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia pyelonephritis				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Genital herpes				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal abscess				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perineal abscess				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Diabetes mellitus inadequate control				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fluid overload				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemic hyperosmolar nonketotic syndrome				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypomagnesaemia				
subjects affected / exposed	0 / 23 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obesity				

subjects affected / exposed	0 / 23 (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	251 / 354 (70.90%)	276 / 351 (78.63%)	135 / 172 (78.49%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 354 (0.56%)	1 / 351 (0.28%)	1 / 172 (0.58%)
occurrences (all)	2	1	1
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	20 / 354 (5.65%)	23 / 351 (6.55%)	12 / 172 (6.98%)
occurrences (all)	21	23	13
Nervous system disorders			
Headache			
subjects affected / exposed	47 / 354 (13.28%)	48 / 351 (13.68%)	21 / 172 (12.21%)
occurrences (all)	55	56	25
Dizziness			
subjects affected / exposed	22 / 354 (6.21%)	23 / 351 (6.55%)	17 / 172 (9.88%)
occurrences (all)	25	26	19
Hepatic encephalopathy			
subjects affected / exposed	7 / 354 (1.98%)	5 / 351 (1.42%)	2 / 172 (1.16%)
occurrences (all)	7	5	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	42 / 354 (11.86%)	51 / 351 (14.53%)	20 / 172 (11.63%)
occurrences (all)	45	53	21
Oedema peripheral			
subjects affected / exposed	20 / 354 (5.65%)	23 / 351 (6.55%)	10 / 172 (5.81%)
occurrences (all)	20	25	13
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	51 / 354 (14.41%)	60 / 351 (17.09%)	40 / 172 (23.26%)
occurrences (all)	59	73	46
Nausea			
subjects affected / exposed	47 / 354 (13.28%)	59 / 351 (16.81%)	17 / 172 (9.88%)
occurrences (all)	53	73	23
Constipation			
subjects affected / exposed	46 / 354 (12.99%)	47 / 351 (13.39%)	18 / 172 (10.47%)
occurrences (all)	50	51	18
Abdominal pain upper			
subjects affected / exposed	42 / 354 (11.86%)	37 / 351 (10.54%)	21 / 172 (12.21%)
occurrences (all)	45	46	22
Abdominal pain			
subjects affected / exposed	34 / 354 (9.60%)	33 / 351 (9.40%)	19 / 172 (11.05%)
occurrences (all)	36	34	20
Vomiting			
subjects affected / exposed	24 / 354 (6.78%)	28 / 351 (7.98%)	7 / 172 (4.07%)
occurrences (all)	27	32	9
Abdominal distension			
subjects affected / exposed	22 / 354 (6.21%)	22 / 351 (6.27%)	12 / 172 (6.98%)
occurrences (all)	22	23	12
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 354 (7.63%)	33 / 351 (9.40%)	14 / 172 (8.14%)
occurrences (all)	32	35	14
Epistaxis			
subjects affected / exposed	7 / 354 (1.98%)	8 / 351 (2.28%)	2 / 172 (1.16%)
occurrences (all)	7	10	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	29 / 354 (8.19%)	27 / 351 (7.69%)	11 / 172 (6.40%)
occurrences (all)	29	29	12
Rash			
subjects affected / exposed	19 / 354 (5.37%)	13 / 351 (3.70%)	10 / 172 (5.81%)
occurrences (all)	20	17	12
Psychiatric disorders			

Insomnia			
subjects affected / exposed	24 / 354 (6.78%)	28 / 351 (7.98%)	7 / 172 (4.07%)
occurrences (all)	24	28	8
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	34 / 354 (9.60%)	30 / 351 (8.55%)	16 / 172 (9.30%)
occurrences (all)	37	32	17
Arthralgia			
subjects affected / exposed	19 / 354 (5.37%)	28 / 351 (7.98%)	15 / 172 (8.72%)
occurrences (all)	20	30	18
Muscle spasms			
subjects affected / exposed	14 / 354 (3.95%)	25 / 351 (7.12%)	10 / 172 (5.81%)
occurrences (all)	14	26	11
Musculoskeletal pain			
subjects affected / exposed	15 / 354 (4.24%)	19 / 351 (5.41%)	9 / 172 (5.23%)
occurrences (all)	15	21	9
Pain in extremity			
subjects affected / exposed	16 / 354 (4.52%)	19 / 351 (5.41%)	5 / 172 (2.91%)
occurrences (all)	16	20	5
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	43 / 354 (12.15%)	52 / 351 (14.81%)	15 / 172 (8.72%)
occurrences (all)	47	65	17
Nasopharyngitis			
subjects affected / exposed	42 / 354 (11.86%)	33 / 351 (9.40%)	28 / 172 (16.28%)
occurrences (all)	52	40	36
Urinary tract infection			
subjects affected / exposed	33 / 354 (9.32%)	39 / 351 (11.11%)	11 / 172 (6.40%)
occurrences (all)	49	50	13
Sinusitis			
subjects affected / exposed	25 / 354 (7.06%)	27 / 351 (7.69%)	11 / 172 (6.40%)
occurrences (all)	32	32	11
Influenza			
subjects affected / exposed	27 / 354 (7.63%)	24 / 351 (6.84%)	8 / 172 (4.65%)
occurrences (all)	28	25	8
Bronchitis			

subjects affected / exposed	16 / 354 (4.52%)	27 / 351 (7.69%)	10 / 172 (5.81%)
occurrences (all)	16	30	13

Non-serious adverse events	Open-Label SEL 18 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 23 (73.91%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	4		
Dizziness			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Hepatic encephalopathy			
subjects affected / exposed	4 / 23 (17.39%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 23 (8.70%)		
occurrences (all)	2		
Nausea			

subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 3 0 / 23 (0.00%) 0 3 / 23 (13.04%) 3 2 / 23 (8.70%) 2 3 / 23 (13.04%) 3 3 / 23 (13.04%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 1 2 / 23 (8.70%) 2		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 2 1 / 23 (4.35%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 2 / 23 (8.70%) 2		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	3 / 23 (13.04%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	0 / 23 (0.00%)		
occurrences (all)	0		

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 and hospitalization (ie, bleeding from esophageal varices, gastric varices, and portal hypertensive gastropathy) and would be adjudicated by the Hepatic Events/Drug-Induced Liver Injury (DILI) Adjudication Committee. 2. Hepatocellular carcinoma (HCC) was removed as a component of the clinical efficacy endpoint. 3. The outcome of "death" was changed to "all-cause mortality" to clarify that all deaths would be included in the EFS analysis. 4. References to a HepQuant substudy were removed. Only subjects enrolled at participating US sites could participate concurrently in a HepQuant-sponsored study with approval by the applicable IRB/IEC. 5. Laboratory parameters and assessments at screening were clarified; international normalised ratio (INR) ≤ 1.4 and platelet count ≥100,000/μL were added as inclusion criteria, and optional measurement of liver stiffness at screening using transient elastography was included. 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 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 (rather than all-cause mortality) would be performed. 9. Clarified that all clinical events except all-cause mortality and liver transplantation required confirmation by the Hepatic Events Adjudication Committee and that the Committee would also review any case of HCC as an event of special interest. 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.
24 May 2017	11. Estimated glomerular filtration rate (eGFR) calculation was included at all visits to identify subjects with severe renal insufficiency. 12. Specified that single PK sampling would be performed at all study visits for subjects who entered the OL phase and had severe hepatic impairment (CP Class C) and renal impairment (eGFR < 30 mL/min). 13. Clarified that subjects in the OL phase who completed study treatment should complete the Week 240/end of treatment (EOT) visit. 14. A telephone follow-up visit to occur 12 weeks after the Week 240 visit was added.
31 May 2018	1. An early termination 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. 2. Clarified that hepatic clinical events would be adjudicated and deaths would be reviewed by the Hepatic Events/Drug-induced liver injury (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. 3. 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? No

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/32147362

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

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