



Clinical trial results:

A Phase 2b, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of GS-6624, a Monoclonal Antibody Against Lysyl Oxidase-Like 2 (LOXL2), in Subjects with Compensated Cirrhosis Secondary to Non-Alcoholic Steatohepatitis (NASH)

Summary

EudraCT number	2012-002489-11
Trial protocol	DE GB ES IT
Global end of trial date	03 January 2017

Results information

Result version number	v1 (current)
This version publication date	17 November 2017
First version publication date	17 November 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-321-0106
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01672879
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	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@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	03 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2016
Global end of trial reached?	Yes
Global end of trial date	03 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To primary objective of this study was to evaluate whether simtuzumab (formerly GS-6624) can reduce portal venous pressure and incidence of clinical events in adults with cirrhosis due to Non-Alcoholic Steatohepatitis (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	29 October 2012
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	Canada: 9
Country: Number of subjects enrolled	United States: 211
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	259
EEA total number of subjects	39

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)	238
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Europe and North America. The first participant was screened on 29 October 2012. The last study visit occurred on 03 January 2017.

Pre-assignment

Screening details:

453 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	SIM 200 mg
------------------	------------

Arm description:

Simtuzumab (SIM) 200 mg every 2 weeks for up to 240 weeks

Arm type	Experimental
Investigational medicinal product name	Simtuzumab 200 mg
Investigational medicinal product code	
Other name	GS-6624
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg intravenous infusion over 30 minutes

Arm title	SIM 700 mg
------------------	------------

Arm description:

Simtuzumab (SIM) 700 mg every 2 weeks for up to 240 weeks

Arm type	Experimental
Investigational medicinal product name	Simtuzumab 700 mg
Investigational medicinal product code	
Other name	GS-6624
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

700 mg intravenous infusion over 30 minutes

Arm title	Placebo
------------------	---------

Arm description:

Placebo to match Simtuzumab (SIM) every 2 weeks for up to 240 weeks

Arm type	Placebo
----------	---------

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Simtuzumab (SIM) placebo intravenous infusion over 30 minutes

Number of subjects in period 1^[1]	SIM 200 mg	SIM 700 mg	Placebo
Started	87	86	85
Completed	0	0	0
Not completed	87	86	85
Withdrew Consent	14	7	6
Adverse Event	10	3	8
Death	-	2	-
Investigator's Discretion	6	-	3
Progressive Disease	1	-	-
Study Terminated by Sponsor	51	71	67
Lost to follow-up	4	3	1
Missing	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: One participant who was enrolled but never treated was not included in the subject disposition table.

Baseline characteristics

Reporting groups

Reporting group title	SIM 200 mg
Reporting group description: Simtuzumab (SIM) 200 mg every 2 weeks for up to 240 weeks	
Reporting group title	SIM 700 mg
Reporting group description: Simtuzumab (SIM) 700 mg every 2 weeks for up to 240 weeks	
Reporting group title	Placebo
Reporting group description: Placebo to match Simtuzumab (SIM) every 2 weeks for up to 240 weeks	

Reporting group values	SIM 200 mg	SIM 700 mg	Placebo
Number of subjects	87	86	85
Age categorical			
Units: Subjects			

Age continuous			
Safety Analysis Set: all enrolled participants who were randomized and received at least one dose of study drug.			
Units: years			
arithmetic mean	56	55	56
standard deviation	± 7.2	± 7.3	± 7.8
Gender categorical			
Units: Subjects			
Female	53	54	56
Male	34	32	29
Race			
Units: Subjects			
Asian	3	1	0
Black	2	3	1
White	80	75	83
Other	2	7	1
Ethnicity			
Units: Subjects			
Hispanic or Latino	12	17	10
Not Hispanic or Latino	75	69	75
Hepatic Venous Pressure Gradient (HVPG)			
Full Analysis Set: all enrolled participants who were randomized and received at least 1 dose of study drug. Only 85 participants in SIM 700 mg arm and 84 participants in placebo arm with available data were analyzed.			
Units: mmHg			
arithmetic mean	12.9	12.8	13.0
standard deviation	± 5.10	± 5.37	± 5.25

Reporting group values	Total		
Number of subjects	258		

Age categorical			
Units: Subjects			
Age continuous			
Safety Analysis Set: all enrolled participants who were randomized and received at least one dose of study drug.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	163		
Male	95		
Race			
Units: Subjects			
Asian	4		
Black	6		
White	238		
Other	10		
Ethnicity			
Units: Subjects			
Hispanic or Latino	39		
Not Hispanic or Latino	219		
Hepatic Venous Pressure Gradient (HVPg)			
Full Analysis Set: all enrolled participants who were randomized and received at least 1 dose of study drug. Only 85 participants in SIM 700 mg arm and 84 participants in placebo arm with available data were analyzed.			
Units: mmHg			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	SIM 200 mg
Reporting group description: Simtuzumab (SIM) 200 mg every 2 weeks for up to 240 weeks	
Reporting group title	SIM 700 mg
Reporting group description: Simtuzumab (SIM) 700 mg every 2 weeks for up to 240 weeks	
Reporting group title	Placebo
Reporting group description: Placebo to match Simtuzumab (SIM) every 2 weeks for up to 240 weeks	

Primary: Change From Baseline in Hepatic Venous Pressure Gradient (HVPG)

End point title	Change From Baseline in Hepatic Venous Pressure Gradient (HVPG)
End point description: Participants in the Full Analysis Set with available data were analyzed. Only 85 participants from SIM 700 mg arm and 84 participants from the placebo arm with available data were analyzed at baseline.	
End point type	Primary
End point timeframe: Baseline to Week 96	

End point values	SIM 200 mg	SIM 700 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87	85	84	
Units: mmHg				
arithmetic mean (standard deviation)				
SIM 200 mg N= 63, SIM 700 mg N= 66, Placebo N=68	-0.1 (± 3.76)	0.0 (± 4.23)	-0.1 (± 4.01)	

Statistical analyses

Statistical analysis title	HVPG- Comparison of Groups
Statistical analysis description: A mixed-effect model for repeated measures (MMRM) with an unstructured variance-covariance matrix for each participant was used to calculate a point estimate and a 95% confidence interval (CI) for the treatment difference between each treatment arm and placebo in least squares mean (LSMean) change from baseline in HVPG at Week 96. With MMRM setting, all participants with available data from 3 treatment groups with change in HVPG at Week 96 contributed to the overall model.	
Comparison groups	SIM 200 mg v Placebo

Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in LSMeans [SIM - Placebo]
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.5

Statistical analysis title	HVPG- Comparison of Groups
-----------------------------------	----------------------------

Statistical analysis description:

A mixed-effect model for repeated measures (MMRM) with an unstructured variance-covariance matrix for each participant was used to calculate a point estimate and a 95% confidence interval (CI) for the treatment difference between each treatment arm and placebo in least squares mean (LSMean) change from baseline in HVPG at Week 96. With MMRM setting, all participants with available data from 3 treatment groups with change in HVPG at Week 96 contributed to the overall model.

Comparison groups	SIM 700 mg v Placebo
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in LSMeans [SIM - Placebo]
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.4

Primary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)
-----------------	---------------------------

End point description:

Event free survival (EFS) was the primary clinical efficacy endpoint and was assessed by time to first liver-related event or death, whichever occurs first. Liver-related events included any of the following:

- Liver transplantation
- Qualification for liver transplantation
- Model for End-Stage Liver Disease (MELD) ≥ 15
- Events indicative of hepatic decompensation
- Esophageal variceal bleeding
- Ascites
- Hepatic Encephalopathy
- ≥ 2 point increase in Child Pugh-Turcotte (CPT) score
- Newly diagnosed varices in a subject without prior varices

The median clinical EFS was not estimable in any treatment group. So, the percent of participants were presented, where only the event(s) with the earliest onset date were included for each participant. Full Analysis Set.

End point type	Primary
----------------	---------

End point timeframe:

Baseline up to the last dose date (maximum: up to 240 weeks in randomized phase)

End point values	SIM 200 mg	SIM 700 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	87	86	85	
Units: percentage of participants				
number (not applicable)	18.4	26.7	15.3	

Statistical analyses

Statistical analysis title	Event-Free Survival- Comparison of Groups
Statistical analysis description: Differences in EFS between a given SIM group and placebo were assessed using the log-rank test stratified by HVPg category (< 10 mmHg vs ≥ 10 mmHg) and presence or absence of diabetes at baseline.	
Comparison groups	SIM 200 mg v Placebo
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Stratified log-rank test
Parameter estimate	Not Applicable
Point estimate	9999
Confidence interval	
level	95 %
sides	2-sided
lower limit	999
upper limit	99999

Statistical analysis title	Event-Free Survival- Comparison of Groups
Statistical analysis description: Differences in EFS between a given SIM group and placebo were assessed using the log-rank test stratified by HVPg category (< 10 mmHg vs ≥ 10 mmHg) and presence or absence of diabetes at baseline.	
Comparison groups	SIM 700 mg v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065
Method	Stratified log-rank test
Parameter estimate	Not Applicable
Point estimate	9999

Confidence interval	
level	95 %
sides	2-sided
lower limit	999
upper limit	99999

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to the last dose date plus 30 days (average exposure: SIM 200 mg= 109.3 weeks, SIM 700 mg= 115.9 weeks, Placebo= 120.2 weeks, Open-label SIM 700 mg= 46.2 weeks)

Adverse event reporting additional description:

Safety Analysis Set: all enrolled participants who were randomized and received at least one dose of study drug and Open-Label Safety Analysis Set :all participants who rolled over into the open-label phase and received at least 1 dose of open-label study drug.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SIM 200 mg
-----------------------	------------

Reporting group description:

Simtuzumab (SIM) 200 mg every 2 week for up to 240 weeks

Reporting group title	SIM 700 mg
-----------------------	------------

Reporting group description:

Simtuzumab (SIM) 700 mg every 2 weeks for up to 240 weeks

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Placebo to match Simtuzumab (SIM) every 2 weeks for up to 240 weeks

Reporting group title	Open-Label 700 mg
-----------------------	-------------------

Reporting group description:

All participants who completed the randomized phase through the Week 240 visit, or were ongoing at the time the study stopped who had progressed cirrhosis of the liver, were offered the opportunity to receive open-label SIM for up to 240 additional weeks. Additionally, participants who developed confirmed progression to cirrhosis prior to completing the randomized phase were eligible to roll over into the open-label phase.

All participants received fixed-dose open-label Simtuzumab (SIM) 700 mg intravenous infusions every 2 weeks for up to 240 weeks.

Serious adverse events	SIM 200 mg	SIM 700 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 87 (42.53%)	36 / 86 (41.86%)	25 / 85 (29.41%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast cancer			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer recurrent			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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 cancer			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic neoplasm			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Hodgkin's disease			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Prostate cancer			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Thyroid cancer			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 87 (0.00%)	2 / 86 (2.33%)	0 / 85 (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
Haematoma			

subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 87 (3.45%)	2 / 86 (2.33%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 3	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Fatigue			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Oedema peripheral			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Peripheral swelling			

subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Pyrexia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 87 (0.00%)	3 / 86 (3.49%)	0 / 85 (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
Dyspnoea			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic hydrothorax			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute respiratory failure			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Asthma			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Cough			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Hydrothorax			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Nasal septum deviation			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Portopulmonary hypertension			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Respiratory depression			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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			

Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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 abuse			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Mental status changes			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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 decompensation			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Psychotic disorder			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Suicidal ideation			

subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood osmolarity decreased			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Electrocardiogram T wave peaked			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Model for end stage liver disease score abnormal			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Model for end stage liver disease score increased			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			

subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	0 / 85 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Laceration			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			

subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural discomfort			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Procedural haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Procedural hypotension			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Road traffic accident			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	0 / 85 (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
Atrioventricular block second degree			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Cardiac failure			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	3 / 87 (3.45%)	4 / 86 (4.65%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Altered state of consciousness			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Cervical myelopathy			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Dizziness			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			

subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Migraine with aura			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Nerve compression			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Temporal lobe epilepsy			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Bandaemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	2 / 87 (2.30%)	3 / 86 (3.49%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			

subjects affected / exposed	1 / 87 (1.15%)	2 / 86 (2.33%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	2 / 86 (2.33%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Abdominal pain upper			
subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	0 / 85 (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
Colitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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	1 / 87 (1.15%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 86 (0.00%)	0 / 85 (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
Umbilical hernia			

subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Abdominal discomfort			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Abdominal distension			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Abdominal hernia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Diverticulum			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Epiplonic appendagitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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 haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Haematochezia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Hernial eventration			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Ileus			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Impaired gastric emptying			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Varices oesophageal			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Haemobilia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Cholelithiasis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder polyp			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Ischaemic hepatitis			

subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 87 (2.30%)	1 / 86 (1.16%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Nephrolithiasis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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 failure			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Ureterolithiasis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Hyperparathyroidism			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Neck pain			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Cervical spinal stenosis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Compartment syndrome			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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 pain			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Myositis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Osteoarthritis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	3 / 87 (3.45%)	1 / 86 (1.16%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 87 (2.30%)	2 / 86 (2.33%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 87 (0.00%)	3 / 86 (3.49%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 87 (2.30%)	1 / 86 (1.16%)	0 / 85 (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
Cellulitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	0 / 85 (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
Abscess limb			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Escherichia bacteraemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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 sepsis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis bacterial			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (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
Kidney infection			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rocky mountain spotted fever			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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			
Hyponatraemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (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
Hyperglycaemia			

subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	0 / 85 (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
Lactic acidosis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-Label 700 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 40 (42.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer recurrent			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial cancer			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic neoplasm			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hodgkin's disease			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thyroid cancer			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Fatigue			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral swelling			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic hydrothorax			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydrothorax			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hypoxia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal septum deviation			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Portopulmonary hypertension			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory depression			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bipolar disorder			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug abuse			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major depression			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric decompensation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood osmolarity decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram T wave peaked			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Model for end stage liver disease score abnormal			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Model for end stage liver disease score increased			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural discomfort			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural hypotension			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 40 (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 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block second degree			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 40 (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	5 / 40 (12.50%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Altered state of consciousness			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical myelopathy			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Migraine with aura			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nerve compression			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Temporal lobe epilepsy			
subjects affected / exposed	0 / 40 (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	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bandaemia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 40 (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 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematemesis			

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal discomfort				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal distension				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal hernia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulum				

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epiploic appendagitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hernial eventration			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired gastric emptying			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 40 (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 / 40 (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 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varices oesophageal			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Haemobilia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gallbladder polyp			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic cirrhosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic hepatitis			
subjects affected / exposed	0 / 40 (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	3 / 40 (7.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dysuria			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperparathyroidism			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical spinal stenosis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Compartment syndrome			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Myositis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoporotic fracture			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			

subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess limb				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial pyelonephritis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia bacteraemia				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	0 / 40 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis bacterial			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kidney infection			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rocky mountain spotted fever			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	0 / 40 (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	SIM 200 mg	SIM 700 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 87 (97.70%)	81 / 86 (94.19%)	83 / 85 (97.65%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 87 (6.90%)	3 / 86 (3.49%)	2 / 85 (2.35%)
occurrences (all)	6	3	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	34 / 87 (39.08%)	32 / 86 (37.21%)	28 / 85 (32.94%)
occurrences (all)	42	35	32
Oedema peripheral			

subjects affected / exposed	13 / 87 (14.94%)	14 / 86 (16.28%)	16 / 85 (18.82%)
occurrences (all)	13	15	19
Pyrexia			
subjects affected / exposed	10 / 87 (11.49%)	9 / 86 (10.47%)	6 / 85 (7.06%)
occurrences (all)	13	13	6
Chest pain			
subjects affected / exposed	8 / 87 (9.20%)	10 / 86 (11.63%)	6 / 85 (7.06%)
occurrences (all)	9	10	9
Peripheral swelling			
subjects affected / exposed	8 / 87 (9.20%)	7 / 86 (8.14%)	6 / 85 (7.06%)
occurrences (all)	8	8	8
Pain			
subjects affected / exposed	7 / 87 (8.05%)	6 / 86 (6.98%)	3 / 85 (3.53%)
occurrences (all)	8	6	3
Asthenia			
subjects affected / exposed	3 / 87 (3.45%)	5 / 86 (5.81%)	5 / 85 (5.88%)
occurrences (all)	4	6	6
Chills			
subjects affected / exposed	3 / 87 (3.45%)	5 / 86 (5.81%)	4 / 85 (4.71%)
occurrences (all)	3	6	4
Infusion site pain			
subjects affected / exposed	7 / 87 (8.05%)	0 / 86 (0.00%)	6 / 85 (7.06%)
occurrences (all)	7	0	8
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	2 / 87 (2.30%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences (all)	2	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 87 (18.39%)	12 / 86 (13.95%)	13 / 85 (15.29%)
occurrences (all)	21	20	14
Oropharyngeal pain			
subjects affected / exposed	11 / 87 (12.64%)	8 / 86 (9.30%)	9 / 85 (10.59%)
occurrences (all)	12	8	10
Epistaxis			

subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 11	9 / 86 (10.47%) 10	6 / 85 (7.06%) 9
Dyspnoea subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 12	6 / 86 (6.98%) 6	4 / 85 (4.71%) 4
Nasal congestion subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3	7 / 86 (8.14%) 8	7 / 85 (8.24%) 12
Pleural effusion subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	1 / 86 (1.16%) 1	1 / 85 (1.18%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	7 / 87 (8.05%) 8	5 / 86 (5.81%) 6	9 / 85 (10.59%) 9
Depression subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	7 / 86 (8.14%) 7	2 / 85 (2.35%) 2
Anxiety subjects affected / exposed occurrences (all)	7 / 87 (8.05%) 8	3 / 86 (3.49%) 3	3 / 85 (3.53%) 3
Investigations Blood glucose increased subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2	1 / 86 (1.16%) 1	5 / 85 (5.88%) 5
Weight increased subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	1 / 86 (1.16%) 1	5 / 85 (5.88%) 5
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	1 / 86 (1.16%) 1	5 / 85 (5.88%) 5
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	10 / 87 (11.49%) 13	6 / 86 (6.98%) 6	16 / 85 (18.82%) 20
Fall			

subjects affected / exposed	7 / 87 (8.05%)	5 / 86 (5.81%)	13 / 85 (15.29%)
occurrences (all)	19	7	18
Infusion related reaction			
subjects affected / exposed	10 / 87 (11.49%)	7 / 86 (8.14%)	11 / 85 (12.94%)
occurrences (all)	17	9	15
Procedural pain			
subjects affected / exposed	8 / 87 (9.20%)	7 / 86 (8.14%)	7 / 85 (8.24%)
occurrences (all)	8	8	7
Ligament sprain			
subjects affected / exposed	5 / 87 (5.75%)	4 / 86 (4.65%)	2 / 85 (2.35%)
occurrences (all)	5	4	3
Muscle strain			
subjects affected / exposed	5 / 87 (5.75%)	1 / 86 (1.16%)	4 / 85 (4.71%)
occurrences (all)	5	1	6
Skin abrasion			
subjects affected / exposed	4 / 87 (4.60%)	1 / 86 (1.16%)	2 / 85 (2.35%)
occurrences (all)	5	1	2
Road traffic accident			
subjects affected / exposed	2 / 87 (2.30%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences (all)	2	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	6 / 87 (6.90%)	1 / 86 (1.16%)	3 / 85 (3.53%)
occurrences (all)	6	1	3
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 87 (29.89%)	28 / 86 (32.56%)	17 / 85 (20.00%)
occurrences (all)	41	40	27
Dizziness			
subjects affected / exposed	14 / 87 (16.09%)	8 / 86 (9.30%)	9 / 85 (10.59%)
occurrences (all)	22	13	12
Hepatic encephalopathy			
subjects affected / exposed	7 / 87 (8.05%)	6 / 86 (6.98%)	6 / 85 (7.06%)
occurrences (all)	7	8	6
Tremor			

subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	4 / 86 (4.65%) 4	5 / 85 (5.88%) 5
Syncope subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	1 / 86 (1.16%) 1	2 / 85 (2.35%) 3
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	10 / 87 (11.49%) 11	7 / 86 (8.14%) 10	6 / 85 (7.06%) 6
Splenomegaly subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3	4 / 86 (4.65%) 4	6 / 85 (7.06%) 6
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	6 / 86 (6.98%) 6	5 / 85 (5.88%) 10
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	29 / 87 (33.33%) 51	28 / 86 (32.56%) 49	28 / 85 (32.94%) 56
Diarrhoea subjects affected / exposed occurrences (all)	24 / 87 (27.59%) 35	23 / 86 (26.74%) 30	33 / 85 (38.82%) 42
Abdominal pain subjects affected / exposed occurrences (all)	19 / 87 (21.84%) 21	23 / 86 (26.74%) 25	14 / 85 (16.47%) 15
Vomiting subjects affected / exposed occurrences (all)	13 / 87 (14.94%) 24	15 / 86 (17.44%) 18	19 / 85 (22.35%) 26
Abdominal pain upper subjects affected / exposed occurrences (all)	15 / 87 (17.24%) 17	19 / 86 (22.09%) 23	13 / 85 (15.29%) 18
Constipation subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 12	15 / 86 (17.44%) 20	10 / 85 (11.76%) 10
Abdominal distension			

subjects affected / exposed	9 / 87 (10.34%)	10 / 86 (11.63%)	9 / 85 (10.59%)
occurrences (all)	10	11	10
Ascites			
subjects affected / exposed	7 / 87 (8.05%)	8 / 86 (9.30%)	9 / 85 (10.59%)
occurrences (all)	11	12	10
Varices oesophageal			
subjects affected / exposed	5 / 87 (5.75%)	10 / 86 (11.63%)	8 / 85 (9.41%)
occurrences (all)	5	15	8
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 87 (5.75%)	4 / 86 (4.65%)	3 / 85 (3.53%)
occurrences (all)	6	4	4
Abdominal pain lower			
subjects affected / exposed	5 / 87 (5.75%)	3 / 86 (3.49%)	4 / 85 (4.71%)
occurrences (all)	7	3	5
Haemorrhoids			
subjects affected / exposed	3 / 87 (3.45%)	2 / 86 (2.33%)	5 / 85 (5.88%)
occurrences (all)	3	2	5
Portal hypertensive gastropathy			
subjects affected / exposed	1 / 87 (1.15%)	0 / 86 (0.00%)	8 / 85 (9.41%)
occurrences (all)	1	0	8
Umbilical hernia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	0 / 85 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	3 / 87 (3.45%)	2 / 86 (2.33%)	7 / 85 (8.24%)
occurrences (all)	3	2	7
Cholelithiasis			
subjects affected / exposed	1 / 87 (1.15%)	2 / 86 (2.33%)	7 / 85 (8.24%)
occurrences (all)	1	2	7
Jaundice			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed occurrences (all)	8 / 87 (9.20%) 10	11 / 86 (12.79%) 11	15 / 85 (17.65%) 19
Pruritus subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 11	11 / 86 (12.79%) 14	6 / 85 (7.06%) 7
Dry skin subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 6	3 / 86 (3.49%) 3	3 / 85 (3.53%) 3
Alopecia subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3	7 / 86 (8.14%) 7	2 / 85 (2.35%) 2
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	1 / 86 (1.16%) 1	3 / 85 (3.53%) 3
Pollakiuria subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1	0 / 86 (0.00%) 0	2 / 85 (2.35%) 2
Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	0 / 86 (0.00%) 0	1 / 85 (1.18%) 1
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	27 / 87 (31.03%) 36	18 / 86 (20.93%) 26	12 / 85 (14.12%) 21
Arthralgia subjects affected / exposed occurrences (all)	17 / 87 (19.54%) 18	19 / 86 (22.09%) 23	13 / 85 (15.29%) 19
Muscle spasms subjects affected / exposed occurrences (all)	16 / 87 (18.39%) 23	13 / 86 (15.12%) 15	10 / 85 (11.76%) 11
Pain in extremity subjects affected / exposed occurrences (all)	11 / 87 (12.64%) 12	9 / 86 (10.47%) 9	9 / 85 (10.59%) 11
Musculoskeletal pain			

subjects affected / exposed	10 / 87 (11.49%)	6 / 86 (6.98%)	7 / 85 (8.24%)
occurrences (all)	11	7	7
Neck pain			
subjects affected / exposed	8 / 87 (9.20%)	3 / 86 (3.49%)	5 / 85 (5.88%)
occurrences (all)	9	3	6
Joint swelling			
subjects affected / exposed	7 / 87 (8.05%)	4 / 86 (4.65%)	2 / 85 (2.35%)
occurrences (all)	7	4	2
Myalgia			
subjects affected / exposed	3 / 87 (3.45%)	2 / 86 (2.33%)	8 / 85 (9.41%)
occurrences (all)	3	2	9
Flank pain			
subjects affected / exposed	3 / 87 (3.45%)	5 / 86 (5.81%)	1 / 85 (1.18%)
occurrences (all)	3	6	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 87 (17.24%)	16 / 86 (18.60%)	19 / 85 (22.35%)
occurrences (all)	22	18	26
Sinusitis			
subjects affected / exposed	14 / 87 (16.09%)	16 / 86 (18.60%)	17 / 85 (20.00%)
occurrences (all)	24	19	27
Upper respiratory tract infection			
subjects affected / exposed	15 / 87 (17.24%)	19 / 86 (22.09%)	11 / 85 (12.94%)
occurrences (all)	28	21	16
Bronchitis			
subjects affected / exposed	14 / 87 (16.09%)	14 / 86 (16.28%)	15 / 85 (17.65%)
occurrences (all)	16	17	18
Urinary tract infection			
subjects affected / exposed	9 / 87 (10.34%)	14 / 86 (16.28%)	18 / 85 (21.18%)
occurrences (all)	25	18	25
Influenza			
subjects affected / exposed	4 / 87 (4.60%)	6 / 86 (6.98%)	8 / 85 (9.41%)
occurrences (all)	4	8	8
Gastroenteritis			
subjects affected / exposed	6 / 87 (6.90%)	4 / 86 (4.65%)	2 / 85 (2.35%)
occurrences (all)	8	4	2

Pneumonia			
subjects affected / exposed	2 / 87 (2.30%)	5 / 86 (5.81%)	2 / 85 (2.35%)
occurrences (all)	2	8	2
Gastroenteritis viral			
subjects affected / exposed	5 / 87 (5.75%)	1 / 86 (1.16%)	2 / 85 (2.35%)
occurrences (all)	7	1	2
Herpes zoster			
subjects affected / exposed	5 / 87 (5.75%)	2 / 86 (2.33%)	1 / 85 (1.18%)
occurrences (all)	6	3	1
Localised infection			
subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	2 / 85 (2.35%)
occurrences (all)	1	2	2
Peritonitis bacterial			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	0 / 85 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 87 (8.05%)	2 / 86 (2.33%)	11 / 85 (12.94%)
occurrences (all)	9	4	13
Hyperglycaemia			
subjects affected / exposed	4 / 87 (4.60%)	10 / 86 (11.63%)	6 / 85 (7.06%)
occurrences (all)	5	10	6
Hypokalaemia			
subjects affected / exposed	3 / 87 (3.45%)	3 / 86 (3.49%)	2 / 85 (2.35%)
occurrences (all)	5	3	2
Hyponatraemia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 86 (1.16%)	2 / 85 (2.35%)
occurrences (all)	1	1	2
Hyperkalaemia			
subjects affected / exposed	1 / 87 (1.15%)	2 / 86 (2.33%)	2 / 85 (2.35%)
occurrences (all)	1	2	2
Hypomagnesaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 86 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	0	1

Non-serious adverse events	Open-Label 700 mg		
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	32 / 40 (80.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Chest pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Infusion site pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			

Gynaecomastia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2 0 / 40 (0.00%) 0 1 / 40 (2.50%) 1 1 / 40 (2.50%) 1 0 / 40 (0.00%) 0 2 / 40 (5.00%) 2		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 1 / 40 (2.50%) 1		
Investigations Blood glucose increased subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		

Weight increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 5		
Fall subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Procedural pain subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Ligament sprain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Muscle strain subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Skin abrasion subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Road traffic accident subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Cardiac disorders			
Palpitations subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Nervous system disorders			

Headache			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hepatic encephalopathy			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Tremor			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Splenomegaly			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	12		
Diarrhoea			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Abdominal pain			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Vomiting			

subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Constipation			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Ascites			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	15		
Varices oesophageal			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Abdominal pain lower			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Portal hypertensive gastropathy			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Umbilical hernia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		

Cholelithiasis subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Jaundice subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		
Dry skin subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1		
Alopecia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Pollakiuria subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Chronic kidney disease subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Arthralgia subjects affected / exposed occurrences (all)	0 / 40 (0.00%) 0		

Muscle spasms			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Bronchitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Urinary tract infection			

subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	5		
Influenza			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Gastroenteritis viral			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Peritonitis bacterial			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	0 / 40 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Hyponatraemia			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	6		

Hyperkalaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2013	<ol style="list-style-type: none">1. Female contraception requirement following last dose of study drug increased from 30 days to 90 days.2. Exclusion Criterion regarding previous history of decompensated liver disease clarified.3. Language modified to make Study Treatment Discontinuation absolute.4. Withdrawal criterion added for participants who develop hypersensitivity reaction to study drug infusion.5. Language added regarding follow-up of Serious Adverse Events.
05 March 2013	<ol style="list-style-type: none">1. Increased number of times anti-GS-6624 antibodies are assessed.2. Addition of Pharmacokinetics (PK) testing.3. Language added regarding Brunt/Kleiner classification and the NAFLD Activity Score (NAS).4. Language added regarding the Cochran-Mantel-Haenszel test.5. New anti-GS-6624 antibodies and PK testing description section added to the Research-related Procedures section.
05 March 2014	<ol style="list-style-type: none">1. The Randomized Treatment Phase has been extended from 96 weeks to 240 weeks.2. An optional Open Label Phase has been added. It will include 240 additional weeks of IV treatment every 2 weeks with a fixed dose of simtuzumab 700 mg3. A Clinical Events Adjudication Committee has been added.4. A composite clinical event endpoint has been defined. The clinical events included which will be adjudicated by the Clinical Events Adjudication Committee were included.
31 July 2015	<ol style="list-style-type: none">1) Updating Study Director2) Revised liver biopsy central reading process3) Removal of the HVPG Cap

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported