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 Advanced Liver Fibrosis but not Cirrhosis Secondary to Non-Alcoholic Steatohepatitis (NASH)

Summary

EudraCT number	2012-002488-88
Trial protocol	IT DE GB ES BE
Global end of trial date	29 December 2016

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-321-0105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01672866
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 Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial 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	29 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 August 2016
Global end of trial reached?	Yes
Global end of trial date	29 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of simtuzumab (formerly GS-6624) at preventing the histologic progression of liver fibrosis and the clinical progression to cirrhosis in adultts with 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	05 December 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	United States: 165
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	222
EEA total number of subjects	45

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)	216
From 65 to 84 years	6
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 05 December 2012. The last study visit occurred on 29 December 2016.

Pre-assignment

Screening details:

631 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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SIM 75 mg

Arm description:

Simtuzumab (SIM) 75 mg weekly for up to 240 weeks

Arm type	Experimental
Investigational medicinal product name	Simtuzumab 75 mg
Investigational medicinal product code	
Other name	GS-6624
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

75 mg subcutaneous injection

Arm title	SIM 125 mg

Arm description:

Simtuzumab (SIM) 125 mg weekly for up to 240 weeks

Arm type	Experimental
Investigational medicinal product name	Simtuzumab 125 mg
Investigational medicinal product code	
Other name	GS-6624
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

125 mg subcutaneous injection

Arm title	Placebo

Arm description:

Placebo to match Simtuzumab (SIM) weekly for up to 240 weeks

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Simtuzumab (SIM) placebo subcutaneous injection

Number of subjects in period 1[1]	SIM 75 mg	SIM 125 mg	Placebo
Started	71	74	74
Completed	0	0	0
Not completed	71	74	74
Withdrew Consent	10	8	13
Adverse Event	3	3	3
Death	1	-	1
Investigator's Discretion	3	3	2
Protocol Violation	2	-	-
Study Terminated by Sponsor	48	57	50
Lost to follow-up	4	3	5

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: Three participants who were enrolled but never treated were not included in the subject disposition table.

Baseline characteristics

Reporting groups	
Reporting group title	SIM 75 mg
Reporting group description:	
Simtuzumab (SIM) 75 mg weekly for up to 240 weeks	
Reporting group title	SIM 125 mg
Reporting group description:	
Simtuzumab (SIM) 125 mg weekly for up to 240 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo to match Simtuzumab (SIM) weekly for up to 240 weeks	

Reporting group values	SIM 75 mg	SIM 125 mg	Placebo
Number of subjects	71	74	74
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	54	53	53
standard deviation	± 8.8	± 9.4	± 8.4
Gender categorical Units: Subjects			
Female	43	47	48
Male	28	27	26
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	1	3	1
Black or African American	2	0	1
Native Hawaiian or Other Pacific Islander	0	0	1
White	66	71	69
Other	2	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	9	14	11
Not Hispanic or Latino	62	60	63
Morphometric Quantitative Collagen (MQC)			
Full Analysis Set: enrolled participants who were randomized and received at least 1 dose of study drug.			
Units: Percentage			
arithmetic mean	7.0	7.2	6.7
standard deviation	± 4.18	± 4.62	± 3.78

Reporting group values	Total		

Number of subjects	219		
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 Male	138 81		
Race Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Other	1 5 3 1 206 3		
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino	34 185		
Morphometric Quantitative Collagen (MQC)			
Full Analysis Set: enrolled participants who were randomized and received at least 1 dose of study drug.			
Units: Percentage arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	SIM 75 mg
Reporting group description:	
Simtuzumab (SIM) 75 mg weekly for up to 240 weeks	
Reporting group title	SIM 125 mg
Reporting group description:	
Simtuzumab (SIM) 125 mg weekly for up to 240 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo to match Simtuzumab (SIM) weekly for up to 240 weeks	

Primary: Change From Baseline in Morphometric Quantitative Collagen (MQC) on Liver Biopsy

End point title	Change From Baseline in Morphometric Quantitative Collagen (MQC) on Liver Biopsy
End point description:	
Participants in the Full Analysis Set with available data were analyzed.	
End point type	Primary
End point timeframe:	
Baseline to Week 96	

End point values	SIM 75 mg	SIM 125 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	74	74	
Units: Percentage				
arithmetic mean (standard deviation)				
SIM 75mg N=46,SIM 125 mg N=49,Placebo N=55	-3.1 (± 4.83)	-2.5 (± 5.11)	-1.9 (± 4.28)	

Statistical analyses

Statistical analysis title	MQC- 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 MQC at Week 96. With MMRM setting, all participants with available data from 3 treatment groups with change in MQC at Week 48 and/or Week 96 contributed to the overall model.	
Comparison groups	SIM 75 mg v Placebo

Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in LSMeans [SIM - Placebo]
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1

Statistical analysis title	MQC- 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 MQC at Week 96. With MMRM setting, all participants with available data from 3 treatment groups with change in MQC at Week 48 and/or Week 96 contributed to the overall model.

Comparison groups	SIM 125 mg v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in LSMeans [SIM - Placebo]
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.8

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 the time to progression to cirrhosis. Participants were considered to have become cirrhotic if they had a post-baseline biopsy consistent with cirrhosis or developed overt signs and symptoms of cirrhosis. All overt signs and symptoms went through an adjudication process and were confirmed before they were considered for the EFS analysis. Participants in the Full Analysis Set with available data were analyzed.

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 75 mg	SIM 125 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	70	74	74	
Units: Percentage of participants				
number (not applicable)				
Total Participants with Events (%)	20.0	23.0	23.0	

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 the presence or absence of diabetes at baseline.	
Comparison groups	SIM 75 mg v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Stratified log-rank test
Parameter estimate	Not Aapplicable
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 the presence or absence of diabetes at baseline.	
Comparison groups	SIM 125 mg v Placebo
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
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 75 mg= 112.3 weeks, SIM 125 mg= 111.0 weeks, Placebo= 111.3 weeks, Open-label SIM= 51.0 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 75 mg

Reporting group description:

Simtuzimab (SIM) 75 mg weekly for up to 240 weeks

Reporting group title	SIM 125 mg

Reporting group description:

Simtuzimab (SIM) 125 mg weekly for up to 240 weeks

Reporting group title	Placebo

Reporting group description:

Placebo to match Simtuzimab (SIM) weekly for up to 240 weeks

Reporting group title	Open-label SIM 125 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) 125 mg subcutaneous injection every week for up to 240 weeks.

Serious adverse events	SIM 75 mg	SIM 125 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 71 (23.94%)	17 / 74 (22.97%)	14 / 74 (18.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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

Basal cell carcinoma			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian adenoma			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Rectal adenocarcinoma			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
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			
Hypertension			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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
Hypotension			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 71 (1.41%)	3 / 74 (4.05%)	2 / 74 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Pleural effusion			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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
Depression			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Major depression			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Weight increased			

subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Seroma			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Upper limb fracture			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
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	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Coronary artery occlusion			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Myocardial infarction			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 71 (1.41%)	1 / 74 (1.35%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 71 (1.41%)	1 / 74 (1.35%)	0 / 74 (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
Carpal tunnel syndrome			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Depressed level of consciousness			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Epilepsy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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			
Abdominal pain			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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 pain lower			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Colitis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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
Diverticular perforation			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Haemorrhoids			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			

subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Intestinal obstruction			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Melaena			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Nausea			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Perforation bile duct			

subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder prolapse			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Urinary retention			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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			
Hyperadrenocorticism			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc protrusion			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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
Joint instability			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	3 / 71 (4.23%)	1 / 74 (1.35%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 71 (0.00%)	2 / 74 (2.70%)	0 / 74 (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
Bacteraemia			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	2 / 74 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess soft tissue			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Appendicitis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	0 / 74 (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
Device related infection			

subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Groin abscess			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (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
Mastoiditis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	0 / 74 (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
Hyperglycaemia			

subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 71 (0.00%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic disorder			
subjects affected / exposed	1 / 71 (1.41%)	0 / 74 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-label SIM 125 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 42 (26.19%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian adenoma			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 42 (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 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-cardiac chest pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weight increased			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seroma			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Upper limb fracture				
subjects affected / exposed	0 / 42 (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 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Syncope				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carpal tunnel syndrome				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Depressed level of consciousness				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic encephalopathy				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Pancytopenia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticular perforation				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				
subjects affected / exposed	0 / 42 (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 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Biliary dilatation				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Perforation bile duct				
subjects affected / exposed	0 / 42 (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	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder prolapse				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperadrenocorticism			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint instability			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess soft tissue			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Groin abscess			

subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus inadequate control				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolic acidosis				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolic disorder				
subjects affected / exposed	0 / 42 (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 75 mg	SIM 125 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 71 (91.55%)	69 / 74 (93.24%)	72 / 74 (97.30%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 71 (4.23%)	5 / 74 (6.76%)	7 / 74 (9.46%)
occurrences (all)	3	5	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 71 (26.76%)	19 / 74 (25.68%)	24 / 74 (32.43%)
occurrences (all)	22	20	27
Oedema peripheral			
subjects affected / exposed	7 / 71 (9.86%)	3 / 74 (4.05%)	6 / 74 (8.11%)
occurrences (all)	8	3	6
Pyrexia			
subjects affected / exposed	6 / 71 (8.45%)	6 / 74 (8.11%)	5 / 74 (6.76%)
occurrences (all)	6	6	5
Injection site bruising			
subjects affected / exposed	9 / 71 (12.68%)	3 / 74 (4.05%)	5 / 74 (6.76%)
occurrences (all)	11	4	6
Pain			
subjects affected / exposed	3 / 71 (4.23%)	5 / 74 (6.76%)	4 / 74 (5.41%)
occurrences (all)	3	6	4
Chest pain			
subjects affected / exposed	1 / 71 (1.41%)	4 / 74 (5.41%)	6 / 74 (8.11%)
occurrences (all)	1	5	6
Influenza like illness			
subjects affected / exposed	2 / 71 (2.82%)	2 / 74 (2.70%)	4 / 74 (5.41%)
occurrences (all)	2	2	4
Injection site erythema			
subjects affected / exposed	3 / 71 (4.23%)	5 / 74 (6.76%)	0 / 74 (0.00%)
occurrences (all)	3	5	0
Injection site pain			

subjects affected / exposed	4 / 71 (5.63%)	1 / 74 (1.35%)	2 / 74 (2.70%)
occurrences (all)	4	2	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 71 (9.86%)	11 / 74 (14.86%)	10 / 74 (13.51%)
occurrences (all)	10	11	11
Oropharyngeal pain			
subjects affected / exposed	4 / 71 (5.63%)	8 / 74 (10.81%)	5 / 74 (6.76%)
occurrences (all)	5	10	5
Dyspnoea			
subjects affected / exposed	4 / 71 (5.63%)	1 / 74 (1.35%)	2 / 74 (2.70%)
occurrences (all)	4	1	2
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 71 (5.63%)	5 / 74 (6.76%)	7 / 74 (9.46%)
occurrences (all)	4	5	7
Anxiety			
subjects affected / exposed	3 / 71 (4.23%)	5 / 74 (6.76%)	3 / 74 (4.05%)
occurrences (all)	3	6	3
Insomnia			
subjects affected / exposed	2 / 71 (2.82%)	4 / 74 (5.41%)	3 / 74 (4.05%)
occurrences (all)	2	4	3
Investigations			
Blood glucose increased			
subjects affected / exposed	4 / 71 (5.63%)	1 / 74 (1.35%)	1 / 74 (1.35%)
occurrences (all)	4	1	1
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	8 / 71 (11.27%)	6 / 74 (8.11%)	7 / 74 (9.46%)
occurrences (all)	8	8	8
Contusion			
subjects affected / exposed	4 / 71 (5.63%)	4 / 74 (5.41%)	6 / 74 (8.11%)
occurrences (all)	4	4	6
Fall			
subjects affected / exposed	5 / 71 (7.04%)	2 / 74 (2.70%)	4 / 74 (5.41%)
occurrences (all)	6	3	4

Ligament sprain			
subjects affected / exposed	4 / 71 (5.63%)	1 / 74 (1.35%)	3 / 74 (4.05%)
occurrences (all)	4	1	3
Laceration			
subjects affected / exposed	0 / 71 (0.00%)	1 / 74 (1.35%)	4 / 74 (5.41%)
occurrences (all)	0	1	5
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 71 (16.90%)	16 / 74 (21.62%)	16 / 74 (21.62%)
occurrences (all)	15	39	20
Dizziness			
subjects affected / exposed	8 / 71 (11.27%)	6 / 74 (8.11%)	7 / 74 (9.46%)
occurrences (all)	9	6	8
Carpal tunnel syndrome			
subjects affected / exposed	4 / 71 (5.63%)	2 / 74 (2.70%)	0 / 74 (0.00%)
occurrences (all)	4	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 71 (2.82%)	2 / 74 (2.70%)	5 / 74 (6.76%)
occurrences (all)	2	2	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 71 (22.54%)	20 / 74 (27.03%)	22 / 74 (29.73%)
occurrences (all)	20	21	30
Diarrhoea			
subjects affected / exposed	19 / 71 (26.76%)	19 / 74 (25.68%)	21 / 74 (28.38%)
occurrences (all)	27	21	21
Abdominal pain upper			
subjects affected / exposed	11 / 71 (15.49%)	19 / 74 (25.68%)	17 / 74 (22.97%)
occurrences (all)	13	20	21
Vomiting			
subjects affected / exposed	11 / 71 (15.49%)	14 / 74 (18.92%)	10 / 74 (13.51%)
occurrences (all)	13	16	10
Abdominal pain			
subjects affected / exposed	13 / 71 (18.31%)	8 / 74 (10.81%)	11 / 74 (14.86%)
occurrences (all)	16	9	13
Constipation			

subjects affected / exposed	6 / 71 (8.45%)	2 / 74 (2.70%)	8 / 74 (10.81%)
occurrences (all)	8	2	9
Abdominal distension			
subjects affected / exposed	6 / 71 (8.45%)	4 / 74 (5.41%)	5 / 74 (6.76%)
occurrences (all)	6	4	6
Abdominal pain lower			
subjects affected / exposed	1 / 71 (1.41%)	4 / 74 (5.41%)	5 / 74 (6.76%)
occurrences (all)	1	4	6
Dyspepsia			
subjects affected / exposed	1 / 71 (1.41%)	2 / 74 (2.70%)	4 / 74 (5.41%)
occurrences (all)	1	2	4
Abdominal tenderness			
subjects affected / exposed	1 / 71 (1.41%)	4 / 74 (5.41%)	1 / 74 (1.35%)
occurrences (all)	1	4	1
Dry mouth			
subjects affected / exposed	1 / 71 (1.41%)	4 / 74 (5.41%)	2 / 74 (2.70%)
occurrences (all)	1	4	2
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	2 / 71 (2.82%)	1 / 74 (1.35%)	4 / 74 (5.41%)
occurrences (all)	2	1	4
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	8 / 71 (11.27%)	7 / 74 (9.46%)	8 / 74 (10.81%)
occurrences (all)	8	7	9
Pruritus			
subjects affected / exposed	7 / 71 (9.86%)	4 / 74 (5.41%)	7 / 74 (9.46%)
occurrences (all)	8	4	7
Alopecia			
subjects affected / exposed	3 / 71 (4.23%)	4 / 74 (5.41%)	4 / 74 (5.41%)
occurrences (all)	3	4	4
Palmar erythema			
subjects affected / exposed	2 / 71 (2.82%)	4 / 74 (5.41%)	2 / 74 (2.70%)
occurrences (all)	2	4	2
Urticaria			

subjects affected / exposed	4 / 71 (5.63%)	2 / 74 (2.70%)	0 / 74 (0.00%)
occurrences (all)	6	4	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 71 (22.54%)	11 / 74 (14.86%)	18 / 74 (24.32%)
occurrences (all)	16	11	18
Back pain			
subjects affected / exposed	11 / 71 (15.49%)	6 / 74 (8.11%)	20 / 74 (27.03%)
occurrences (all)	12	6	23
Pain in extremity			
subjects affected / exposed	13 / 71 (18.31%)	8 / 74 (10.81%)	8 / 74 (10.81%)
occurrences (all)	13	8	8
Muscle spasms			
subjects affected / exposed	5 / 71 (7.04%)	9 / 74 (12.16%)	5 / 74 (6.76%)
occurrences (all)	5	10	5
Musculoskeletal pain			
subjects affected / exposed	7 / 71 (9.86%)	7 / 74 (9.46%)	5 / 74 (6.76%)
occurrences (all)	7	7	6
Myalgia			
subjects affected / exposed	7 / 71 (9.86%)	2 / 74 (2.70%)	4 / 74 (5.41%)
occurrences (all)	7	2	4
Neck pain			
subjects affected / exposed	0 / 71 (0.00%)	5 / 74 (6.76%)	6 / 74 (8.11%)
occurrences (all)	0	5	6
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 71 (15.49%)	12 / 74 (16.22%)	10 / 74 (13.51%)
occurrences (all)	15	17	12
Sinusitis			
subjects affected / exposed	10 / 71 (14.08%)	8 / 74 (10.81%)	14 / 74 (18.92%)
occurrences (all)	12	9	17
Urinary tract infection			
subjects affected / exposed	10 / 71 (14.08%)	7 / 74 (9.46%)	14 / 74 (18.92%)
occurrences (all)	11	8	20
Bronchitis			

subjects affected / exposed	16 / 71 (22.54%)	7 / 74 (9.46%)	8 / 74 (10.81%)
occurrences (all)	20	8	10
Nasopharyngitis			
subjects affected / exposed	5 / 71 (7.04%)	8 / 74 (10.81%)	16 / 74 (21.62%)
occurrences (all)	7	13	26
Influenza			
subjects affected / exposed	8 / 71 (11.27%)	8 / 74 (10.81%)	10 / 74 (13.51%)
occurrences (all)	11	10	11
Tooth abscess			
subjects affected / exposed	6 / 71 (8.45%)	1 / 74 (1.35%)	4 / 74 (5.41%)
occurrences (all)	6	1	4
Cellulitis			
subjects affected / exposed	4 / 71 (5.63%)	2 / 74 (2.70%)	2 / 74 (2.70%)
occurrences (all)	4	2	2
Gastroenteritis viral			
subjects affected / exposed	1 / 71 (1.41%)	5 / 74 (6.76%)	1 / 74 (1.35%)
occurrences (all)	1	5	1
Gastroenteritis			
subjects affected / exposed	4 / 71 (5.63%)	1 / 74 (1.35%)	1 / 74 (1.35%)
occurrences (all)	4	1	1
Localised infection			
subjects affected / exposed	4 / 71 (5.63%)	0 / 74 (0.00%)	1 / 74 (1.35%)
occurrences (all)	4	0	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	4 / 71 (5.63%)	3 / 74 (4.05%)	4 / 74 (5.41%)
occurrences (all)	4	7	4
Decreased appetite			
subjects affected / exposed	3 / 71 (4.23%)	3 / 74 (4.05%)	5 / 74 (6.76%)
occurrences (all)	3	3	5
Diabetes mellitus			
subjects affected / exposed	6 / 71 (8.45%)	3 / 74 (4.05%)	2 / 74 (2.70%)
occurrences (all)	6	3	2
Vitamin D deficiency			
subjects affected / exposed	2 / 71 (2.82%)	4 / 74 (5.41%)	2 / 74 (2.70%)
occurrences (all)	2	4	2

Non-serious adverse events	Open-label SIM 125 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 42 (69.05%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Injection site bruising			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Injection site erythema			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Ligament sprain			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Laceration			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Carpal tunnel syndrome			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Constipation			

subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Abdominal distension				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Abdominal pain lower				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Dyspepsia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Abdominal tenderness				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Hepatobiliary disorders				
Hepatomegaly				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Pruritus				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Alopecia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences (all)	1			
Palmar erythema				
subjects affected / exposed	0 / 42 (0.00%)			
occurrences (all)	0			
Urticaria				

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	5		
Bronchitis			

subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Diabetes mellitus			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vitamin D deficiency			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2013	1. Female contraception requirement following last does 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
26 February 2013	1. Additional anti-GS-6624 antibodies and pharmacokinetics testing. 2. Language added regarding Brunt/Kleiner and the NAFLD Activity Score (NAS). 3. Language added regarding the Cochran-Mantel-Haenszel test. 4. New anti-GS-6624 antibodies and pharmacokinetics testing section.
30 September 2014	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 treatment via SC injection every week with a fixed dose of simtuzumab 125 mg. 3) A clinical efficacy endpoint of event free survival (EFS) has been added, EFS will be assessed by time to progression to cirrhosis and progression to cirrhosis events will be followed up to Week 240 to assess whether simtuzumab can reduce the incidence of progression to cirrhosis. Any participant found to have a liver biopsy consistent with cirrhosis at Week 48, Week 96 or Week 240 will be considered to have met this endpoint. 4) A Progression to Cirrhosis Events Adjudication Committee has been added and participants suspected to have progressed to cirrhosis will be presented to the committee to confirm if it is progression to cirrhosis or not. 5) Inclusion/ Exclusion criteria updated.
31 July 2015	1. Updating Study Director 2. Revised liver biopsy central reading process

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported