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 Primary Sclerosing Cholangitis (PSC)

Summary

EudraCT number	2012-002473-61
Trial protocol	DE GB SE IT DK ES BE NL
Global end of trial date	24 August 2016

Results information

Result version number	v1 (current)
This version publication date	09 September 2017
First version publication date	09 September 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-321-0102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01672853
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, 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	24 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2016
Global end of trial reached?	Yes
Global end of trial date	24 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of simtuzumab (SIM) for the prevention of progression of liver fibrosis in adults with Primary Sclerosing Cholangitis (PSC).

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	04 March 2013
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: 120
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	235
EEA total number of subjects	69

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)	229
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America and Europe. The first participant was screened on 04 March 2013. The last study visit occurred on 24 August 2016.

Pre-assignment

Screening details:

298 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	Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	SIM 75 mg

Arm description:

SIM 75 mg weekly for 96 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:

SIM 125 mg weekly for 96 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 SIM weekly for 96 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:

Placebo to match SIM

Number of subjects in period 1[1]	SIM 75 mg	SIM 125 mg	Placebo
Started	79	77	78
Completed	69	60	65
Not completed	10	17	13
Withdrew Consent	5	5	5
Adverse Event	4	6	8
Protocol Specified Criteria for Withdrawal	-	4	-
Investigator's Discretion	1	-	-
Pregnancy	-	1	-
Lost to follow-up	-	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 75 mg
Reporting group description: SIM 75 mg weekly for 96 weeks	
Reporting group title	SIM 125 mg
Reporting group description: SIM 125 mg weekly for 96 weeks	
Reporting group title	Placebo
Reporting group description: Placebo to match SIM weekly for 96 weeks	

Reporting group values	SIM 75 mg	SIM 125 mg	Placebo
Number of subjects	79	77	78
Age categorical Units: Subjects			
Age continuous			
Safety Analysis Set: participants who received at least one dose of study drug.			
Units: years			
arithmetic mean	45	43	44
standard deviation	± 11.3	± 10.1	± 12.8
Gender categorical Units: Subjects			
Female	27	25	33
Male	52	52	45
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	0	1	3
Black	7	6	8
White	71	68	62
Other	1	2	4
Ethnicity Units: Subjects			
Hispanic or Latino	1	4	1
Not Hispanic or Latino	78	73	77
Morphometric Quantitative Collagen (MQC)			
Only 76 participants in the SIM 75 mg arm with available data were analyzed at baseline.			
Units: Percentage			
arithmetic mean	5.6	5.6	5.1
standard deviation	± 5.09	± 3.36	± 3.98

Reporting group values	Total		
Number of subjects	234		

Age categorical Units: Subjects			

Age continuous			
Safety Analysis Set: participants who received at least one dose of study drug.			
Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female Male	85 149		
Race Units: Subjects			
American Indian or Alaska Native Asian Black White Other	1 4 21 201 7		
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino	6 228		
Morphometric Quantitative Collagen (MQC)			
Only 76 participants in the SIM 75 mg arm with available data were analyzed at baseline.			
Units: Percentage arithmetic mean standard deviation	 -		

End points

End points reporting groups	
Reporting group title	SIM 75 mg
Reporting group description: SIM 75 mg weekly for 96 weeks	
Reporting group title	SIM 125 mg
Reporting group description: SIM 125 mg weekly for 96 weeks	
Reporting group title	Placebo
Reporting group description: Placebo to match SIM weekly for 96 weeks	

Primary: Change From Baseline in Morphometric Quantitative Collagen on Liver Biopsy	
End point title	Change From Baseline in Morphometric Quantitative Collagen on Liver Biopsy
End point description: Participants in the Full Analysis Set (enrolled participants who were randomized and received at least 1 dose of study drug) 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	61	61	62	
Units: Percentage				
arithmetic mean (standard deviation)				
Change at Week 96	-0.5 (± 5.78)	0.5 (± 6.94)	0 (± 4.76)	

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	123
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LSMeans [SIM - Placebo]
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	1.6

Statistical analysis title	MQC- Comparison of Groups

Statistical analysis description:

A MMRM with an unstructured variance-covariance matrix for each participant was used to calculate a point estimate and a 95% CI for the treatment difference between each treatment arm and placebo in 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	123
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LSMeans [SIM - Placebo]
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	3

Secondary: Percentage of Participants Who Permanently Discontinued Any Study Drug Due to an Adverse Event

End point title	Percentage of Participants Who Permanently Discontinued Any Study Drug Due to an Adverse Event

End point description:

Safety Analysis Set

End point type	Secondary

End point timeframe:

Baseline up to the last dose date (maximum: 96 weeks)

End point values	SIM 75 mg	SIM 125 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	77	78	
Units: percentage of participants				
number (not applicable)	5.1	7.8	10.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Study Drug Exposure

End point title	Study Drug Exposure

End point description:

The average SIM exposure was summarized. Safety Analysis Set.

End point type	Secondary

End point timeframe:

Baseline up to the last dose date (maximum: 96 weeks)

End point values	SIM 75 mg	SIM 125 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	77	78	
Units: Weeks				
arithmetic mean (standard deviation)	92 (± 15.33)	83.8 (± 26.12)	87.4 (± 22.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Any Treatment-Emergent Laboratory Abnormality

End point title	Percentage of Participants Experiencing Any Treatment-Emergent Laboratory Abnormality

End point description:

Treatment-emergent laboratory abnormalities were defined as an increase of at least one toxicity grade from baseline at any time postbaseline up to and including the date of last study drug dose plus 30 days. The most severe graded abnormality from all tests was counted for each participant. Grade 1 (mild) or Grade 2 (moderate) Grade 3 (severe) and Grade 4 (life-threatening) in severity.

Participants in the Safety Analysis Set with at least 1 postbaseline measurement were analyzed.

End point type	Secondary

End point timeframe:

Baseline up to the last dose date plus 30 days (maximum: 96 weeks)

End point values	SIM 75 mg	SIM 125 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	77	78	
Units: percentage of participants				
number (not applicable)				
Grade 1	11.4	16.9	17.9	
Grade 2	26.6	20.8	25.6	
Grade 3	48.1	46.8	48.7	
Grade 4	11.4	13	7.7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to the last dose date plus 30 days (maximum: 96 weeks)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	SIM 75 mg
Reporting group description: SIM 75 mg weekly for 96 weeks.	
Reporting group title	SIM 125 mg
Reporting group description: SIM 125 mg weekly for 96 weeks	
Reporting group title	Placebo
Reporting group description: Placebo to match SIM weekly for 96 weeks	

Serious adverse events	SIM 75 mg	SIM 125 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 79 (20.25%)	23 / 77 (29.87%)	21 / 78 (26.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign biliary neoplasm			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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
Cholangiocarcinoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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

Lipoma			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
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 adenoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic stress disorder			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
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 bilirubin increased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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
Liver function test increased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intestinal anastomosis complication			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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
Post procedural complication			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative fever			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Procedural complication			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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
Procedural pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma obstruction			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 79 (2.53%)	3 / 77 (3.90%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 79 (1.27%)	1 / 77 (1.30%)	0 / 78 (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 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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
Colitis ulcerative			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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
Diverticular perforation			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	2 / 79 (2.53%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
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 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	6 / 79 (7.59%)	5 / 77 (6.49%)	3 / 78 (3.85%)
occurrences causally related to treatment / all	0 / 9	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			

subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 79 (1.27%)	1 / 77 (1.30%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder perforation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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
Jaundice cholestatic			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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
Portal vein thrombosis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
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 colic			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
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			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 79 (1.27%)	1 / 77 (1.30%)	0 / 78 (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
Infections and infestations			
Cholangitis infective			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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
Infected skin ulcer			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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

Pelvic abscess			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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
Pharyngitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	2 / 78 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 79 (0.00%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 77 (0.00%)	0 / 78 (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			
Failure to thrive			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	0 / 78 (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

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	71 / 79 (89.87%)	72 / 77 (93.51%)	75 / 78 (96.15%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 79 (3.80%)	2 / 77 (2.60%)	4 / 78 (5.13%)
occurrences (all)	3	2	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 79 (1.27%)	4 / 77 (5.19%)	3 / 78 (3.85%)
occurrences (all)	1	5	3
Fatigue			
subjects affected / exposed	19 / 79 (24.05%)	21 / 77 (27.27%)	16 / 78 (20.51%)
occurrences (all)	22	27	20
Influenza like illness			
subjects affected / exposed	3 / 79 (3.80%)	4 / 77 (5.19%)	4 / 78 (5.13%)
occurrences (all)	3	6	10
Injection site erythema			
subjects affected / exposed	2 / 79 (2.53%)	5 / 77 (6.49%)	0 / 78 (0.00%)
occurrences (all)	5	5	0
Injection site pain			
subjects affected / exposed	4 / 79 (5.06%)	0 / 77 (0.00%)	3 / 78 (3.85%)
occurrences (all)	4	0	3
Pain			
subjects affected / exposed	0 / 79 (0.00%)	6 / 77 (7.79%)	5 / 78 (6.41%)
occurrences (all)	0	7	5
Pyrexia			
subjects affected / exposed	11 / 79 (13.92%)	10 / 77 (12.99%)	13 / 78 (16.67%)
occurrences (all)	14	25	27
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 79 (17.72%)	7 / 77 (9.09%)	7 / 78 (8.97%)
occurrences (all)	16	9	7
Dyspnoea			

subjects affected / exposed	5 / 79 (6.33%)	3 / 77 (3.90%)	1 / 78 (1.28%)
occurrences (all)	6	3	2
Oropharyngeal pain			
subjects affected / exposed	5 / 79 (6.33%)	3 / 77 (3.90%)	4 / 78 (5.13%)
occurrences (all)	5	3	4
Sinus congestion			
subjects affected / exposed	3 / 79 (3.80%)	4 / 77 (5.19%)	1 / 78 (1.28%)
occurrences (all)	4	6	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 79 (2.53%)	3 / 77 (3.90%)	4 / 78 (5.13%)
occurrences (all)	3	4	4
Insomnia			
subjects affected / exposed	5 / 79 (6.33%)	5 / 77 (6.49%)	4 / 78 (5.13%)
occurrences (all)	7	5	4
Investigations			
Blood bilirubin increased			
subjects affected / exposed	4 / 79 (5.06%)	2 / 77 (2.60%)	3 / 78 (3.85%)
occurrences (all)	5	3	3
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 79 (5.06%)	3 / 77 (3.90%)	0 / 78 (0.00%)
occurrences (all)	4	4	0
Procedural pain			
subjects affected / exposed	4 / 79 (5.06%)	7 / 77 (9.09%)	7 / 78 (8.97%)
occurrences (all)	4	7	7
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 79 (7.59%)	5 / 77 (6.49%)	4 / 78 (5.13%)
occurrences (all)	7	6	4
Headache			
subjects affected / exposed	18 / 79 (22.78%)	12 / 77 (15.58%)	17 / 78 (21.79%)
occurrences (all)	23	22	21
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	4 / 79 (5.06%)	3 / 77 (3.90%)	4 / 78 (5.13%)
occurrences (all)	4	3	4
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 79 (5.06%)	4 / 77 (5.19%)	3 / 78 (3.85%)
occurrences (all)	4	4	4
Abdominal distension			
subjects affected / exposed	4 / 79 (5.06%)	3 / 77 (3.90%)	6 / 78 (7.69%)
occurrences (all)	6	3	7
Abdominal pain			
subjects affected / exposed	13 / 79 (16.46%)	18 / 77 (23.38%)	17 / 78 (21.79%)
occurrences (all)	15	28	20
Abdominal pain lower			
subjects affected / exposed	2 / 79 (2.53%)	3 / 77 (3.90%)	4 / 78 (5.13%)
occurrences (all)	2	3	4
Abdominal pain upper			
subjects affected / exposed	18 / 79 (22.78%)	14 / 77 (18.18%)	18 / 78 (23.08%)
occurrences (all)	26	20	22
Colitis ulcerative			
subjects affected / exposed	1 / 79 (1.27%)	1 / 77 (1.30%)	5 / 78 (6.41%)
occurrences (all)	1	1	5
Constipation			
subjects affected / exposed	7 / 79 (8.86%)	1 / 77 (1.30%)	7 / 78 (8.97%)
occurrences (all)	7	1	10
Diarrhoea			
subjects affected / exposed	19 / 79 (24.05%)	15 / 77 (19.48%)	15 / 78 (19.23%)
occurrences (all)	23	19	19
Dyspepsia			
subjects affected / exposed	2 / 79 (2.53%)	2 / 77 (2.60%)	9 / 78 (11.54%)
occurrences (all)	2	2	10
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 79 (0.00%)	1 / 77 (1.30%)	5 / 78 (6.41%)
occurrences (all)	0	1	5
Haemorrhoids			
subjects affected / exposed	4 / 79 (5.06%)	1 / 77 (1.30%)	0 / 78 (0.00%)
occurrences (all)	4	1	0

Nausea			
subjects affected / exposed	16 / 79 (20.25%)	17 / 77 (22.08%)	17 / 78 (21.79%)
occurrences (all)	24	28	22
Rectal haemorrhage			
subjects affected / exposed	5 / 79 (6.33%)	2 / 77 (2.60%)	3 / 78 (3.85%)
occurrences (all)	5	2	3
Varices oesophageal			
subjects affected / exposed	2 / 79 (2.53%)	5 / 77 (6.49%)	4 / 78 (5.13%)
occurrences (all)	2	6	4
Vomiting			
subjects affected / exposed	9 / 79 (11.39%)	5 / 77 (6.49%)	7 / 78 (8.97%)
occurrences (all)	16	5	8
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	6 / 79 (7.59%)	6 / 77 (7.79%)	4 / 78 (5.13%)
occurrences (all)	13	7	15
Jaundice			
subjects affected / exposed	5 / 79 (6.33%)	4 / 77 (5.19%)	3 / 78 (3.85%)
occurrences (all)	6	5	3
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	21 / 79 (26.58%)	22 / 77 (28.57%)	31 / 78 (39.74%)
occurrences (all)	30	27	36
Rash			
subjects affected / exposed	10 / 79 (12.66%)	2 / 77 (2.60%)	3 / 78 (3.85%)
occurrences (all)	11	2	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 79 (6.33%)	12 / 77 (15.58%)	10 / 78 (12.82%)
occurrences (all)	5	13	11
Back pain			
subjects affected / exposed	8 / 79 (10.13%)	8 / 77 (10.39%)	9 / 78 (11.54%)
occurrences (all)	8	9	10
Flank pain			
subjects affected / exposed	0 / 79 (0.00%)	2 / 77 (2.60%)	4 / 78 (5.13%)
occurrences (all)	0	2	4

Muscle spasms			
subjects affected / exposed	7 / 79 (8.86%)	2 / 77 (2.60%)	4 / 78 (5.13%)
occurrences (all)	8	2	4
Musculoskeletal pain			
subjects affected / exposed	4 / 79 (5.06%)	3 / 77 (3.90%)	2 / 78 (2.56%)
occurrences (all)	5	3	2
Myalgia			
subjects affected / exposed	2 / 79 (2.53%)	7 / 77 (9.09%)	1 / 78 (1.28%)
occurrences (all)	2	8	1
Pain in extremity			
subjects affected / exposed	7 / 79 (8.86%)	2 / 77 (2.60%)	4 / 78 (5.13%)
occurrences (all)	7	2	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 79 (2.53%)	3 / 77 (3.90%)	7 / 78 (8.97%)
occurrences (all)	2	4	7
Gastroenteritis			
subjects affected / exposed	2 / 79 (2.53%)	5 / 77 (6.49%)	2 / 78 (2.56%)
occurrences (all)	2	5	3
Gastroenteritis viral			
subjects affected / exposed	5 / 79 (6.33%)	1 / 77 (1.30%)	4 / 78 (5.13%)
occurrences (all)	5	2	4
Influenza			
subjects affected / exposed	5 / 79 (6.33%)	2 / 77 (2.60%)	7 / 78 (8.97%)
occurrences (all)	6	2	8
Lower respiratory tract infection			
subjects affected / exposed	5 / 79 (6.33%)	0 / 77 (0.00%)	1 / 78 (1.28%)
occurrences (all)	7	0	2
Nasopharyngitis			
subjects affected / exposed	19 / 79 (24.05%)	17 / 77 (22.08%)	14 / 78 (17.95%)
occurrences (all)	28	31	16
Sinusitis			
subjects affected / exposed	5 / 79 (6.33%)	11 / 77 (14.29%)	5 / 78 (6.41%)
occurrences (all)	6	11	5
Upper respiratory tract infection			

subjects affected / exposed	11 / 79 (13.92%)	9 / 77 (11.69%)	10 / 78 (12.82%)
occurrences (all)	11	10	10
Urinary tract infection			
subjects affected / exposed	6 / 79 (7.59%)	4 / 77 (5.19%)	4 / 78 (5.13%)
occurrences (all)	14	4	6
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 79 (5.06%)	3 / 77 (3.90%)	5 / 78 (6.41%)
occurrences (all)	5	4	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2012	1. Updated Medical Monitors 2. Updated IND number 3. Further clarification to exclusion #6 4. Updated SAE reporting information 5. Stratification clarification 6. Updated Unblinding Procedure 7. Removal of duplicate laboratory procedures 8. Revision of table of assessments
15 November 2012	1. Language to exclude adults with ulcerative colitis. 2. Language to manage adults with history of ulcerative colitis. 3. Additional safety stopping points and parameters. 4. Additional electrocardiogram (ECG) collection at baseline and at every 12 weeks.
04 December 2012	1.Changes in eligibility criteria 2.Additional handling information for peripheral blood collection 3.Changes in ulcerative colitis criteria 4.Collection time points and detail to 12-lead ECG 5.New anti-simtuzumab and pharmacokinetic testing section 6.Update to Adverse Event follow up 7.Update to Contraception Requirements 8.Clarifications to stopping rules
15 February 2013	1.Additional secondary objective regarding pharmacokinetics sampling. 2.Administrative change to reflect the 8 week screening period. 3.Revision to exclusion criteria #19 to provide example of conditions to exclude participants. 4.Addition of new benefit risk section. 5.Further guidance for adults with concomitant UC who meet criteria for annual screening colonoscopy. 6.Discontinue criteria for adults who develop sensitivity to simtuzumab. 7.Further clarification to serious adverse reporting requirements. 8.Additional language to male contraception requirements.
08 January 2014	1. Updating Data Monitoring Committee (DMC) language 2. Revision to age, liver biopsy, magnetic Resonance Cholangiopancreatography (MRCP) and male contraception inclusion criteria 3. Historical liver biopsy allowance language 4. Revision to ulcerative colitis exclusion criterion 5. Additional exclusion criterion applicable to France only 6. Updated Biostatistics related sections 7. New language regarding dextran sulfate sodium (DSS) animal study with simtuzumab 8. Revised unblinding process language 9. Extension of screening window under special circumstances 10. Insertion of VAS assessment at Weeks 24 and 72 11. New MRCP language 12. Revised partial Mayo Score language to make the study population more generalizable to the PSC population 13. Updated pharmacogenomics testing language 14. Updated special situation reporting section 15. Stopping rules revision 16. Additional information for contraception 17. Clarification to adverse event determination and utilization of Common Terminology Criteria for Adverse Events (CTCAE)

31 July 2015	1. Revised liver biopsy central reading process

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported