Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy and Safety of GS-6624 in Subjects with Idiopathic Pulmonary Fibrosis (RAINIER)

Summary

EudraCT number	2012-001571-36
Trial protocol	IT BE GB DE CZ ES PL
Global end of trial date	23 February 2016

Results information

Result version number	v1
This version publication date	11 March 2017
First version publication date	11 March 2017

Trial information

Trial identification

Sponsor protocol code	GS-US-322-0207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01769196
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2016
Global end of trial reached?	Yes
Global end of trial date	23 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to determine the effect of simtuzumab (GS-6624) on progression-free survival (PFS) as determined by either a categorical decline in forced vital capacity (FVC) or all-cause mortality, in all participants enrolled or in a subset of participants who are classified as lysyl oxidase-like-2 (LOXL2) high based on a prespecified level in serum at baseline.

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	31 January 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	Poland: 28
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 208

Country: Number of subjects enrolled	Korea, Republic of: 69
Worldwide total number of subjects	544
EEA total number of subjects	201

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)	189
From 65 to 84 years	352
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Europe, and Asia Pacific. The first participant was screened on 31 January 2013. The last study visit occurred on 23 February 2016.

Pre-assignment

Screening details:

1250 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

Arms

Are arms mutually exclusive?	Yes
Arm title	Simtuzumab

Arm description:

Simtuzumab 125 mg/mL administered subcutaneously once a week

Arm type	Experimental
Investigational medicinal product name	Simtuzumab
Investigational medicinal product code	
Other name	GS-6624
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

125 mg/mL administered once a week

Arm title	Simtuzumab Placebo

Arm description:

Simtuzumab placebo administered subcutaneously once a week

Arm type	Experimental
Investigational medicinal product name	Simtuzumab Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Simtuzumab placebo administered subcutaneously once a week

Number of subjects in period 1	Simtuzumab	Simtuzumab Placebo
Started	272	272
Completed	0	0
Not completed	272	272
Adverse event, non-fatal	24	20
Death	21	26
Protocol specified criteria for withdrawal	9	11
Study terminated by sponsor	160	161
Protocol Violation	-	3
Investigator's discretion	7	3
Progressive disease	11	6
Withdrew consent	36	40
Lack of efficacy	3	2
Participant never dosed with study drug	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Simtuzumab
Reporting group description: Simtuzumab 125 mg/mL administered subcutaneously once a week	
Reporting group title	Simtuzumab Placebo
Reporting group description: Simtuzumab placebo administered subcutaneously once a week	

Reporting group values	Simtuzumab	Simtuzumab Placebo	Total
Number of subjects	272	272	544
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	67.7	68.5	
standard deviation	± 7.6	± 7.07	-
Gender categorical Units: Subjects			
Female	45	47	92
Male	227	225	452
Race Units: Subjects			
Asian	35	36	71
Black	3	3	6
White	231	229	460
Other	3	4	7
Ethinicity Units: Subjects			
Hispanic or Latino	5	7	12
Not Hispanic or Latino	267	264	531
Not Permitted	0	1	1
FVC % Predicted Category Units: Subjects			
Mild	37	46	83
Moderate	152	150	302
Severe	83	76	159
Forced vital capacity (FVC) Percent Predicted Units: FVC % predicted			
arithmetic mean	61.4	62.3	
standard deviation	± 12.7	± 12.22	-
Baseline Serum LOXL2 Units: pg/mL			
arithmetic mean	89.8	86.7	
standard deviation	± 70.06	± 51.99	-

End points

End points reporting groups

Reporting group title	Simtuzumab
Reporting group description:	
Simtuzumab 125 mg/mL administered subcutaneously once a week	
Reporting group title	Simtuzumab Placebo
Reporting group description:	
Simtuzumab placebo administered subcutaneously once a week	

Primary: Progression Free Survival

End point title	Progression Free Survival
End point description:	
Progression free survival (PFS) was defined as the categorical decrease in forced vital capacity (FVC) % predicted (≥ 10% relative decrease in FVC and ≥ 5% absolute decrease in FVC from baseline) with confirmation at a consecutive visit at least 2 weeks later using the same criteria. Intent-to-Treat (ITT) Analysis Set	
End point type	Primary
End point timeframe:	
Up to 148 weeks	

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	272		
Units: Months				
median (confidence interval 95%)	12.6 (11.3 to 14.4)	15.4 (12.6 to 19.1)		

Statistical analyses

Statistical analysis title	Statistical analysis - Simtuzumab vs Placebo
Statistical analysis description:	
The null hypothesis was that there is no difference in PFS between Simtuzumab and Simtuzumab placebo. The alternative hypothesis was that there is a difference. These hypotheses were evaluated using stratified log-rank test, adjusted for screening post-bronchodilator FVC % predicted, sLOXL2 level categories, and concomitant use of pirfenidone or nintedanib (P/N) at time of screening.	
Comparison groups	Simtuzumab Placebo v Simtuzumab
Number of subjects included in analysis	544
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.329
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.45

Primary: PFS Among the Participants With sLOXL2 ≥ 50th Percentile

End point title	PFS Among the Participants With sLOXL2 ≥ 50th Percentile

End point description:

Participants in the ITT Analysis Set with serum LOXL2 (sLOXL2) ≥ 50th percentile in peripheral blood were analyzed.

End point type	Primary

End point timeframe:

Up to 148 weeks

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	140		
Units: months				
median (confidence interval 95%)	11.7 (9.9 to 15.9)	14.3 (10.4 to 19.1)		

Statistical analyses

Statistical analysis title	Statistical analysis - Simtuzumab vs Placebo
Comparison groups	Simtuzumab v Simtuzumab Placebo
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.851
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.43

Notes:

[1] - The null hypothesis was that there is no difference in PFS between Simtuzumab and Simtuzumab placebo in participants with sLOXL2 ≥ 50th percentile. The alternative hypothesis was that there is a difference. These hypotheses were evaluated using stratified log-rank test, adjusted for screening post-bronchodilator FVC % predicted and concomitant use of pirfenidone or nintedanib (P/N) at time of screening.

Primary: PFS Among the Participants With sLOXL2 ≥ 75th Percentile

End point title	PFS Among the Participants With sLOXL2 ≥ 75th Percentile
End point description:	
Participants in the ITT Analysis Set with sLOXL2 ≥ 75th percentile in peripheral blood were analyzed.	
End point type	Primary
End point timeframe:	
Up to 148 weeks	

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	71		
Units: months				
median (confidence interval 95%)	11.6 (9 to 15)	16.9 (7.7 to 21.7)		

Statistical analyses

Statistical analysis title	Statistical analysis - Simtuzumab vs Placebo
Comparison groups	Simtuzumab v Simtuzumab Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.475
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2

Notes:

[2] - The null hypothesis was that there is no difference in PFS between simtuzumab and simtuzumab placebo in participants with sLOXL2 ≥ 75th percentile. The alternative hypothesis was that there is a difference. These hypotheses were evaluated using stratified log-rank test, adjusted for screening post-bronchodilator FVC % predicted and concomitant use of pirfenidone or nintedanib (P/N) at time of screening.

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
1) Overall survival was defined as the time from randomization date to death that occurred prior to the last dose date plus 30 days. 2) ITT Analysis Set 3) 999 = not reached due to insufficient number of events	
End point type	Secondary
End point timeframe:	
Up to 151 weeks	

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	272		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Statistical analysis - Simtuzumab vs Placebo
Comparison groups	Simtuzumab Placebo v Simtuzumab
Number of subjects included in analysis	544
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.602
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	2.37

Secondary: Relative Change From Baseline in FVC % Predicted

End point title	Relative Change From Baseline in FVC % Predicted

End point description:

- FVC was defined as the volume of air (liters) that can forcibly be blown out after taking a full breath. FVC % predicted was defined as FVC % of the participant divided by the average FVC % in the population for any person of similar age, sex, and body composition.
- Adjusted means are from mixed model repeated measures (MMRM) model with baseline FVC % predicted, sLOXL2 level, concomitant pirfenidone/nintedanib use (never vs. ever), treatment, visit, and treatment-by-visit interaction terms, including all data up to Week 130.
- Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Weeks 54, 106, and 130

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	272		
Units: percent change in FVC % predicted				
least squares mean (standard error)				
Wk 54 (Simtuzumab: N= 124; Placebo: N = 117)	-9.2 (± 0.643)	-8.88 (± 0.658)		
Wk 106 (Simtuzumab: N=60; Placebo: N= 55)	-13.7 (± 0.883)	-12.16 (± 0.908)		
Wk 130 (Simtuzumab: N=10; Placebo: N= 12)	-18.09 (± 1.712)	-11.83 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Definite Acute Exacerbations of IPF Among Adjudicated Respiratory Hospitalizations

End point title	Number of Definite Acute Exacerbations of IPF Among Adjudicated Respiratory Hospitalizations

End point description:

End point type	Secondary

End point timeframe:

Participants in the ITT Analysis Set with adjudicated respiratory hospitalizations were analyzed.

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	84		
Units: Exacerbations per participant year				
number (not applicable)	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Adjudicated Respiratory Hospitalizations (ARP) Among Total Hospitalizations

End point title	Number of Adjudicated Respiratory Hospitalizations (ARP) Among Total Hospitalizations

End point description:

Participants in ITT Analysis Set with total hospitalizations were analyzed.

End point type	Secondary

End point timeframe:

Up to 148 weeks

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	154		
Units: Number of ARP				
number (not applicable)	99	84		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Adjudicated Respiratory Deaths Among Those With Adjudicated Death

End point title	Number of Participants Experiencing Adjudicated Respiratory Deaths Among Those With Adjudicated Death

End point description:

Participants in the ITT Analysis Set with adjudicated deaths were analyzed.

End point type	Secondary

End point timeframe:

Up to 148 weeks

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Participants	17	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in 6 Minute Walk Distance (6MWD)

End point title	Absolute Change From Baseline in 6 Minute Walk Distance (6MWD)

End point description:

- Adjusted means were from MMRM model with baseline 6MWD, FVC % predicted, sLOXL2 level, concomitant pirfenidone/nintedanib use (never vs. ever), treatment, visit, and treatment-by-visit interaction terms, including all data up to Week 130.
- Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Weeks 58, 106, and 130

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	272		
Units: Meters				
least squares mean (standard error)				
Wk 58 (Simtuzumab: N= 95; Placebo: N= 98)	-33.76 (± 6.617)	-14.7 (± 6.596)		
Wk 106 (Simtuzumab: N= 44; Placebo: N= 37)	-37.43 (± 9.71)	-24.3 (± 10.318)		
Wk 58 (Simtuzumab: N= 7; Placebo: N= 9)	-71.2 (± 19.14)	-31.65 (± 18.458)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in St. George's Respiratory Questionnaire (SGRQ) Score

End point title	Absolute Change From Baseline in St. George's Respiratory Questionnaire (SGRQ) Score

End point description:

The SGRQ is a disease-specific questionnaire designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. Patients respond to questions about symptoms (frequency & severity) and impact components (social functioning and psychological disturbances resulting from airways disease). Scores range from 0 to 100, with higher scores indicating more limitations.

End point type	Secondary

End point timeframe:

Week 58, 106, and 130

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	272		
Units: units on a scale				
least squares mean (standard error)				
Wk 58 (Simtuzumab: N = 101; Placebo: N = 104)	6.07 (± 1.015)	3.62 (± 1.01)		
Wk 106 (Simtuzumab: N = 48; Placebo: N = 37)	10.34 (± 1.425)	6.54 (± 1.559)		
Wk 106 (Simtuzumab: N = 10; Placebo: N = 10)	18.1 (± 2.424)	1.08 (± 2.473)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Among the Participants With sLOXL2 ≥ 50th Percentile

End point title	Overall Survival Among the Participants With sLOXL2 ≥ 50th Percentile

End point description:

1) Participants in the ITT Analysis Set with sLOXL2 ≥ 50th percentile in peripheral blood were analyzed.
2) 999 = not reached due to insufficient number of events

End point type	Secondary

End point timeframe:

Up to 151 weeks

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	140		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Statistical analysis - Simtuzumab vs Placebo
Comparison groups	Simtuzumab v Simtuzumab Placebo
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.988
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	2.28

Notes:

[3] - The difference in OS between the treatment groups was assessed using the stratified logrank test, adjusted for screening post-bronchodilator FVC % predicted and concomitant use of pirfenidone or nintedanib (P/N) at time of screening.

Secondary: Overall Survival Among the Participants With sLOXL2 ≥ 75th Percentile	
End point title	Overall Survival Among the Participants With sLOXL2 ≥ 75th Percentile
End point description:	
1) Participants in the ITT Analysis Set with sLOXL2 ≥ 75th percentile in peripheral blood were analyzed. 2) 999 = not reached due to insufficient number of events	
End point type	Secondary
End point timeframe:	
Up to 151 weeks	

End point values	Simtuzumab	Simtuzumab Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	71		
Units: months				
median (confidence interval 95%)	999 (19.2 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	Statistical analysis - Simtuzumab vs Placebo
Comparison groups	Simtuzumab v Simtuzumab Placebo
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.925
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.99

Notes:

[4] - The difference in OS between the treatment groups was assessed using the stratified logrank test, adjusted for screening post-bronchodilator FVC % predicted and concomitant use of pirfenidone or nintedanib (P/N) at time of screening.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 days post last study treatment (up to 148 weeks)

Adverse event reporting additional description:

Safety Analysis Set: included all randomized participants who received at least 1 dose of study drug and was analyzed according to treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Simtuzumab

Reporting group description:

Simtuzumab 125 mg/mL administered subcutaneously once a week

Reporting group title	Simtuzumab Placebo

Reporting group description:

Simtuzumab placebo administered subcutaneously once a week

Serious adverse events	Simtuzumab	Simtuzumab Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 271 (37.27%)	97 / 272 (35.66%)	
number of deaths (all causes)	31	32	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchioloalveolar carcinoma			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metastases to lung			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			

subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	2 / 271 (0.74%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 271 (0.37%)	2 / 272 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Chest discomfort			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 271 (0.74%)	3 / 272 (1.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	6 / 271 (2.21%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cough			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysponea			
subjects affected / exposed	10 / 271 (3.69%)	7 / 272 (2.57%)	
occurrences causally related to treatment / all	1 / 12	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea exertional			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	3 / 271 (1.11%)	2 / 272 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	31 / 271 (11.44%)	35 / 272 (12.87%)	
occurrences causally related to treatment / all	3 / 40	2 / 42	
deaths causally related to treatment / all	1 / 9	0 / 10	
Interstitial lung disease			

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 271 (0.74%)	3 / 272 (1.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 271 (0.37%)	3 / 272 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			

subjects affected / exposed	3 / 271 (1.11%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	5 / 271 (1.85%)	4 / 272 (1.47%)	
occurrences causally related to treatment / all	1 / 5	2 / 4	
deaths causally related to treatment / all	0 / 1	1 / 3	
Tachypnoea			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural stroke			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 271 (1.11%)	5 / 272 (1.84%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Acute right ventricular failure			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	6 / 271 (2.21%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 271 (0.00%)	2 / 272 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 271 (0.37%)	3 / 272 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic inflammatory demyelinating polyradiculoneuropathy			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Polyneuropathy			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 271 (0.74%)	2 / 272 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	2 / 271 (0.74%)	2 / 272 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric venous occlusion			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 271 (0.37%)	2 / 272 (0.74%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 271 (0.00%)	2 / 272 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	4 / 271 (1.48%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic necrosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goodpasture's syndrome			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolysis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 271 (0.74%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 271 (0.00%)	4 / 272 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycetoma mycotic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngitis fungal			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Osteomyelitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	16 / 271 (5.90%)	18 / 272 (6.62%)	
occurrences causally related to treatment / all	0 / 18	0 / 18	
deaths causally related to treatment / all	0 / 3	0 / 4	
Pneumonia klebsiella			

subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory moniliasis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 271 (0.00%)	3 / 272 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 271 (0.37%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 271 (1.11%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	1 / 271 (0.37%)	0 / 272 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 271 (0.00%)	1 / 272 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Simtuzumab	Simtuzumab Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	237 / 271 (87.45%)	246 / 272 (90.44%)	
Investigations			
Weight decreased			
subjects affected / exposed	25 / 271 (9.23%)	24 / 272 (8.82%)	
occurrences (all)	25	26	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 271 (5.54%)	12 / 272 (4.41%)	
occurrences (all)	15	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 271 (11.44%)	26 / 272 (9.56%)	
occurrences (all)	35	32	
Headache			
subjects affected / exposed	32 / 271 (11.81%)	35 / 272 (12.87%)	
occurrences (all)	45	42	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	15 / 271 (5.54%)	17 / 272 (6.25%)	
occurrences (all)	18	18	
Chest pain			
subjects affected / exposed	18 / 271 (6.64%)	16 / 272 (5.88%)	
occurrences (all)	18	16	
Fatigue			
subjects affected / exposed	49 / 271 (18.08%)	48 / 272 (17.65%)	
occurrences (all)	68	54	
Injection site bruising			
subjects affected / exposed	17 / 271 (6.27%)	10 / 272 (3.68%)	
occurrences (all)	19	12	
Pyrexia			
subjects affected / exposed	21 / 271 (7.75%)	12 / 272 (4.41%)	
occurrences (all)	24	12	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	16 / 271 (5.90%)	13 / 272 (4.78%)	
occurrences (all)	20	13	
Diarrhoea			
subjects affected / exposed	44 / 271 (16.24%)	47 / 272 (17.28%)	
occurrences (all)	77	71	
Gastrooesophageal reflux disease			
subjects affected / exposed	21 / 271 (7.75%)	22 / 272 (8.09%)	
occurrences (all)	21	224	
Nausea			
subjects affected / exposed	33 / 271 (12.18%)	35 / 272 (12.87%)	
occurrences (all)	39	43	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	102 / 271 (37.64%)	93 / 272 (34.19%)	
occurrences (all)	134	123	
Dyspnoea			
subjects affected / exposed	98 / 271 (36.16%)	73 / 272 (26.84%)	
occurrences (all)	122	95	
Dyspnoea exertional			

subjects affected / exposed	30 / 271 (11.07%)	29 / 272 (10.66%)	
occurrences (all)	35	32	
Epistaxis			
subjects affected / exposed	16 / 271 (5.90%)	9 / 272 (3.31%)	
occurrences (all)	19	10	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	33 / 271 (12.18%)	27 / 272 (9.93%)	
occurrences (all)	40	32	
Oropharyngeal pain			
subjects affected / exposed	16 / 271 (5.90%)	15 / 272 (5.51%)	
occurrences (all)	22	15	
Productive cough			
subjects affected / exposed	22 / 271 (8.12%)	18 / 272 (6.62%)	
occurrences (all)	28	20	
Rhinorrhoea			
subjects affected / exposed	19 / 271 (7.01%)	15 / 272 (5.51%)	
occurrences (all)	23	16	
Sputum increased			
subjects affected / exposed	14 / 271 (5.17%)	4 / 272 (1.47%)	
occurrences (all)	14	4	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	17 / 271 (6.27%)	8 / 272 (2.94%)	
occurrences (all)	20	9	
Rash			
subjects affected / exposed	22 / 271 (8.12%)	21 / 272 (7.72%)	
occurrences (all)	25	26	
Psychiatric disorders			
Depression			
subjects affected / exposed	14 / 271 (5.17%)	12 / 272 (4.41%)	
occurrences (all)	15	13	
Insomnia			
subjects affected / exposed	15 / 271 (5.54%)	17 / 272 (6.25%)	
occurrences (all)	19	17	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	35 / 271 (12.92%)	22 / 272 (8.09%)	
occurrences (all)	41	27	
Back Pain			
subjects affected / exposed	27 / 271 (9.96%)	28 / 272 (10.29%)	
occurrences (all)	31	36	
Pain in extremity			
subjects affected / exposed	9 / 271 (3.32%)	14 / 272 (5.15%)	
occurrences (all)	13	15	
Infections and infestations			
Bronchitis			
subjects affected / exposed	32 / 271 (11.81%)	39 / 272 (14.34%)	
occurrences (all)	41	53	
Lower respiratory tract congestion			
subjects affected / exposed	8 / 271 (2.95%)	15 / 272 (5.51%)	
occurrences (all)	13	34	
Nasopharyngitis			
subjects affected / exposed	36 / 271 (13.28%)	43 / 272 (15.81%)	
occurrences (all)	44	60	
Respiratory tract infection			
subjects affected / exposed	14 / 271 (5.17%)	17 / 272 (6.25%)	
occurrences (all)	26	23	
Sinusitis			
subjects affected / exposed	16 / 271 (5.90%)	14 / 272 (5.15%)	
occurrences (all)	21	16	
Upper respiratory tract infection			
subjects affected / exposed	57 / 271 (21.03%)	57 / 272 (20.96%)	
occurrences (all)	86	91	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 271 (10.70%)	34 / 272 (12.50%)	
occurrences (all)	31	37	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2013	• Clarification provided on collection time points for RNA biomarker samples • Updated table of contents to include new sections and ensure consistency in page/section numbers • Increased the number of study sites from 120 to 180 to support enrollment • Updated Study drug name from GS-6624 to the international non-proprietary name, simtuzumab • Updated all Gilead Sciences DSPH references for SAE reporting to PRA Safety
11 June 2014	• The primary endpoint was modified to include an additional primary endpoint of progression free survival in subjects with high serum levels of LOXL2 antibody. • Clarification of reversibility to reduce the risk of including subjects with reversible airway disease • Exclusion Criterion was modified to allow enrollment of subjects with certain cancers that have a low risk of reoccurrence. • Exclusion Criterion was updated to include the following text: "Concomitant use of pirfenidone or nintedanib is being allowed, but must be administered in accordance with the approved prescribing instructions in the country where the clinical trial site is located" . • The caps on the moderate and the severe strata were removed. • Revised the timing of the final analysis
03 September 2015	• Study subjects will have the option of continuing in an open-label rollover extension. • Duration of randomized, double-blind, placebo-controlled study was extended for up to 6 months after the accumulation of at least 250 PFS events. • Statistical components of the protocol were updated with respect to the testing strategy and handling of multiple comparisons which are aligned with the approved Statistical Analysis Plan. • Study visit procedures were added for the open-label phase of the study. • Editorial changes were made throughout the protocol, where appropriate, to improve clarity and consistency. • References to "pharmacogenomic" were updated to "genomic testing". • Early Termination visit was revised to be scheduled "approximately 28 days after last dose of IMP". • References to specific study visits at which procedures were performed were removed to avoid any confusion and inconsistencies in the protocol. • Corresponding changes to the protocol body text were also made in the Protocol Synopsis, where appropriate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported