Clinical trial results:
A randomized, open label, controlled, multiple dose study to evaluate the clinical efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of LFG316 in patients with transplant associated microangiopathy after hematopoietic precursor cell transplantation

Summary

EudraCT number	2014-004972-49
Trial protocol	DE FR GB
Global end of trial date	30 June 2017

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification

Sponsor protocol code	CLFG316X2202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02763644
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.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	30 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the hematological response rate in patients with transplant associated microangiopathy (TAM) receiving LFG316 compared to Standard of Care (SoC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	7
EEA total number of subjects	6

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)	6
From 65 to 84 years	1

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Due to low confidence of clinical benefit, this study was closed. In the beginning 3 participants were assigned to LFG316 on top of SoC & 4 subjects to only SoC (so total 7 randomized). 2 were randomized to SoC switched arm to LFG316 plus SoC. This means that 2 SoC and 2 in SoC then LFG316 are the same subjects as All SOC first.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LFG316 plus SoC

Arm description:

LFG316 plus SoC (excluding plasmapheresis and prohibited treatment)

Arm type	Experimental
Investigational medicinal product name	tesidolumab
Investigational medicinal product code	LFG316
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

LFG316 administered weekly as intravenous injection (i.v.) plus standard of care (SoC).

Arm title	All SoC first

Arm description:

Standard of Care then LFG316 plus SoC

Arm type	Experimental
Investigational medicinal product name	tesidolumab
Investigational medicinal product code	LFG316
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard of care (SoC). first then LFG316 administered weekly as intravenous injection (i.v.) plus standard of care (SoC).

Number of subjects in period 1	LFG316 plus SoC	All SoC first
Started	3	4
Completed	0	2
Not completed	3	2
Adverse event, serious fatal	1	1
Adverse event, non-fatal	1	1
Patient/guardian decision	1	-

Baseline characteristics

Reporting groups	
Reporting group title	LFG316 plus SoC
Reporting group description:	
LFG316 plus SoC (excluding plasmapheresis and prohibited treatment)	
Reporting group title	All SoC first
Reporting group description:	
Standard of Care then LFG316 plus SoC	

Reporting group values	LFG316 plus SoC	All SoC first	Total
Number of subjects	3	4	7
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	4	6
From 65-84 years	1	0	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	57.7	43.3	
standard deviation	± 8.50	± 8.54	-
Sex: Female, Male Units: Subjects			
Female	2	1	3
Male	1	3	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	3	3	6
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	LFG316 plus SoC
Reporting group description:	
LFG316 plus SoC (excluding plasmapheresis and prohibited treatment)	
Reporting group title	All SoC first
Reporting group description:	
Standard of Care then LFG316 plus SoC	

Primary: Hematological responder rate at 17 weeks

End point title	Hematological responder rate at 17 weeks[1]
End point description:	
Proportion of study participants achieving a hematological response in schistocytes count (<2/microscopic high power field) and need of TAM-related tranfusion (platelets and erythrocytes) Only seven adult patients were enrolled prior to the early study termination decision. Due to low confidence of clinical benefit, this study was closed. There was too few patients for statistical inference.	
End point type	Primary
End point timeframe:	
17 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to low confidence of clinical benefit, this study was closed. There was too few patients for statistical inference.

End point values	LFG316 plus SoC	All SoC first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: percentage of participants				

Notes:

[2] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

[3] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

Statistical analyses

No statistical analyses for this end point

Secondary: Peak plasma concentration (Cmax) at 52 weeks

End point title	Peak plasma concentration (Cmax) at 52 weeks
End point description:	
Peak plasma concentration (Cmax) Only seven adult patients were enrolled prior to the early study termination decision. Due to low confidence of clinical benefit, this study was closed. There was too few patients for statistical inference.	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	LFG316 plus SoC	All SoC first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: ng/mL				

Notes:

[4] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

[5] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration versus time curve (AUC)

End point title	Area under the plasma concentration versus time curve (AUC)

End point description:

Area under the plasma concentration versus time curve (AUC) Only seven adult patients were enrolled prior to the early study termination decision. Due to low confidence of clinical benefit, this study was closed. There was too few patients for statistical inference.

End point type	Secondary

End point timeframe:

52 weeks

End point values	LFG316 plus SoC	All SoC first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: h*µg/mL				

Notes:

[6] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

[7] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach the maximal concentration (Tmax)

End point title	Time to reach the maximal concentration (Tmax)

End point description:

Time to reach the maximal concentration (Tmax)Only seven adult patients were enrolled prior to the early study termination decision. Due to low confidence of clinical benefit, this study was closed. There was too few patients for statistical inference.

End point type	Secondary

End point timeframe:

52 weeks

End point values	LFG316 plus SoC	All SoC first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: hours				

Notes:

[8] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

[9] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate at 17 weeks

End point title	Complete Response Rate at 17 weeks

End point description:

Complete response rate was planned to be assessed at 17 weeks. However, due to early termination and low sample size the comparison between the two treatment arms LFG316 and SoC was not performed. Only seven adult patients were enrolled prior to the early study termination decision. Due to low confidence of clinical benefit, this study was closed. There was too few patients for statistical inference.

End point type	Secondary

End point timeframe:

17 weeks

End point values	LFG316 plus SoC	All SoC first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Response rate				

Notes:

[10] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

[11] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

Statistical analyses

No statistical analyses for this end point

Secondary: non-relapse mortality

End point title	non-relapse mortality

End point description:

Time to non-relapse-related mortality up to 17 weeks was not assessed due to the paucity of data. Only seven adult patients were enrolled prior to the early study termination decision. Due to low confidence of clinical benefit, this study was closed. There was too few patients for statistical inference.

End point type	Secondary

End point timeframe:

52 weeks

End point values	LFG316 plus SoC	All SoC first		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: number of non-relapse mortality				

Notes:

[12] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

[13] - Due to low confidence of clinical benefit study closed w/too few patients for statistical inference

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

3 patients died during the study,1 patient from the LFG316 only due to sepsis & related to the study drug per Investigator assessment.2 patients who switched from SoC to LFG316 died 5 & 9 days after switching,1 due to respiratory failure &1 due to thrombotic microangiopathy.1 patient the reason for discontinuation was reported as AE not death

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	LFG316

Reporting group description:

LFG316

Reporting group title	Standard of Care (SoC)

Reporting group description:

Standard of Care (SoC)

Reporting group title	SoC then LFG316

Reporting group description:

SoC then LFG316

Reporting group title	All SoC first

Reporting group description:

All SoC first

Serious adverse events	LFG316	Standard of Care (SoC)	SoC then LFG316
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	1 / 2 (50.00%)	2 / 2 (100.00%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (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
Vascular disorders			
Microangiopathy			

subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (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
Immune system disorders			
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft versus host disease in liver			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (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
Graft versus host disease in skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Pulmonary haemorrhage			

subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (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
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (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
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (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
Duodenal ulcer perforation			

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (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
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (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
Cytomegalovirus infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (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
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Serious adverse events	All SoC first		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Microangiopathy			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Graft versus host disease in gastrointestinal tract			

subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Graft versus host disease in liver				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Graft versus host disease in skin				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary haemorrhage				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 4 (25.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Platelet count decreased				
subjects affected / exposed	0 / 4 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Spinal compression fracture				

subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer perforation			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cytomegalovirus infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fungal infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	LFG316	Standard of Care (SoC)	SoC then LFG316
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	2 / 2 (100.00%)	2 / 2 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 3 (66.67%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	4	0	1
Hypotension			
subjects affected / exposed	2 / 3 (66.67%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Orthostatic hypotension			
subjects affected / exposed	1 / 3 (33.33%)	2 / 2 (100.00%)	0 / 2 (0.00%)
occurrences (all)	1	3	0
Peripheral vascular disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Shock			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	2 / 2 (100.00%)	1 / 2 (50.00%)
occurrences (all)	1	5	1
Localised oedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	2 / 3 (66.67%)	2 / 2 (100.00%)	0 / 2 (0.00%)
occurrences (all)	2	6	0
Pyrexia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
occurrences (all)	0	3	1
Immune system disorders			
Graft versus host disease in skin			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 3 (66.67%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	2	2	0
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 2 (100.00%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Epistaxis			
subjects affected / exposed	2 / 3 (66.67%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pleurisy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Pneumothorax			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Psychotic behaviour			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Norovirus test positive			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Cardiomyopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1

Supraventricular tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Tachyarrhythmia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Tinnitus			

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eyelid oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Keratitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Dysphagia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Glossitis			

subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Mouth haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Tongue ulceration			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hepatocellular injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Penile ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Pruritus			

subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	2 / 3 (66.67%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Skin ulcer			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Anuria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Nephrotic syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Intervertebral disc compression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			

subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 3 (66.67%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Myopathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Cytomegalovirus colitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus infection			
subjects affected / exposed	1 / 3 (33.33%)	2 / 2 (100.00%)	0 / 2 (0.00%)
occurrences (all)	1	3	0
Epstein-Barr virus infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Pertussis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	1 / 2 (50.00%)
occurrences (all)	0	1	1
Pneumonia staphylococcal			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Staphylococcal infection			
subjects affected / exposed	1 / 3 (33.33%)	1 / 2 (50.00%)	1 / 2 (50.00%)
occurrences (all)	1	1	1
Streptococcal infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Diabetes mellitus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Fluid retention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 2 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Hypernatraemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	2 / 3 (66.67%)	1 / 2 (50.00%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Hypomagnesaemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Metabolic acidosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	All SoC first		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Orthostatic hypotension			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Peripheral vascular disorder			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Shock			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Fatigue			

subjects affected / exposed occurrences (all) Localised oedema subjects affected / exposed occurrences (all) Non-cardiac chest pain subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 6 0 / 4 (0.00%) 0 1 / 4 (25.00%) 1 2 / 4 (50.00%) 6 2 / 4 (50.00%) 4		
Immune system disorders Graft versus host disease in skin subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Reproductive system and breast disorders Vulvovaginal dryness subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all) Pleurisy	 1 / 4 (25.00%) 2 2 / 4 (50.00%) 2 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		

subjects affected / exposed occurrences (all) Pneumonitis subjects affected / exposed occurrences (all) Pneumothorax subjects affected / exposed occurrences (all) Pulmonary haemorrhage subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1 1 / 4 (25.00%) 2		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all) Psychotic behaviour subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Investigations C-reactive protein increased subjects affected / exposed occurrences (all) Norovirus test positive subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all)	 1 / 4 (25.00%) 1 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0 0 / 4 (0.00%) 0		
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiomyopathy			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Supraventricular tachycardia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Tachyarrhythmia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Tachycardia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sciatica			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Eyelid oedema			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Keratitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Diarrhoea			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Glossitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Mouth haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Tongue ulceration			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

Hepatocellular injury			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Penile ulceration			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Anuria			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nephrotic syndrome			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Urinary incontinence			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc compression			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Myopathy			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Clostridium difficile colitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Cytomegalovirus colitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cytomegalovirus infection			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	3		
Epstein-Barr virus infection			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pertussis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Pneumonia staphylococcal			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Staphylococcal infection			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Streptococcal infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Diabetes mellitus			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Fluid retention			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Hypernatraemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Metabolic acidosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2015	Amendment 1: This amendment implemented FDA comments communicated during the pre-IND meeting that took place on 11 June 2015. -Allow the inclusion of patients ≥12 years old from the beginning of the study. -An interim analysis was to be performed after 5 adult or adolescent patients had been dosed with LFG316 for at least 4 weeks. After a safety assessment by the DMC, patients aged 2 years and older were allowed to be included in the study. -As per request of FDA, an exclusion criterion was added to exclude patients with highly elevated transaminases (liver enzymes). -The design was modified to be adaptive, based on efficacy results of the third interim analysis. -In order to accommodate standard of care in some clinical centers, IVIg, which was previously listed as a prohibited medication, was now allowed in some cases -Inclusion criterion had been expanded to allow patients on new or additional antihypertensive medication since HSCT to join the study even if their blood pressure was not elevated.
11 November 2015	Amendment 2: This amendment implemented comments received from the French Regulatory Authority. - New inclusion was added to confirm that study would enroll recipients of all currently used hematopoietic allograft sources. -Updated to mention the possible risk of anaphylaxis or hypersensitivity reactions that could occur with any therapeutic antibody and that fluids, vasopressors, antihistamines, bronchodilatators, and oxygen should be on hand.
20 January 2016	Amendment 3: This amendment implemented comments received from the FDA and German Regulatory Authority. -Change of history of hypersensitivity to study drug or to drugs of similar chemical classes to: Known hypersensitivity to any constituent of the study medication. -CTCAE (Common Terminology Criteria for Adverse Events) was to be used to categorize and grade adverse events collected in this study. -Inclusion/exclusion criteria were modified as the requirements for male contraception was missing, to clarify the definition for hypertensive patients and to remove exclusion criterion 13 excluding from the study patients with hereditary complement pathway deficiencies. The exclusion criterion 13 has been deleted without replacement. -Details regarding the randomization process were amended for stratified randomization within three, not two, age group strata.
02 May 2016	Amendment 4: This protocol amendment was generated based on the input provided by Investigators from the US and Europe during Investigator Meetings and serves a substantial improvement for the treatment of patients in this study. Main changes included adding more flexible wording in the inclusion criteria for the vaccinations, addition of prophylactic antibiotic in the inclusion criteria, re-wording of the liver and renal safety monitoring sections, and addition of the pharmacogenetics sample that would be specific to recipients of HSCT.

16 August 2016	Amendment 5 : This amendment was generated based on the request of French Health Regulatory Authorities to re-introduce and re-phrase protocol exclusion criterion 13. -Exclusion criterion 1 was re-worded to allow concomitant investigational drug administration after case by case approval from Sponsor -Exclusion criterion 13 was re-introduced to exclude patients with hereditary complement pathway deficiencies. -Requirement for prophylactic antibiotics was removed for patients not receiving LFG316. -It was clarified that collection buccal cell for DNA extraction can be performed anytime during the study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

LFG316, had been studied in seven patients with transplantation-associated microangiopathy. Due to low confidence of clinical benefit, this study was closed.

Notes: