Clinical trial results:
A Phase 2, Multicenter, Double-Blind, Parallel Dosing, Randomized Study of Fresolimumab or Placebo in Patients with Steroid-Resistant Primary Focal Segmental Glomerulosclerosis

Summary

EudraCT number	2012-002365-35
Trial protocol	DE IT ES
Global end of trial date	11 November 2014

Results information

Result version number	v1 (current)
This version publication date	01 May 2016
First version publication date	01 May 2016

Trial information

Trial identification

Sponsor protocol code	DRI12792/ GC1008FSGS03110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01665391
WHO universal trial number (UTN)	U1111-1139-9082

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	17 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the achievement of partial remission (PR) or complete remission (CR) in urinary protein:creatinine ratio (Up/c ratio) and to compare the safety profile of subjects treated with fresolimumab versus placebo.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	36
EEA total number of subjects	10

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	33
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 32 sites in 5 countries. A total of 82 subjects were screened between 29 March 2013 and 23 April 2014, 4 of whom were re-screened and 46 were screen failures. Screen failures were mainly due to violation of inclusion/exclusion criteria.

Pre-assignment

Screening details:

Subjects were stratified by race (Black vs non-Black) and prior calcineurin inhibitor (CNI) therapy (yes, no) at a ratio of 3:3:2 (fresolimumab 1 mg/kg: fresolimumab 4 mg/kg: placebo) using an Interactive Response Technology system.

Period 1

Period 1 title	Treatment 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	Fresolimumab 1 mg/kg

Arm description:

Fresolimumab 1 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Arm type	Experimental
Investigational medicinal product name	Fresolimumab
Investigational medicinal product code	FSGS03110 / GZ402669
Other name	GC1008
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Fresolimumab 1 mg/kg infusion, administered over approximately 30 minutes.

Arm title	Fresolimumab 4 mg/kg

Arm description:

Fresolimumab 4 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Arm type	Experimental
Investigational medicinal product name	Fresolimumab
Investigational medicinal product code	FSGS03110 / GZ402669
Other name	GC1008
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Fresolimumab 4 mg/kg infusion, administered over approximately 30 minutes.

Arm title	Placebo

Arm description:

Placebo (for fresolimumab) administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo (for fresolimumab) infusion, administered over approximately 30 minutes.

Number of subjects in period 1	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo
Started	14	12	10
Completed	14	12	10

Period 2

Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Fresolimumab 1 mg/kg

Arm description:

Fresolimumab 1 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Fresolimumab 4 mg/kg

Arm description:

Fresolimumab 4 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo

Arm description:

Placebo (for fresolimumab) administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo
Started	14	12	10
Completed	14	11	10
Not completed	0	1	0
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Fresolimumab 1 mg/kg
Reporting group description:	
Fresolimumab 1 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	
Reporting group title	Fresolimumab 4 mg/kg
Reporting group description:	
Fresolimumab 4 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	
Reporting group title	Placebo
Reporting group description:	
Placebo (for fresolimumab) administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	

Reporting group values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo
Number of subjects	14	12	10
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 45.08 ± 17.653	 41.03 ± 12.311	 46.77 ± 19.285
Gender categorical Units: Subjects			
Female	7	6	4
Male	7	6	6

Reporting group values	Total		
Number of subjects	36		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	17		
Male	19		

End points

End points reporting groups

Reporting group title	Fresolimumab 1 mg/kg
Reporting group description:	
Fresolimumab 1 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	
Reporting group title	Fresolimumab 4 mg/kg
Reporting group description:	
Fresolimumab 4 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	
Reporting group title	Placebo
Reporting group description:	
Placebo (for fresolimumab) administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	
Reporting group title	Fresolimumab 1 mg/kg
Reporting group description:	
Fresolimumab 1 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	
Reporting group title	Fresolimumab 4 mg/kg
Reporting group description:	
Fresolimumab 4 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	
Reporting group title	Placebo
Reporting group description:	
Placebo (for fresolimumab) administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).	

Primary: Percentage of Subjects Achieving Partial Remission (PR) or Complete Remission (CR) in Urinary Protein: Creatinine Ratio (Up/c ratio) at Day 112

End point title	Percentage of Subjects Achieving Partial Remission (PR) or Complete Remission (CR) in Urinary Protein: Creatinine Ratio (Up/c ratio) at Day 112
End point description:	
PR was defined as a 50% or greater decline in Up/c ratio from baseline to a level between ≥ 0.3 and ≤ 3.0 mg protein/mg creatinine. CR was defined as a decline in Up/c ratio to a level <0.3 mg protein/mg creatinine. Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study drug with at least 1 post-baseline Up/c assessment. Missing data was imputed using last observation carried forward (LOCF).	
End point type	Primary
End point timeframe:	
At Day 112 (LOCF)	

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	10	
Units: Percentage of subjects				
number (not applicable)	14.3	0	0	

Statistical analyses

Statistical analysis title	Fresolimumab 1 mg/kg vs Placebo
Comparison groups	Fresolimumab 1 mg/kg v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.833
Method	Fisher's exact test
Parameter estimate	Treatment Difference
Point estimate	14.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.7
upper limit	52.34

Primary: Overview of Adverse Events

End point title	Overview of Adverse Events[1]

End point description:

An AE was any unfavorable and unintended symptom, sign, disease or condition, or test abnormality whether or not considered related to the study drug. Serious adverse event (SAE) was defined as any of following outcomes: Death, life-threatening event, required prolonged in-patient hospitalization, persistent/significant disability, congenital anomaly, or considered as important medical events. Medical events of interest (MEOIs) included herpes zoster, treatment-emergent skin lesions, bleeding events, cancers and other events deemed of interest by sponsor. Safety set included all randomized subjects who received at least 1 dose of study drug. Treatment-emergent adverse events (TEAEs) were defined as AEs that developed or worsened or became serious during the TEAE period. TEAE period was defined as the time form first infusion of study drug upto 252 days.

End point type	Primary

End point timeframe:

Up to Day 252

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 descriptive nature of endpoint, statistical analysis was not planned.

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	10	
Units: percentage of subjects				
number (not applicable)				
Any TEAE	64.3	91.7	70	
Serious TEAEs	0	25	10	

MEOIs	28.6	33.3	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving CR in Up/c ratio at Day 112

End point title	Percentage of Subjects Achieving CR in Up/c ratio at Day 112

End point description:

CR was defined as a decline in Up/c ratio to a level < 0.3 mg protein/mg creatinine. Analysis was performed on FAS. Missing data was imputed using LOCF.

End point type	Secondary

End point timeframe:

Day 112 (LOCF)

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	10	
Units: Percentage of subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving PR in Up/c ratio at Day 112

End point title	Percentage of Subjects Achieving PR in Up/c ratio at Day 112

End point description:

PR was defined as a 50% or greater decline in Up/c ratio from baseline to a level between ≥ 0.3 and ≤ 3.0 mg protein/mg creatinine. Analysis was performed on FAS. Missing data was imputed using LOCF.

End point type	Secondary

End point timeframe:

Day 112 (LOCF)

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	10	
Units: Percentage of subjects				
number (not applicable)	14.3	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Up/c Ratio at Day 112

End point title	Change From Baseline in Up/c Ratio at Day 112

End point description:

Analysis was performed on full analysis set. Missing data was imputed using LOCF.

End point type	Secondary

End point timeframe:

Baseline, Day 112 (LOCF)

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	10	
Units: mg protein/mg creatinine				
arithmetic mean (standard deviation)	-1.9 (± 2.27)	1 (± 5.39)	-0.1 (± 2.93)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urinary Protein Excretion Rate at Day 112

End point title	Change From Baseline in Urinary Protein Excretion Rate at Day 112

End point description:

Analysis was performed on full analysis set. Missing data was imputed using LOCF.

End point type	Secondary

End point timeframe:

Baseline, Day 112 (LOCF)

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	11	8	
Units: mg per 24hr				
arithmetic mean (standard deviation)	-1637.9 (± 4270.65)	-1716.5 (± 4455.31)	-669.4 (± 10833.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Achievement of PR or CR in Up/c Ratio

End point title	Time to First Achievement of PR or CR in Up/c Ratio

End point description:

Time from the first infusion of the study drug to PR or CR, whichever occurred first. PR was defined as a 50% or greater decline in Up/c ratio from baseline to a level between ≥ 0.3 and ≤ 3.0 mg protein/mg creatinine. CR was defined as a decline in Up/c ratio to a level <0.3 mg protein/mg creatinine. Analysis was performed on full analysis set. In this section, 99999 represents that data not available for median and full range (min-max) in respective arms.

End point type	Secondary

End point timeframe:

From the first infusion of the study drug up to Day 112

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	10	
Units: days				
median (full range (min-max))	78 (21 to 115)	99999 (99999 to 99999)	53 (53 to 53)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) at Day 112

End point title	Change From Baseline in Estimated Glomerular Filtration Rate (eGFR) at Day 112

End point description:

GFR is a measure of the rate at which blood filtered by the kidney. Analysis was performed on full analysis set. Missing data was imputed using LOCF.

End point type	Secondary

End point timeframe:

Baseline, Day 112 (LOCF)

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	10	
Units: mL/min per 1.73 m^2				
arithmetic mean (standard deviation)	-2.8 (± 15.05)	-6.1 (± 18.31)	-9.9 (± 18.07)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving PR or CR with stable eGFR at Day 112

End point title	Percentage of subjects achieving PR or CR with stable eGFR at Day 112

End point description:

Stable eGFR was defined as <35% reduction in eGFR. GFR was measured for the rate at which blood filtered by the kidney. Analysis was performed on full analysis set. Missing data was imputed using LOCF.

End point type	Secondary

End point timeframe:

Day 112 (LOCF)

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	10	
Units: Percentage of subjects				
number (not applicable)	7.1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Fresolimumab Serum Concentration

End point title	Fresolimumab Serum Concentration

End point description:

Analysis was performed on pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of study drug with at least 1 PK sample taken and analysed. In this section, 99999 represents that data not available for mean and standard deviation in respective arms. Here n= number of subjects for each arm.

End point type	Secondary

End point timeframe:

Days 01, 28, 56, 84 (Pre and post infusion); Days 112, 140, 168 and 252

End point values	Fresolimumab 1 mg/kg	Fresolimumab 4 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-infusion day 01 (n=1, n=0)	14.3 (± 99999)	99999 (± 99999)		
Post-infusion day 01 (n=12, n=12)	26034.75 (± 11066.01)	126412.2 (± 49814.84)		
Pre-infusion day 28 (n=14, n=12)	4173.07 (± 6121.266)	5206.67 (± 5382.262)		
Post-infusion day 28 (n=14, n=12)	31209.36 (± 16992.5)	159302.5 (± 38913.64)		
Pre-infusion day 56 (n=14, n=12)	7313.5 (± 12330.26)	7617.58 (± 8217.674)		
Post-infusion day 56 (n=14, n=11)	29591.93 (± 22113.08)	141026.5 (± 24028.76)		
Pre-infusion day 84 (n=14, n=12)	3717 (± 2571.526)	7822.66 (± 7831.148)		
Post-infusion day 84 (n=12, n=09)	34622.42 (± 15074.99)	149286 (± 38668.79)		
Day 112 (n=14, n=11)	2573.48 (± 2520.555)	8530.31 (± 15371.46)		
Day 140 (n=13, n=08)	877.24 (± 1064.762)	1776.49 (± 2256.125)		
Day 168 (n=11, n=07)	354.35 (± 509.894)	871.99 (± 814.182)		
Day 252 (n=05, n=04)	34.84 (± 21.88)	23.19 (± 11.923)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Day 252) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (from first infusion of study drug upto 252 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Fresolimumab 1 mg/kg

Reporting group description:

Fresolimumab 1 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Reporting group title	Placebo

Reporting group description:

Placebo (for Fresolimumab) administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Reporting group title	Fresolimumab 4 mg/kg

Reporting group description:

Fresolimumab 4 mg/kg administered every 28 days up to 112 days (treatment period). Subjects were then followed up to Day 252 (follow up period).

Serious adverse events	Fresolimumab 1 mg/kg	Placebo	Fresolimumab 4 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	3 / 12 (25.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Anastomotic Complication			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Generalised Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large Intestine Perforation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Prolapse			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal Failure Acute			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal Abscess			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic Abscess			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Fresolimumab 1 mg/kg	Placebo	Fresolimumab 4 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)	7 / 10 (70.00%)	11 / 12 (91.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Keratoacanthoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 14 (7.14%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Orthostatic Hypotension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter Site Erythema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Catheter Site Oedema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Chest Discomfort			

subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Generalised Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oedema Peripheral			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Breast Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Penile Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Scrotal Oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Asthmatic Crisis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Dysphonia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Oropharyngeal Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Nasal Congestion			
subjects affected / exposed	2 / 14 (14.29%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Productive Cough			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory Distress			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Investigations			
Blood Pressure Increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Transaminases Increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Ligament Sprain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle Strain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tongue Injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Sinus Tachycardia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ventricular Extrasystoles			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)	1 / 10 (10.00%)	2 / 12 (16.67%)
occurrences (all)	3	1	2
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Leukopenia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Frequent Bowel Movements			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Gingival Bleeding			
subjects affected / exposed	2 / 14 (14.29%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	4	0	4
Haemorrhoids Thrombosed			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Mouth Ulceration			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Actinic Keratosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)	2 / 10 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Rash			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Rash Maculo-Papular			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Pollakiuria			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal Failure Chronic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urine Odour Abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Back Pain			
subjects affected / exposed	2 / 14 (14.29%)	1 / 10 (10.00%)	1 / 12 (8.33%)
occurrences (all)	2	1	3
Muscle Contracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle Spasms			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 10 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Herpes Simplex			
subjects affected / exposed	2 / 14 (14.29%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	1 / 10 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Oral Herpes			

subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumonia Mycoplasmal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 14 (7.14%)	1 / 10 (10.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Viral Infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypervolaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 10 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vitamin D Deficiency			
subjects affected / exposed	1 / 14 (7.14%)	0 / 10 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2012	- Study Follow-up period was extended to Day 252. - Pharmacokinetic parameters to be calculated for this study was expanded. - clarified that the efficacy endpoints will be evaluated at Day 112/ET. - use of immunosuppressive medications including steroids during the Follow-up period. - clarified the blinding procedures. - assessment of height was added. - was to clarify 24-hour urine collections. - was to add the assessment of international normalized ratio. - updated the definition of MEOI - was to specify that only drug-related and protocol-related SAEs and all MEOIs will be collected during the Follow-up - was to reflect changes in company ownership and department name changes
07 August 2013	- That amendment was only for Germany. - Extension of the follow-up observation period following an infusion to 6 hours and to added a follow-up clinic assessment between hours 16 to 24 following the infusion. - Medical instructions for the treatment of allergic reactions was included. - Subjects with non-melanomatous skin cancer within 5 years prior to Visit 1 was excluded. - Contact information was revised of study team to reflect changes in study personnel and corporate organization.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported