Clinical trial results:
A multi-center, randomized, double-blind, placebocontrolled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome

Summary

EudraCT number	2013-004808-19
Trial protocol	GB HU DE
Global end of trial date	29 June 2018

Results information

Result version number	v1 (current)
This version publication date	14 July 2019
First version publication date	14 July 2019

Trial information

Trial identification

Sponsor protocol code	CCFZ533X2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02291029
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	29 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of multiple i.v. infusions of iscalimab in patients with pSS as measured by adverse events (AEs).
To compare the effect of multiple i.v. infusions of iscalimab versus placebo on the clinical disease activity of pSS patients as measured by the change of the European league Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks treatment.

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	22 October 2014
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	Germany: 11
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	69
EEA total number of subjects	50

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)	57
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 69 patients were enrolled in Germany (1 center), Hungary (1 center), Switzerland (1 center), United Kingdom (3 centers), United
States (3 centers)

Pre-assignment

Screening details:

For each patient, there was a screening period from Day -28 to Day -2, followed by baseline evaluations at Day -1.

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, Data analyst

Blinding implementation details:

Cohorts 1 and 2 were double-blind. Cohort 3 was open-label. However, subjects and investigator staff remained blinded to the study treatment allocation (dosing arm) until first dosing.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 CFZ533

Arm description:

CFZ533 3 mg/kg s.c.

Arm type	Experimental
Investigational medicinal product name	CFZ533 s.c. injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

multiple doses of CFZ533 s.c. injection

Arm title	Cohort 1 Placebo

Arm description:

Placebo s.c./CFZ533 3 mg/kg s.c.

Arm type	Placebo
Investigational medicinal product name	Placebo s.c. injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

multiple doses of Placebo s.c. injection

Arm title	Cohort 2 CFZ533

Arm description:

CFZ533 10 mg/kg i.v.

Arm type	Experimental

Investigational medicinal product name	CFZ533 intravenous infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
multiple doses of CFZ533 intravenous infusion

Arm title	Cohort 2 Placebo

Arm description:
Placebo i.v./CFZ533 10 mg/kg i.v.

Arm type	Placebo
Investigational medicinal product name	Placebo intravenous infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
multiple doses of Placebo intravenous infusion

Arm title	Cohort 3 CFZ533 Arm 1

Arm description:
CFZ533 600 mg s.c./CFZ533 300 mg s.c.

Arm type	Experimental
Investigational medicinal product name	CFZ533 s.c. injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
multiple doses of CFZ533 s.c. injection

Arm title	Cohort 3 CFZ533 Arm 2

Arm description:
CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.

Arm type	Experimental
Investigational medicinal product name	CFZ533 s.c. injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
multiple doses of CFZ533 s.c. injection

Investigational medicinal product name	CFZ533 intravenous infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
multiple doses of CFZ533 intravenous infusion

Number of subjects in period 1	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533
Started	8	4	21
Completed	8	3	20
Not completed	0	1	1
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	1	-

Number of subjects in period 1	Cohort 2 Placebo	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2
Started	11	13	12
Completed	11	13	12
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 CFZ533
Reporting group description:	
CFZ533 3 mg/kg s.c.	
Reporting group title	Cohort 1 Placebo
Reporting group description:	
Placebo s.c./CFZ533 3 mg/kg s.c.	
Reporting group title	Cohort 2 CFZ533
Reporting group description:	
CFZ533 10 mg/kg i.v.	
Reporting group title	Cohort 2 Placebo
Reporting group description:	
Placebo i.v./CFZ533 10 mg/kg i.v.	
Reporting group title	Cohort 3 CFZ533 Arm 1
Reporting group description:	
CFZ533 600 mg s.c./CFZ533 300 mg s.c.	
Reporting group title	Cohort 3 CFZ533 Arm 2
Reporting group description:	
CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.	

Reporting group values	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533
Number of subjects	8	4	21
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)	6	4	18
From 65-84 years	2	0	3
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	56.4	48.8	51.7
full range (min-max)	34 to 72	45 to 52	24 to 72
Sex: Female, Male Units: Subjects			
Female	8	4	19
Male	0	0	2
Race/Ethnicity, Customized Units: Subjects			
Caucasian	7	4	18
Asian	1	0	2

Black	0	0	1

Reporting group values	Cohort 2 Placebo	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2
Number of subjects	11	13	12
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)	9	10	10
From 65-84 years	2	3	2
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	50.6	52.3	54.8
full range (min-max)	25 to 69	23 to 74	23 to 68
Sex: Female, Male Units: Subjects			
Female	11	12	10
Male	0	1	2
Race/Ethnicity, Customized Units: Subjects			
Caucasian	10	12	10
Asian	1	1	2
Black	0	0	0

Reporting group values	Total		
Number of subjects	69		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	57		
From 65-84 years	12		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
full range (min-max)	-		

Sex: Female, Male Units: Subjects			
Female	64		
Male	5		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	61		
Asian	7		
Black	1		

End points

End points reporting groups

Reporting group title	Cohort 1 CFZ533
Reporting group description: CFZ533 3 mg/kg s.c.	
Reporting group title	Cohort 1 Placebo
Reporting group description: Placebo s.c./CFZ533 3 mg/kg s.c.	
Reporting group title	Cohort 2 CFZ533
Reporting group description: CFZ533 10 mg/kg i.v.	
Reporting group title	Cohort 2 Placebo
Reporting group description: Placebo i.v./CFZ533 10 mg/kg i.v.	
Reporting group title	Cohort 3 CFZ533 Arm 1
Reporting group description: CFZ533 600 mg s.c./CFZ533 300 mg s.c.	
Reporting group title	Cohort 3 CFZ533 Arm 2
Reporting group description: CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.	

Primary: Change from baseline in EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI)

End point title	Change from baseline in EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI)

End point description:

The effect of CFZ533 on clinical disease activity was measured by the change in ESSDAI (EULAR Sjögren's syndrome disease activity index) between baseline and week 12. The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score (range 0-123). A reduction from baseline indicates improvement in patients.

End point type	Primary

End point timeframe:

12 weeks

End point values	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	4	21	11
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	12.0 (± 3.78)	11.8 (± 3.86)	10.6 (± 4.44)	11.0 (± 5.16)
Week 12	9.6 (± 5.45)	9.8 (± 3.30)	4.2 (± 4.25)	9.7 (± 9.05)
Chage from Baseline to Week 12	-2.4 (± 2.77)	-2.0 (± 2.45)	-6.4 (± 4.00)	-1.3 (± 8.06)

End point values	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	12.7 (± 6.06)	10.4 (± 5.87)		
Week 12	7.2 (± 6.69)	2.8 (± 2.48)		
Chage from Baseline to Week 12	-5.5 (± 5.49)	-7.6 (± 7.14)		

Statistical analyses

Statistical analysis title	Change from baseline in ESSDAI
Comparison groups	Cohort 1 CFZ533 v Cohort 1 Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.397 [1]
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	2.89

Notes:

[1] - One-sided p-value

Statistical analysis title	Change from baseline in ESSDAI
Comparison groups	Cohort 2 CFZ533 v Cohort 2 Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.009 [2]
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-5.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.46
upper limit	-0.96

Notes:

[2] - One-sided p-value

Statistical analysis title	Change from baseline in ESSDAI
Comparison groups	Cohort 3 CFZ533 Arm 1 v Cohort 3 CFZ533 Arm 2
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.344 [3]
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	7.45

Notes:

[3] - two-sided p-value

Secondary: Change from baseline in EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI)

End point title	Change from baseline in EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI)

End point description:

The ESSPRI is a patient self-reported outcome measure to assess dryness, limb pain, fatigue and mental fatigue, where each of the domains normally reported as 0 (not at all) to 10 (extremely severe). The final ESSPRI score is the average of three: dryness, pain and fatigue. A reduction from baseline indicates the improvement of symptoms.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	4	21	11
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	6.75 (± 1.909)	7.00 (± 1.826)	6.71 (± 1.678)	7.18 (± 1.486)
Week 12	5.71 (± 1.240)	7.08 (± 2.251)	5.03 (± 2.413)	6.24 (± 2.039)
Change from Baseline to Week 12	-1.04 (± 1.201)	0.08 (± 0.631)	-1.68 (± 1.954)	-0.94 (± 1.246)

End point values	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	7.00 (± 1.604)	6.00 (± 2.344)		
Week 12	5.33 (± 2.269)	4.83 (± 2.552)		
Change from Baseline to Week 12	-1.67 (± 1.841)	-1.17 (± 2.333)		

Statistical analyses

Statistical analysis title	Change from baseline in ESSPRI
Comparison groups	Cohort 1 CFZ533 v Cohort 1 Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.205
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	0.8

Statistical analysis title	Change from baseline in ESSPRI
Comparison groups	Cohort 2 CFZ533 v Cohort 2 Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.188
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	0.5

Statistical analysis title	Change from baseline in ESSPRI
Comparison groups	Cohort 3 CFZ533 Arm 1 v Cohort 3 CFZ533 Arm 2

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.663
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	1.35

Secondary: Change from baseline in Physician global assessment of the patient's overall disease activity (VAS)

End point title	Change from baseline in Physician global assessment of the patient's overall disease activity (VAS)

End point description:

The visual analogue scale used is a 100 mm VAS ranging from "no disease" (0 mm) to "maximal disease activity" (100 mm).

End point type	Secondary

End point timeframe:

12 weeks

End point values	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	4	21	11
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	57.9 (± 15.72)	57.8 (± 17.19)	51.9 (± 12.62)	47.9 (± 19.18)
Week 12	40.5 (± 16.42)	55.5 (± 12.01)	22.8 (± 11.78)	34.2 (± 13.90)
Change from Baseline to Week 12	-17.6 (± 24.60)	-2.3 (± 10.90)	-28.7 (± 16.02)	-13.7 (± 22.97)

End point values	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	50.4 (± 12.39)	47.1 (± 18.34)		
Week 12	25.4 (± 16.65)	27.3 (± 16.74)		
Change from Baseline to Week 12	-25.0 (± 15.30)	-19.8 (± 21.96)		

Statistical analyses

Statistical analysis title	Change from baseline in VAS
Comparison groups	Cohort 1 CFZ533 v Cohort 1 Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.161
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-15.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.9
upper limit	7.38

Statistical analysis title	Change from baseline in VAS
Comparison groups	Cohort 2 CFZ533 v Cohort 2 Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.017
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-12.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.94
upper limit	-2.38

Secondary: Change from baseline in Patient’s global assessment of their disease activity (VAS)

End point title	Change from baseline in Patient’s global assessment of their disease activity (VAS)

End point description:

The visual analogue scale used is a 100 mm VAS ranging from "no disease" (0 mm) to "maximal disease activity" (100 mm).

End point type	Secondary

End point timeframe:
12 weeks

End point values	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	4	21	11
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	47.13 (± 32.406)	73.00 (± 12.623)	58.43 (± 19.881)	54.91 (± 21.002)
Week 12	49.06 (± 24.519)	75.50 (± 24.393)	34.85 (± 24.564)	42.27 (± 24.483)
Change from Baseline to Week 12	1.94 (± 26.023)	2.50 (± 17.861)	-23.05 (± 26.920)	-12.64 (± 26.871)

End point values	Cohort 3 CFZ533 Arm 1	Cohort 3 CFZ533 Arm 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	63.69 (± 25.799)	52.08 (± 22.138)		
Week 12	38.46 (± 26.965)	53.17 (± 25.305)		
Change from Baseline to Week 12	-25.23 (± 29.833)	1.08 (± 23.283)		

Statistical analyses

Statistical analysis title	Change from baseline in VAS
Comparison groups	Cohort 1 CFZ533 v Cohort 1 Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.456
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-9.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.2
upper limit	17.3

Statistical analysis title	Change from baseline in VAS
Comparison groups	Cohort 2 CFZ533 v Cohort 2 Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.376
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-8.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.67
upper limit	10.39

Secondary: Change from baseline in Short Form (36) Health Survey (SF-36) Physical component score

End point title	Change from baseline in Short Form (36) Health Survey (SF-36) Physical component score[4]

End point description:

The SF-36 is a 36-item, patient self-reported outcome measure (questionnaires) of patient health. The outcome of the questionnaires in eight scales results in two summary scores, physical component and mental component, both ranging from 0 - 100. An increase from baseline in either component summary score indicates reduced disease burden.

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Anylysis not conducted for all arms.

End point values	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	4	21	11
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	42.218 (± 6.9437)	31.215 (± 12.5562)	38.163 (± 8.5905)	38.819 (± 5.9689)
Week 12	40.374 (± 9.2230)	36.123 (± 13.0002)	44.001 (± 9.3943)	40.298 (± 8.9392)
Change from Baseline to Week 12	-1.005 (± 4.5380)	4.908 (± 4.2349)	5.546 (± 7.1760)	1.479 (± 8.2497)

Statistical analyses

Statistical analysis title	Change from baseline in SF-36
Comparison groups	Cohort 1 CFZ533 v Cohort 1 Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.172
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.91
upper limit	2.91

Statistical analysis title	Change from baseline in SF-36
Comparison groups	Cohort 2 CFZ533 v Cohort 2 Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.175
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	3.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	9.48

Secondary: Change from baseline in Short Form (36) Health Survey (SF-36) Mental component score

End point title	Change from baseline in Short Form (36) Health Survey (SF-36) Mental component score[5]

End point description:

The SF-36 is a 36-item, patient self-reported outcome measure (questionnaires) of patient health. The outcome of the questionnaires in eight scales results in two summary scores, physical component and mental component, both ranging from 0 - 100. An increase from baseline in either component summary score indicates reduced disease burden.

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Anylysis not conducted for all arms.

End point values	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	4	21	11
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	46.838 (± 7.8986)	43.118 (± 16.3701)	37.071 (± 12.2914)	39.512 (± 15.4212)
Week 12	48.076 (± 12.5197)	43.660 (± 13.9997)	44.688 (± 10.2469)	43.785 (± 13.2982)
Change from Baseline to Week 12	0.373 (± 6.3174)	0.543 (± 4.0309)	8.212 (± 11.1378)	4.273 (± 10.7671)

Statistical analyses

Statistical analysis title	Change from baseline in SF-36
Comparison groups	Cohort 1 CFZ533 v Cohort 1 Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.986
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.49
upper limit	8.35

Statistical analysis title	Change from baseline in SF-36
Comparison groups	Cohort 2 CFZ533 v Cohort 2 Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.175
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	3.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	9.48

Secondary: Change from baseline in Multidimensional Fatigue Inventory (MFI)	
End point title	Change from baseline in Multidimensional Fatigue Inventory (MFI)[6]

End point description:

The MFI is a patient self-reported outcome measure (questionnaires) to assess fatigue covering the following dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation and Reduced Activity. Each dimension has a posible range from 4-20. The reported total score has a range from 20-100. A reduction from baseline in MFI indicates improvement.

End point type	Secondary

End point timeframe:

12 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Anylysis not conducted for all arms.

End point values	Cohort 1 CFZ533	Cohort 1 Placebo	Cohort 2 CFZ533	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	4	21	11
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	54.1 (± 16.23)	78.0 (± 17.80)	70.0 (± 17.51)	66.2 (± 17.59)
Week 12	53.5 (± 13.96)	69.8 (± 17.75)	55.2 (± 16.65)	63.3 (± 16.99)
Change from Baseline to Week 12	-0.6 (± 8.12)	-8.3 (± 8.18)	-14.5 (± 18.09)	-2.9 (± 12.37)

Statistical analyses

Statistical analysis title	Change from baseline in MFI
Comparison groups	Cohort 1 CFZ533 v Cohort 1 Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.807
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.48
upper limit	13.15

Statistical analysis title	Change from baseline in MFI
Comparison groups	Cohort 2 CFZ533 v Cohort 2 Placebo

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.074
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-9.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.66
upper limit	1.01

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Cohort 1 and 2: 255 days (30 days post study completion) Cohort 3: 171 days (30 days post study completion)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	CFZ533 3 mg/kg s.c.
Reporting group description: CFZ533 3 mg/kg s.c.	
Reporting group title	Placebo s.c./CFZ533 3 mg/kg s.c.
Reporting group description: Placebo s.c./CFZ533 3 mg/kg s.c.	
Reporting group title	CFZ533 10 mg/kg i.v.
Reporting group description: CFZ533 10 mg/kg i.v.	
Reporting group title	Placebo i.v./CFZ533 10 mg/kg i.v.
Reporting group description: Placebo i.v./CFZ533 10 mg/kg i.v.	
Reporting group title	CFZ533 600 mg s.c./CFZ533 300 mg s.c.
Reporting group description: CFZ533 600 mg s.c./CFZ533 300 mg s.c.	
Reporting group title	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Reporting group description: CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.	

Serious adverse events	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 21 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post procedural swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Conjunctivitis bacterial			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post procedural swelling			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (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
Procedural pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (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
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (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			
Conjunctivitis bacterial			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	CFZ533 3 mg/kg s.c.	Placebo s.c./CFZ533 3 mg/kg s.c.	CFZ533 10 mg/kg i.v.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	4 / 4 (100.00%)	11 / 21 (52.38%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal wall neoplasm			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cyst			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Inflammation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Injection site bruising			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Injection site haematoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Injection site reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nodule			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site bruise			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Seasonal allergy			

subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Breast cyst			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Endometrial disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Menstruation irregular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Polymenorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Uterine pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Uterine prolapse			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Allergic sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Asthma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dry throat			

subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hyperventilation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Rhinalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Depression			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Intraocular pressure increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Red blood cells urine positive			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
White blood cells urine positive			

subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	4
Corneal abrasion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Epicondylitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	3
Incision site hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Post procedural swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Procedural dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Procedural nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Procedural pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Spinal compression fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tendon injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tooth fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Carpal tunnel syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Headache			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	2 / 21 (9.52%)
occurrences (all)	0	1	3
Hemianopia homonymous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			

subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Increased tendency to bruise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Lymphadenopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Lymphopenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Deafness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Hypoacusis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Tinnitus			

subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cataract			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Diplopia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Ocular hyperaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Vitreous detachment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Vitreous floaters			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			

subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	1 / 21 (4.76%)
occurrences (all)	1	2	2
Parotid gland enlargement			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Salivary gland enlargement			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Tongue ulceration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 8 (12.50%)	1 / 4 (25.00%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Vomiting			
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	3	0	1
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cutaneous vasculitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dermatitis allergic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Onychoclasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Photosensitivity reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	1 / 21 (4.76%)
occurrences (all)	2	2	1
Rash macular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Rosacea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Arthritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Joint range of motion decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Plantar fasciitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Sjogren's syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Angular cheilitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Bacterial infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Body tinea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Herpes zoster			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Localised infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Lower respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Lymph gland infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nail bed infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Skin infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	2 / 4 (50.00%)	2 / 21 (9.52%)
occurrences (all)	3	2	2
Urinary tract infection			
subjects affected / exposed	2 / 8 (25.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Urogenital infection bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo i.v./CFZ533 10 mg/kg i.v.	CFZ533 600 mg s.c./CFZ533 300 mg	CFZ533 10 mg/kg i.v./CFZ533 300 mg s.c.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 11 (63.64%)	12 / 13 (92.31%)	12 / 12 (100.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal wall neoplasm			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cyst			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Inflammation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Injection site erythema			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Injection site haematoma			
subjects affected / exposed	0 / 11 (0.00%)	2 / 13 (15.38%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Injection site reaction			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nodule			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Non-cardiac chest pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Vessel puncture site bruise			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Breast cyst			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Endometrial disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Menstruation irregular			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Polymenorrhoea			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Uterine pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Uterine prolapse			

subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Allergic sinusitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Asthma			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dry throat			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperventilation			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nasal dryness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Rhinalgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Psychiatric disorders			

Abnormal dreams			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Body temperature increased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
C-reactive protein increased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram abnormal			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Intraocular pressure increased			

subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	2 / 11 (18.18%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Red blood cells urine positive			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
White blood cells urine positive			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Corneal abrasion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Epicondylitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Incision site hypoaesthesia			

subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Post procedural swelling			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Procedural dizziness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Procedural nausea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Spinal compression fracture			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Tendon injury			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 11 (9.09%)	2 / 13 (15.38%)	4 / 12 (33.33%)
occurrences (all)	2	3	5
Hemianopia homonymous			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Increased tendency to bruise			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Lymphopenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Deafness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			

subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Dysphagia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Parotid gland enlargement			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Salivary gland enlargement			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tongue ulceration			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cutaneous vasculitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Onychoclasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Photosensitivity reaction			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pruritus			

subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Rash macular			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rosacea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Arthritis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Joint stiffness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Myalgia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Plantar fasciitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Sjogren's syndrome			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bacterial infection			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Body tinea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Candida infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	3	0

Conjunctivitis viral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lymph gland infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nail bed infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 11 (18.18%)	1 / 13 (7.69%)	4 / 12 (33.33%)
occurrences (all)	2	1	4

Oral herpes			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Otitis media			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 11 (18.18%)	4 / 13 (30.77%)	2 / 12 (16.67%)
occurrences (all)	4	5	3
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Urogenital infection bacterial			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 13 (7.69%) 1	0 / 12 (0.00%) 0
Metabolism and nutrition disorders Appetite disorder subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0
Dehydration subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 13 (7.69%) 1	1 / 12 (8.33%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2014	This amended protocol was developed to incorporate the changes requested by UK Health Authority Medicines and Healthcare Products Regulatory Agency (MHRA).
09 February 2015	This protocol amendment was primarily written to update the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) table based on a published correction where the neurological domain scoring was updated.
05 March 2015	This protocol amendment was developed to provide clarification of the inclusion criterion of stimulated salivary flow to include only patients who have detectable saliva upon stimulation and assessment schedule aligned with complement ESSDAI assessments requirements.
06 August 2015	This protocol amendment was developed to change the dosing regimen of iscalimab. Furthermore, changes in the permitted concomitant medications were made 1) to clarify the use of medications that may potentially cause sicca symptoms and 2) to allow azathioprine in a stable dose.
24 February 2016	The protocol was amended to reflect the use of the new 6 mL ACD-B tubes. This change lead to an increase of the total blood taken from approximately 606 mL to 669 mL for the entire study over 36 weeks.
31 January 2017	This amendment was developed to include an additional cohort of pSS patients (Cohort 3) to explore whether either an i.v. loading dose or an s.c. loading dose, both followed by a s.c. maintenance dose, would be adequate to overcome target mediated disposition and to deliver steady state plasma concentrations similar to the i.v. Cohort 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported