Clinical trial results:
A multiple-dose, subject- and investigator-blinded, placebo-controlled, parallel design study to assess the efficacy, safety, and tolerability of ACZ885 (canakinumab) in pediatric and young adult patients with sickle cell anemia.

Summary

EudraCT number	2016-002101-19
Trial protocol	GB DE
Global end of trial date	27 April 2020

Results information

Result version number	v1 (current)
This version publication date	12 November 2020
First version publication date	12 November 2020

Trial information

Trial identification

Sponsor protocol code	CACZ885X2206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02961218
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to determine the effect of ACZ885 versus placebo on daily pain experienced by SCA subjects.

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:

Subjects were maintained on their pre-existing stable medical regimen for treatment of preexisting medical conditions, including SCA. Common potential concomitant medications in this study population were anticipated to include analgesics and stable hydroxyurea therapy, defined as a hydroxyurea dosing regimen that remained fixed except for any adjustments according to hematologic parameters or other standard of care clinical monitoring.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study was recorded on the concomitant medications/significant non-drug therapies section of the CRF.

Evidence for comparator: -

Actual start date of recruitment	05 April 2017
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	Canada: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Turkey: 21
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	49
EEA total number of subjects	14

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)	4
Adolescents (12-17 years)	28
Adults (18-64 years)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 49 participants were randomized into the study from 15 centers in seven countries: Greater Britain (5), Israel (1), Germany (1), Turkey (3), South Africa (1), USA (3) and Canada (1).

Pre-assignment

Screening details:

Subjects who met the eligibility criteria at screening underwent evaluation of baseline clinical and biomarker assessments prior to first dose administration.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	ACZ885

Arm description:

Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects

Arm title	Placebo

Arm description:

Monthly doses of placebo to match the administered dose of ACZ885 s.c.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Monthly doses of placebo to match the administered dose of canakinumab s.c.

Number of subjects in period 1	ACZ885	Placebo
Started	25	24
Safety analysis set	25	24
Primary PD analysis set	25	24
Completed	22	19
Not completed	3	5
Physician decision	-	2
Subject/Guardian Decision	3	1
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	ACZ885
Reporting group description:	
Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	
Reporting group title	Placebo
Reporting group description:	
Monthly doses of placebo to match the administered dose of ACZ885 s.c.	

Reporting group values	ACZ885	Placebo	Total
Number of subjects	25	24	49
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)	2	2	4
Adolescents (12-17 years)	14	14	28
Adults (18-64 years)	9	8	17
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	15.8	15.6	
standard deviation	± 2.69	± 3.28	-
Sex: Female, Male Units: Participants			
Female	10	11	21
Male	15	13	28
Race/Ethnicity, Customized Units: Subjects			
Black or African American	12	13	25
White	12	10	22
Other	1	1	2

End points

End points reporting groups	
Reporting group title	ACZ885
Reporting group description:	
Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	
Reporting group title	Placebo
Reporting group description:	
Monthly doses of placebo to match the administered dose of ACZ885 s.c.	

Primary: Change from baseline of 4- week average daily pain measured by Visual analog score (VAS) over the period of Week 8 to 12

End point title	Change from baseline of 4- week average daily pain measured by Visual analog score (VAS) over the period of Week 8 to 12
End point description:	
Visual analog scale (VAS) was used to record severity. Pediatric and young adult participants rated their daily sickle cell associated pain intensity once each day in the evening using an 11-point numerical rating scale from 0 to 10 with higher ratings associated with more intense pain (0 = no pain, 10 = worst pain). For each subject, there was a maximum 28-day screening period that included recording of daily pain intensity by e-diary for at least 1 week. The average daily pain results in the screening period were used to derive the baseline value. The average over week 8 to 12 was calculated and the change from baseline in the average daily pain VAS was analyzed using a Bayesian model for repeated measures.	
End point type	Primary
End point timeframe:	
Baseline (upto 28 days prior to start of treatment), Week 8 to 12	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.45 (± 0.384)	-0.37 (± 0.402)		

Statistical analyses

Statistical analysis title	Change in average daily-pain
Comparison groups	ACZ885 v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55 [1]
Method	Bayesian model for repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.07

Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.03
upper limit	0.85
Variability estimate	Standard deviation
Dispersion value	0.57

Notes:

[1] - probability reduction of average pain score in ACZ885 > Placebo

Secondary: Change from baseline of average daily pain VAS over 4 weeks intervals up to Week 24

End point title	Change from baseline of average daily pain VAS over 4 weeks intervals up to Week 24

End point description:

Visual analog scale (VAS) was used to record severity. Pediatric and young adult participants rated their daily sickle cell associated pain intensity once each day in the evening using an 11-point numerical rating scale from 0 to 10 with higher ratings associated with more intense pain (0 = no pain, 10 = worst pain). The average of 4 weeks interval up to week 24 was calculated.

End point type	Secondary

End point timeframe:

Baseline (upto 28 days prior to start of treatment), Week 0 to 4, Week 4 to 8, Week 8 to 12, Week 12 to 16, Week 16 to 20 and Week 20 to 24

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: Score on a scale				
arithmetic mean (standard deviation)				
0-4 Weeks	-0.337 (± 1.629)	0.007 (± 1.428)		
4-8 Weeks	-0.173 (± 1.515)	0.158 (± 1.847)		
8-12 Weeks	-0.444 (± 1.437)	-0.376 (± 2.104)		
12-16 Weeks	-0.505 (± 1.744)	0.057 (± 2.371)		
16-20 Weeks	-0.388 (± 1.772)	0.151 (± 1.811)		
20-24 Weeks	-0.752 (± 1.678)	0.036 (± 2.131)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Concentration of High Sensitivity C-Reactive Protein (hsCRP) from Baseline to Week 12

End point title	Change in the Concentration of High Sensitivity C-Reactive

	Protein (hsCRP) from Baseline to Week 12
End point description:	
hs-CRP is a biomarker that represents the inflammation process.	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: mg/L				
least squares mean (confidence interval 90%)	0.338 (0.237 to 0.483)	0.830 (0.576 to 1.194)		

Statistical analyses

Statistical analysis title	Change in concentration of hsCRP
Comparison groups	ACZ885 v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed-effect Model for Repeated Measures
Parameter estimate	Ratio
Point estimate	0.408
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.253
upper limit	0.658

Secondary: Change in the Concentration of White Blood Cell (WBC) count from baseline to Week 12

End point title	Change in the Concentration of White Blood Cell (WBC) count from baseline to Week 12
End point description:	
WBC count was used as a laboratory marker to determine the effect of the drug	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: 10^9/liter				
least squares mean (confidence interval 90%)	0.813 (0.737 to 0.898)	1.081 (0.973 to 1.201)		

Statistical analyses

Statistical analysis title	Change in concentration of WBC count
Comparison groups	ACZ885 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed-effect Model for Repeated Measures
Parameter estimate	Ratio
Point estimate	0.752
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.657
upper limit	0.862

Secondary: Change in the Concentration of absolute count of neutrophils from baseline to Week 12

End point title	Change in the Concentration of absolute count of neutrophils from baseline to Week 12
End point description:	
Absolute count of neutrophils was measured as a laboratory marker to determine the effect of the drug	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: 10^9/liter				
least squares mean (confidence interval 90%)	0.717 (0.611 to 0.842)	1.052 (0.888 to 1.246)		

Statistical analyses

Statistical analysis title	Change in absolute count of neutrophils
Comparison groups	ACZ885 v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed-effect Model for Repeated Measures
Parameter estimate	Ratio
Point estimate	0.682
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.547
upper limit	0.849

Secondary: Change in the Concentration of absolute count of blood monocytes from baseline to Week 12

End point title	Change in the Concentration of absolute count of blood monocytes from baseline to Week 12
End point description:	
Absolute count of blood monocytes was measured as a laboratory marker to determine the effect of the drug.	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: 10^9/liter				
least squares mean (confidence interval 90%)	0.712 (0.590 to 0.859)	0.992 (0.813 to 1.209)		

Statistical analyses

Statistical analysis title	Change in absolute count of blood monocytes
Comparison groups	ACZ885 v Placebo

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	Mixed-effect Model for Repeated Measures
Parameter estimate	Ratio
Point estimate	0.718
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.556
upper limit	0.925

Secondary: Change in the Concentration of Hemoglobin from baseline to Week 12

End point title	Change in the Concentration of Hemoglobin from baseline to Week 12
End point description:	
Hemoglobin was used as a hemolysis marker to determine the effect of the drug.	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: g/L				
arithmetic mean (standard deviation)	-0.97 (± 4.727)	1.11 (± 7.975)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the reticulocyte count from baseline to Week 12

End point title	Change in the reticulocyte count from baseline to Week 12
End point description:	
Reticulocyte count was used as a hemolysis marker to determine the effect of the drug	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: 10^9/liter				
arithmetic mean (standard deviation)	-6.578 (± 64.1131)	25.358 (± 47.6483)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Concentration of bilirubin from baseline to Week 12

End point title	Change in the Concentration of bilirubin from baseline to Week 12

End point description:

Bilirubin was used as a hemolysis marker to determine the effect of the drug

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: umol/L				
arithmetic mean (standard deviation)	5.05 (± 19.796)	-1.95 (± 11.591)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Concentration of Lactate Dehydrogenase (LDH) from baseline to Week 12

End point title	Change in the Concentration of Lactate Dehydrogenase (LDH) from baseline to Week 12

End point description:

LDH was used as a hemolysis marker to determine the effect of the drug

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)	19.06 (± 70.862)	-33.74 (± 209.259)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Concentration of haptoglobin from baseline to Week 12

End point title	Change in the Concentration of haptoglobin from baseline to Week 12

End point description:

Haptoglobin was used as a hemolysis marker to determine the effect of the drug

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	19		
Units: g/L				
arithmetic mean (standard deviation)	-0.0112 (± 0.04022)	-0.0213 (± 0.07923)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the Concentration of oxygen percent saturation (SAO2) from baseline to Week 12

End point title	Change in the Concentration of oxygen percent saturation (SAO2) from baseline to Week 12

End point description:

SAO2 was used as a hemolysis marker to determine the effect of the drug

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: Oxygen Saturation Percent				
arithmetic mean (standard deviation)	-0.5 (± 2.16)	-0.3 (± 1.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days absent from school or work due to pain as recorded by e-diary

End point title	Number of days absent from school or work due to pain as recorded by e-diary
End point description:	
The number of SCA-related days absent from school or work were derived from eDiary records.	
End point type	Secondary
End point timeframe:	
up to Week 24	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	19		
Units: Days				
arithmetic mean (confidence interval 90%)	2.20 (1.69 to 2.70)	1.86 (1.31 to 2.41)		

Statistical analyses

Statistical analysis title	SCA-related days absent from school/work
Comparison groups	ACZ885 v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.455
Method	Generalized Linear Model (GLM)
Parameter estimate	Ratio
Point estimate	1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.58
upper limit	3.4

Variability estimate	Standard error of the mean
Dispersion value	0.45

Secondary: Mean serum concentration after repeated dosing of ACZ885

End point title	Mean serum concentration after repeated dosing of ACZ885[2]

End point description:

PK samples were collected at Baseline, Week 4, 12, 20 and 24. Mean and standard deviation of the ACZ885 concentration was reported. Only those participants available at the specified time points were analyzed

End point type	Secondary

End point timeframe:

Baseline, Week 4, 12, 20 and 24

Notes:

[2] - 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: Placebo patients were excluded from the PK analyses.

End point values	ACZ885			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)			
Week 4	13100 (± 5490)			
Week 12	18700 (± 5860)			
Week 20	19700 (± 5810)			
Week 24	20600 (± 5930)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment (Week 48) plus 8 weeks post treatment, up to maximum duration of 56 weeks.

Adverse event reporting additional description:

Any sign or symptom collected in the double-blinded period i.e 24 weeks followed by an additional 24-week open label phase (optional). Adverse events were reported separately for the double-blind and the open-label phase.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	ACZ885

Reporting group description:

Double-blind period (Week 0 to 24): Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects

Reporting group title	Placebo

Reporting group description:

Double-blind period (Week 0 to 24): Monthly doses of placebo to match the administered dose of ACZ885 s.c.

Reporting group title	ACZ885 / ACZ885

Reporting group description:

Open label Phase (after Week 24 to Week 56) for the participants originally randomized to ACZ885: Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects

Reporting group title	Placebo / ACZ885

Reporting group description:

Open label Phase (after Week 24 to Week 56) for the participants originally randomized to placebo: Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects

Serious adverse events	ACZ885	Placebo	ACZ885 / ACZ885
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 25 (44.00%)	15 / 24 (62.50%)	11 / 22 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (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
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Headache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Blood and lymphatic system disorders			
Aplasia pure red cell			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sickle cell anaemia with crisis			
subjects affected / exposed	10 / 25 (40.00%)	11 / 24 (45.83%)	9 / 22 (40.91%)
occurrences causally related to treatment / all	0 / 17	0 / 28	0 / 26
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Immune system disorders			
Alloimmunisation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Reproductive system and breast disorders			
Priapism			

subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (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
Respiratory, thoracic and mediastinal disorders			
Acute chest syndrome			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (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
Hypoxia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (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
Rhinitis allergic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (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

Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (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
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (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
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	2 / 22 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (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			
Hypocalcaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			

subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo / ACZ885		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 20 (55.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Aplasia pure red cell			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sickle cell anaemia with crisis			
subjects affected / exposed	10 / 20 (50.00%)		
occurrences causally related to treatment / all	0 / 21		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Alloimmunisation				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Priapism				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholelithiasis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute chest syndrome				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				

subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinitis allergic				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteonecrosis				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Lower respiratory tract infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia mycoplasmal				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Sinusitis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ACZ885	Placebo	ACZ885 / ACZ885
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 25 (76.00%)	20 / 24 (83.33%)	17 / 22 (77.27%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign lymph node neoplasm			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Meningioma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	2 / 25 (8.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	2	3	0
Injection site pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injection site pruritus			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Medical device site irritation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	3 / 22 (13.64%)
occurrences (all)	2	1	3
Pain			
subjects affected / exposed	6 / 25 (24.00%)	5 / 24 (20.83%)	3 / 22 (13.64%)
occurrences (all)	11	11	7
Pyrexia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	2	0	3
Immune system disorders			
Allergy to metals			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Polymenorrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Priapism			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	0	6	0
Respiratory, thoracic and mediastinal disorders			

Acute chest syndrome			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Cough			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Dyspnoea exertional			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Oropharyngeal pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Pharyngeal swelling			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Illness anxiety disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Pica			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Cardiac murmur			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	3	0
Oxygen saturation abnormal			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Spleen palpable			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Ultrasound Doppler abnormal			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Urine albumin/creatinine ratio increased			

subjects affected / exposed	1 / 25 (4.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Vitamin B12 decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Vitamin D decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Soft tissue injury			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Wrist fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Benign enlargement of the subarachnoid spaces			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	5 / 25 (20.00%)	3 / 24 (12.50%)	2 / 22 (9.09%)
occurrences (all)	8	7	3
Lethargy			

subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Spinal cord oedema			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Thrombocytosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	2
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Periorbital oedema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Vision blurred			

subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	1 / 22 (4.55%)
occurrences (all)	0	3	1
Abdominal tenderness			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Gingival bleeding			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Lip swelling			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 25 (4.00%)	2 / 24 (8.33%)	0 / 22 (0.00%)
occurrences (all)	1	2	0

Swollen tongue			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	3	0	1
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Xeroderma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Nephropathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Renal colic			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	2 / 22 (9.09%)
occurrences (all)	4	0	2
Back pain			
subjects affected / exposed	2 / 25 (8.00%)	2 / 24 (8.33%)	2 / 22 (9.09%)
occurrences (all)	3	4	2
Bone infarction			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Degenerative bone disease			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Groin pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Muscle swelling			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			

subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	3	0	0
Myalgia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Osteonecrosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Osteoporosis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	3 / 25 (12.00%)	3 / 24 (12.50%)	0 / 22 (0.00%)
occurrences (all)	7	16	0
Pain in jaw			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Spinal deformity			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1

Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	2	0	1
Oral candidiasis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Otitis media			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Tonsillitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)	5 / 24 (20.83%)	2 / 22 (9.09%)
occurrences (all)	1	7	2
Urinary tract infection			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	2 / 22 (9.09%)
occurrences (all)	2	1	3
Viral infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1

Viral upper respiratory tract infection			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	0 / 22 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Increased appetite			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Vitamin B complex deficiency			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Vitamin B12 deficiency			
subjects affected / exposed	0 / 25 (0.00%)	0 / 24 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 22 (4.55%)
occurrences (all)	0	1	1

Non-serious adverse events	Placebo / ACZ885		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 20 (90.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign lymph node neoplasm			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Meningioma			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injection site pruritus			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Medical device site irritation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	18		
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Allergy to metals			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Polymenorrhoea			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Priapism			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	9		

Respiratory, thoracic and mediastinal disorders			
Acute chest syndrome			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dyspnoea exertional			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pharyngeal swelling			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Illness anxiety disorder			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Pica			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Blood bilirubin increased				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Blood creatine phosphokinase increased				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Blood pressure increased				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Cardiac murmur				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Haemoglobin decreased				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Oxygen saturation abnormal				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Oxygen saturation decreased				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Spleen palpable				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Transaminases increased				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Ultrasound Doppler abnormal				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Urine albumin/creatinine ratio increased				

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Vitamin B12 decreased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Vitamin D decreased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Soft tissue injury			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Wrist fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Benign enlargement of the subarachnoid spaces			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	11		
Lethargy			

subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Migraine subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Spinal cord oedema subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Leukopenia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Neutropenia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Thrombocytosis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Eye disorders			
Eye pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Periorbital oedema subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Vision blurred			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Abdominal tenderness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Gingival bleeding			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Lip swelling			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	4		

Swollen tongue subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Toothache subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Dermatitis contact subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Eczema subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Pruritus subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 3		
Rash subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Urticaria subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Xeroderma subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 3		
Renal and urinary disorders			

Dysuria				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Nephropathy				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Renal colic				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Urinary retention				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Back pain				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	14			
Bone infarction				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Degenerative bone disease				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Flank pain				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Groin pain				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Muscle swelling				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Musculoskeletal pain				

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Osteonecrosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	10		
Pain in jaw			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Spinal deformity			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		

Nasopharyngitis				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Oral candidiasis				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Oral herpes				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Otitis media				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	2			
Tonsillitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Tooth abscess				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	6 / 20 (30.00%)			
occurrences (all)	9			
Urinary tract infection				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	2			
Viral infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences (all)	0			

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Increased appetite subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Vitamin B complex deficiency subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0		
Vitamin B12 deficiency subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2016	The protocol was amended to implement the changes requested by the Medicines and Healthcare Products Regulatory Agency (UK): - The protocol was updated to reflect the contraceptive advice in the Summary of Product Characteristics i.e. Women should use effective contraceptives during treatment and for up to 3 months after the last dose. - Pregnancy testing was performed monthly in sexually active females. Additional changes were implemented to ensure consistency thought the protocol and to add clarifications to some sections.
14 June 2017	The protocol was amended to implement the changes requested by the Food and Drug Administration (FDA) to clarify the stopping rules by applying a threshold of 20% higher SAE rate in the ACZ885 arm compared to placebo arm to identify an overt change in the SAE incidence rate.
09 August 2017	The protocol was amended to improve clarity and update elements of secondary and exploratory outcomes, study design, inclusion/exclusion criteria, stopping rules and data analysis based on study investigators' input and initial trial experience. In addition, total volume requirements for blood sampling were reduced.
03 November 2017	The protocol was amended to implement changes requested by the German Health Authority (Paul Ehrlich Institut) concerning exclusion criteria, study design wording and elements of the data analysis plan.
22 March 2018	The protocol was amended to implement changes to inclusion and exclusion criteria such as expanding age range to 8-20 years to improve the feasibility of study recruitment and implementation – which was based on feedback from Investigators

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported