



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 (\pm 0.384) | -0.37 (\pm 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 |
|-----------------|--|

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 (\pm 70.862) | -33.74 (\pm 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 (\pm 0.04022) | -0.0213 (\pm 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 occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 24 (4.17%) 2 | 0 / 22 (0.00%) 0 |
| Cough subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 22 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 2 | 1 / 22 (4.55%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Pharyngeal swelling subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Psychiatric disorders | | | |
| Bipolar disorder subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Depression subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Illness anxiety disorder subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 22 (0.00%) 0 |
| Pica subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Investigations | | | |

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

| | | | |
|---|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 2 / 24 (8.33%) 2 | 0 / 22 (0.00%) 0 |
| Vitamin B12 decreased subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Vitamin D decreased subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Skin abrasion subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Soft tissue injury subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 22 (0.00%) 0 |
| Wrist fracture subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Nervous system disorders | | | |
| Benign enlargement of the subarachnoid spaces subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Headache subjects affected / exposed occurrences (all) | 5 / 25 (20.00%) 8 | 3 / 24 (12.50%) 7 | 2 / 22 (9.09%) 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 occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 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 occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Toothache subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 1 / 24 (4.17%) 1 | 0 / 22 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all) | 2 / 25 (8.00%) 3 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Dermatitis contact subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 22 (0.00%) 0 |
| Eczema subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Xeroderma subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 0 / 22 (0.00%) 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 occurrences (all) | 2 / 25 (8.00%) 2 | 1 / 24 (4.17%) 1 | 0 / 22 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Increased appetite subjects affected / exposed occurrences (all) | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Vitamin B complex deficiency subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Vitamin B12 deficiency subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 | 1 / 22 (4.55%) 1 |

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|--|---------------------|--|--|
| 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 occurrences (all) | 0 / 20 (0.00%) 0 | | |
| Meningioma subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | | |
| Vascular disorders | | | |
| Venous thrombosis subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 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 | | | |

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

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