NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Canakinumab

Trial Indication(s)

Sickle cell anemia

Protocol Number

CACZ885X2206

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

II

Study Start/End Dates

Study Start Date: April 2017 (Actual)
Primary Completion Date: June 2019 (Actual)

Study Completion Date: April 2020 (Actual)

Reason for Termination (If applicable)

The study was terminated early by Novartis on 24-Feb-2020 after enrollment of 49 subjects, for strategic reasons. Novartis decided that no additional enrollment was needed in order to interpret the study objectives

Study Design/Methodology

This was an ambulatory-based 24-week study followed by an additional 24-week open label phase. It was a subject- and investigator-blinded, randomized, placebo-controlled, parallel group, non-confirmatory study to assess the clinical efficacy of ACZ885 administered s.c. in six injections given 28 days apart (in each phase of the study). Pediatric and young adult subjects diagnosed with sickle cell anemia (SCA) were planned to be randomized to either ACZ885 treatment or placebo treatment in a 1:1 ratio. For each subject, there was a maximum 28-day screening period that included recording of daily pain frequency and intensity by e-diary for at least 1 week. Subjects who met the eligibility criteria at screening underwent evaluation of baseline clinical and biomarker assessments prior to first dose administration.

On Day 1, monthly s.c. dosing with ACZ885 started at 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects. Subjects in the placebo treatment arm were injected with placebo in a like manner. All subjects returned to the study centers for safety checks on a monthly basis when they received treatment with either ACZ885 or placebo. The final blinded dosing was given on Week 20, followed by blinded clinical assessments at Week 24. Subjects from both study arms were then offered optional, open label monthly dosing of ACZ885 for an additional 24 weeks (Weeks 24-48) with clinical outcome assessment.

Subjects returned for the end of study (EOS) visit at Week 56. For subjects who chose not to participate in the optional, open label portion of the study, or for those stopping treatment early for any other reason, an EOS visit occurred approximately 8 weeks after last dose received. After enrollment of 49 subjects, Novartis decided to terminate the study early due to strategic reasons not related to safety and decided that no additional enrollment was needed in order to interpret the study objectives.

Centers

15 centers in 7 countries: Israel(1), United Kingdom(5), Turkey(3), Germany(1), South Africa(1), United States(3), Canada(1)

Objectives:

Primary objective

- To determine the effect of ACZ885 versus placebo on daily pain experienced by SCA subjects

Secondary objectives

- To determine the effect of ACZ885 versus placebo on laboratory markers of inflammation
- To determine the effect of ACZ885 versus placebo on laboratory and functional markers of hemolysis
- To determine the effect of ACZ885 versus placebo on SCA-related days missed from school or work
- To determine the effect of ACZ885 versus placebo on reducing the need for acute blood transfusion
- To determine the pharmacokinetics (PK) of ACZ885 in SCA subjects

Test Product (s), Dose(s), and Mode(s) of Administration

Subjects were assigned to the following treatments:

Double-blind period:

- Monthly doses of 300 mg (4 mg/kg for subjects ≤40 kg) ACZ885 s.c.
- Monthly doses of placebo to match the administered dose of ACZ885 s.c.

Open-label period:

- Monthly doses of 300 mg (4 mg/kg for subjects ≤40 kg) ACZ885 s.c.

Statistical Methods

Analysis of the primary endpoint: The primary endpoint was the reduction from baseline of 4-weekly average daily pain VAS scores for Week 8-12, which were truncated from the time point a subject had received an acute blood transfusion. A Bayesian analysis was

conducted including average daily pain scores up to Week 24 and the differences between the treatment arms were evaluated according to pre-defined criteria.

Analysis of secondary endpoint(s):

Efficacy
- The treatment differences of the average daily pain score at all time points during the double-blind period were reported as estimated in the primary analysis.
- Biomarkers for inflammation and hemolysis, oxygen saturation and the incidences of acute blood transfusions were summarized. Total number of days with absence from work/school during the double-blind period was analyzed applying a negative binomial Generalized Linear model.

Safety
- Adverse events, SAEs and deaths were summarized by period (double-blind and open-label).

Pharmacokinetics
Summary statistics were provided for ACZ885 trough levels.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Male and female subjects ages 8-20 years of age (both inclusive) diagnosed with sickle cell anemia (HbSS) or sickle beta0 thalassemia (documented by family studies, or analysis of either hemoglobin or DNA).
- Patient's written informed consent from those ≥18 years of age must be obtained before any assessment is performed. Parent or legal guardian's written informed consent and child's assent, if appropriate, are required before any assessment is performed for patients < 18 years of age.
- Detectable baseline of background or episodic pain measured by daily e-diary over 1 to 2 weeks during screening period as defined below:
Average daily pain score ≥ 1 cm without analgesic use over a period of at least 7 days and/or, At least one episode of pain requiring analgesic use during a period of up to 14 days.
- History of ≥2 vaso-occlusive pain episodes in the past year, as defined as pain with no other, non-sickle cell identifiable cause that requires analgesia and interferes with the patient's normal daily routine.

Exclusion Criteria:
- History of known hypersensitivity to canakinumab.
- Ongoing or treatment with the past 3 months with red blood cell transfusion therapy, or have evidence of iron overload requiring chelation therapy.
- Transcranial Doppler ultrasound in the past year or at screening in patients with an accessible transtemporal window, demonstrating
velocity in middle or anterior cerebral or internal carotid artery ≥200
cm/sec.
- Administration of any other blood products within 3 weeks of screening visit.

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Overall Study

	ACZ885	Placebo	Total
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.	
Started	25	24	49
Safety analysis set	25	24	49
Pharmacokinetics (PK) analysis set	25	0[1]	25
Primary PD analysis set	25	24	49
Completed	22	19	41
Not Completed	3	5	8

Lost to Follow-up	0	2	2
Physician Decision	0	2	2
Subject/Guardian Decision	3	1	4

[1] Placebo patients were excluded from the PK analyses

Baseline Characteristics

	ACZ885	Placebo	Total
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.	
Number of Participants [units: participants]	25	24	49
Age Continuous (units: Years) Mean ± Standard Deviation			
	15.8±2.69	15.6±3.28	15.7±2.97
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	10	11	21
Male	15	13	28

Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)			
Black or African American	12	13	25
White	12	10	22
Other	1	1	2

Primary Outcome Result(s)

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

(Time Frame: Baseline (upto 28 days prior to start of treatment), Week 8 to 12)

	ACZ885	Placebo
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	25	24
Change from baseline of 4- week average daily pain measured by Visual analog score (VAS) over the period of Week 8 to 12 (units: Score on a scale)		

Mean ± Standard Deviation		
	-0.45 ± 0.384	-0.37 ± 0.402

Statistical Analysis

Groups	ACZ885, Placebo	
P Value	0.55	probability reduction of average pain score in ACZ885 > Placebo
Method	Other Bayesian model for repeated measures	
Mean Difference (Net)	-0.07	Lower limit and upper limit represents the credibility interval from the Bayesian analysis.
Standard Deviation	0.57	
90 % Confidence Interval 2-Sided	-1.03 to 0.85	

Secondary Outcome Result(s)

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

(Time Frame: 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)

	ACZ885	**Placebo**
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300	Monthly doses of placebo to match the administered

	mg for all other subjects	dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	25	24
Change from baseline of average daily pain VAS over 4 weeks intervals up to Week 24 (units: Score on a scale) 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

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

(Time Frame: Baseline, Week 12)

	ACZ885	**Placebo**
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	20	19
Change in the Concentration of High Sensitivity C-Reactive		

Protein (hsCRP) from Baseline to Week 12 (units: mg/L) Geometric Least Squares Mean (90% Confidence Interval)		
	0.338 (0.237 to 0.483)	0.830 (0.576 to 1.194)

Statistical Analysis

Groups	ACZ885, Placebo
P Value	0.002
Method	Other Mixed-effect Model for Repeated Measures
Other Ratio	0.408
90 % Confidence Interval 2-Sided	0.253 to 0.658

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

(Time Frame: Baseline, Week 12)

	ACZ885	**Placebo**
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.

Number of Participants Analyzed [units: participants]	19	17
Change in the Concentration of White Blood Cell (WBC) count from baseline to Week 12 (units: 10^9 cells/liter) Geometric Least Squares Mean (90% Confidence Interval)		
	0.813 (0.737 to 0.898)	1.081 (0.973 to 1.201)

Statistical Analysis

Groups	ACZ885, Placebo
P Value	<.001
Method	Other Mixed-effect Model for Repeated Measures
Other Ratio	0.752
90 % Confidence Interval 2-Sided	0.657 to 0.862

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

(Time Frame: Baseline, Week 12)

	ACZ885	**Placebo**
Arm/Group Description	Monthly doses of 4 mg/kg for subjects	Monthly doses of placebo to match the

	weighing ≤40 kg and 300 mg for all other subjects	administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	19	17
Change in the Concentration of absolute count of neutrophils from baseline to Week 12 (units: 10^9 cells/liter) Geometric Least Squares Mean (90% Confidence Interval)		
	0.717 (0.611 to 0.842)	1.052 (0.888 to 1.246)

Statistical Analysis

Groups	ACZ885, Placebo
P Value	0.004
Method	Other Mixed-effect Model for Repeated Measures
Other Ratio	0.682
90 % Confidence Interval 2-Sided	0.547 to 0.849

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

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	19	17
Change in the Concentration of absolute count of blood monocytes from baseline to Week 12 (units: 10^9 cells/liter) Geometric Least Squares Mean (90% Confidence Interval)		
	0.712 (0.590 to 0.859)	0.992 (0.813 to 1.209)

Statistical Analysis

Groups	ACZ885, Placebo
P Value	0.032
Method	Other Mixed-effect Model for Repeated Measures
Other Ratio	0.718

90 % Confidence Interval 2-Sided	0.556 to 0.925

Change in the Concentration of Hemoglobin from baseline to Week 12

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	19	19
Change in the Concentration of Hemoglobin from baseline to Week 12 (units: g/L) Mean ± Standard Deviation		
	-0.97 ± 4.727	1.11 ± 7.975

Change in the reticulocyte count from baseline to Week 12

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300	Monthly doses of placebo to match the administered

	mg for all other subjects	dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	18	19
Change in the reticulocyte count from baseline to Week 12 (units: 10^9 cells/liter) Mean ± Standard Deviation	-6.578 ± 64.1131	25.358 ± 47.6483

Change in the Concentration of bilirubin from baseline to Week 12

(Time Frame: Baseline, Week 12)

	ACZ885	**Placebo**
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	20	19
Change in the Concentration of bilirubin from baseline to Week 12 (units: umol/L) Mean ± Standard Deviation		

5.05 ± 19.796	-1.95 ± 11.591

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

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	18	19
Change in the Concentration of Lactate Dehydrogenase (LDH) from baseline to Week 12 (units: Units per liter (U/L)) Mean ± Standard Deviation		
	19.06 ± 70.862	-33.74 ± 209.259

Change in the Concentration of haptoglobin from baseline to Week 12

(Time Frame: Baseline, Week 12)

	ACZ885	Placebo
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300	Monthly doses of placebo to match the administered

	mg for all other subjects	dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	13	19
Change in the Concentration of haptoglobin from baseline to Week 12 (units: g/L) Mean ± Standard Deviation		
	-0.0112 ± 0.04022	-0.0213 ± 0.07923

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

(Time Frame: Baseline, Week 12)

	ACZ885	**Placebo**
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	20	19
Change in the Concentration of oxygen percent saturation (SAO2) from baseline to Week 12 (units: Oxygen Saturation Percent)		

Mean ± Standard Deviation		
	-0.5 ± 2.16	-0.3 ± 1.82

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

(Time Frame: up to Week 24)

	ACZ885	**Placebo**
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	22	19
Number of days absent from school or work due to pain as recorded by e-diary (units: Days) Mean (90% Confidence Interval)		
	2.20 (1.69 to 2.70)	1.86 (1.31 to 2.41)

Statistical Analysis

Groups	ACZ885, Placebo
P Value	0.455

Method	Other Generalized Linear Model (GLM)
Other Ratio	1.40
Standard Error of the mean	0.45
90 % Confidence Interval 2-Sided	0.58 to 3.40

Number of acute blood transfusions per patient by study period - Double-blind period

(Time Frame: 12 weeks)

	ACZ885	Placebo
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	Monthly doses of placebo to match the administered dose of ACZ885 s.c.
Number of Participants Analyzed [units: participants]	25	24
Number of acute blood transfusions per patient by study period - Double-blind period (units: Participants) Count of Participants (Not Applicable)		
Overall Acute blood transfusion : 0 transfusions	20 (80%)	18 (75%)
Overall Acute blood transfusion : 1 transfusion	4 (16%)	4 (16.67%)
Overall Acute blood transfusion : 2 transfusions	1 (4%)	1 (4.17%)

Overall Acute blood transfusion : 3 transfusions	0 (%)	1 (4.17%)
Acute blood transfusion: Rescue : 0 transfusions	23 (92%)	19 (79.17%)
Acute blood transfusion: Rescue : 1 transfusion	2 (8%)	4 (16.67%)
Acute blood transfusion: Rescue : 2 transfusions	0 (%)	1 (4.17%)
Acute blood transfusion: Rescue : 3 transfusions	0 (%)	0 (%)
Acute blood transfusion: Prophylactic : 0 transfusions	22 (88%)	22 (91.67%)
Acute blood transfusion: Prophylactic : 1 transfusion	2 (8%)	1 (4.17%)
Acute blood transfusion: Prophylactic : 2 transfusions	1 (4%)	1 (4.17%)
Acute blood transfusion: Prophylactic : 3 transfusions	0 (%)	0 (%)

Mean serum concentration after repeated dosing of ACZ885

(Time Frame: Baseline, Week 4, 12, 20 and 24)

	ACZ885
Arm/Group Description	Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects

Number of Participants Analyzed [units: participants]	25
Mean serum concentration after repeated dosing of ACZ885 (units: ng/mL) Mean ± Standard Deviation	
Baseline	0 ± 0
Week 4	13100 ± 5490
Week 12	18700 ± 5860
Week 20	19700 ± 5810
Week 24	20600 ± 5930

Safety Results

All-Cause Mortality

	ACZ885 N = 25	Placebo N = 24	ACZ885 / ACZ885 N = 22	Placebo / ACZ885 N = 20
Arm/Group Description	Double-blind period (Week 0 to 24): Monthly doses of 4 mg/kg for subjects weighing ≤40 kg and 300	Double-blind period (Week 0 to 24): Monthly doses of placebo to match the administered dose of ACZ885 s.c.	Open label Phase (after Week 24 to Week 56) for the participants originally randomized to ACZ885: Monthly doses	Open label Phase (after Week 24 to Week 56) for the participants originally randomized to placebo: Monthly doses

	mg for all other subjects		of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects	of 4 mg/kg for subjects weighing ≤40 kg and 300 mg for all other subjects
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	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.
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.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment

	ACZ885 N = 25	**Placebo N = 24**	**ACZ885 / ACZ885 N = 22**	**Placebo / ACZ885 N = 20**
Arm/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	Double-blind period (Week 0 to 24): Monthly doses of placebo to match the administered dose of ACZ885 s.c.	Open label Phase (after Week 24 to Week 56) for the participants originally randomized to ACZ885: Monthly doses of 4 mg/kg for subjects	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	weighing ≤40 kg and 300 mg for all other subjects
Total participants affected	11 (44.00%)	15 (62.50%)	11 (50.00%)	11 (55.00%)
Blood and lymphatic system disorders				
Aplasia pure red cell	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Sickle cell anaemia with crisis	10 (40.00%)	11 (45.83%)	9 (40.91%)	10 (50.00%)
General disorders and administration site conditions				
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Pyrexia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Hepatobiliary disorders				
Cholelithiasis	0 (0.00%)	1 (4.17%)	0 (0.00%)	1 (5.00%)
Hyperbilirubinaemia	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Immune system disorders				
Alloimmunisation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Infections and infestations				
Lower respiratory tract infection	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Pneumonia	0 (0.00%)	1 (4.17%)	2 (9.09%)	1 (5.00%)
Pneumonia mycoplasmal	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Sinusitis	0 (0.00%)	1 (4.17%)	1 (4.55%)	0 (0.00%)

Upper respiratory tract infection	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Investigations				
Alanine aminotransferase increased	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders				
Hypocalcaemia	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Hypomagnesaemia	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Osteonecrosis	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Nervous system disorders				
Dizziness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Reproductive system and breast disorders				
Priapism	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Acute chest syndrome	0 (0.00%)	2 (8.33%)	0 (0.00%)	0 (0.00%)
Epistaxis	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoxia	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Pulmonary embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Rhinitis allergic	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	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.
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.
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	ACZ885 N = 25	**Placebo N = 24**	**ACZ885 / ACZ885 N = 22**	**Placebo / ACZ885 N = 20**
Arm/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	Double-blind period (Week 0 to 24): Monthly doses of placebo to match the administered dose of ACZ885 s.c.	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	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
Total participants affected	19 (76.00%)	20 (83.33%)	17 (77.27%)	18 (90.00%)

Blood and lymphatic system disorders				
Anaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Leukopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Neutropenia	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Thrombocytopenia	0 (0.00%)	1 (4.17%)	0 (0.00%)	1 (5.00%)
Thrombocytosis	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Cardiac disorders				
Bradycardia	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders				
Eye pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Ocular hyperaemia	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Periorbital oedema	1 (4.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Vision blurred	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (15.00%)
Abdominal pain upper	0 (0.00%)	2 (8.33%)	1 (4.55%)	1 (5.00%)
Abdominal tenderness	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Constipation	0 (0.00%)	0 (0.00%)	1 (4.55%)	2 (10.00%)
Diarrhoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Dyspepsia	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastritis	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Gingival bleeding	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Haemorrhoids	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)

Lip swelling	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Nausea	1 (4.00%)	2 (8.33%)	0 (0.00%)	2 (10.00%)
Swollen tongue	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Toothache	1 (4.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Vomiting	1 (4.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
General disorders and administration site conditions				
Fatigue	2 (8.00%)	2 (8.33%)	0 (0.00%)	1 (5.00%)
Injection site pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Injection site pruritus	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Medical device site irritation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Non-cardiac chest pain	1 (4.00%)	1 (4.17%)	3 (13.64%)	2 (10.00%)
Pain	6 (24.00%)	5 (20.83%)	3 (13.64%)	7 (35.00%)
Pyrexia	2 (8.00%)	0 (0.00%)	2 (9.09%)	0 (0.00%)
Hepatobiliary disorders				
Cholelithiasis	2 (8.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Immune system disorders				
Allergy to metals	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Infections and infestations				
Conjunctivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Influenza	0 (0.00%)	1 (4.17%)	0 (0.00%)	2 (10.00%)

Lower respiratory tract infection	1 (4.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Nasopharyngitis	2 (8.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Oral candidiasis	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Oral herpes	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Otitis media	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia	1 (4.00%)	1 (4.17%)	0 (0.00%)	1 (5.00%)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Sinusitis	0 (0.00%)	1 (4.17%)	1 (4.55%)	1 (5.00%)
Tonsillitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Tooth abscess	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	1 (4.00%)	5 (20.83%)	2 (9.09%)	6 (30.00%)
Urinary tract infection	2 (8.00%)	1 (4.17%)	2 (9.09%)	1 (5.00%)
Viral infection	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Viral upper respiratory tract infection	2 (8.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications				
Skin abrasion	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Soft tissue injury	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Wrist fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Investigations				
Alanine aminotransferase increased	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)

Blood bilirubin increased	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Blood pressure increased	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Cardiac murmur	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Haemoglobin decreased	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Oxygen saturation abnormal	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Oxygen saturation decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Spleen palpable	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Transaminases increased	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ultrasound Doppler abnormal	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Urine albumin/creatinine ratio increased	1 (4.00%)	2 (8.33%)	0 (0.00%)	0 (0.00%)
Vitamin B12 decreased	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Vitamin D decreased	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
White blood cell count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Metabolism and nutrition disorders				
Dehydration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Increased appetite	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitamin B complex deficiency	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)

Vitamin B12 deficiency	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (10.00%)
Vitamin D deficiency	0 (0.00%)	1 (4.17%)	1 (4.55%)	1 (5.00%)
Musculoskeletal and connective tissue disorders				
Arthralgia	2 (8.00%)	0 (0.00%)	2 (9.09%)	1 (5.00%)
Back pain	2 (8.00%)	2 (8.33%)	2 (9.09%)	5 (25.00%)
Bone infarction	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Degenerative bone disease	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Flank pain	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Groin pain	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Muscle swelling	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal pain	2 (8.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Myalgia	0 (0.00%)	0 (0.00%)	1 (4.55%)	1 (5.00%)
Neck pain	1 (4.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Osteonecrosis	0 (0.00%)	0 (0.00%)	1 (4.55%)	1 (5.00%)
Osteoporosis	1 (4.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Pain in extremity	3 (12.00%)	3 (12.50%)	0 (0.00%)	3 (15.00%)
Pain in jaw	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Spinal deformity	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Benign lymph node neoplasm	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Meningioma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)

Nervous system disorders				
Benign enlargement of the subarachnoid spaces	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Dizziness	1 (4.00%)	0 (0.00%)	1 (4.55%)	2 (10.00%)
Headache	5 (20.00%)	3 (12.50%)	2 (9.09%)	4 (20.00%)
Lethargy	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Migraine	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Spinal cord oedema	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders				
Bipolar disorder	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depression	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Illness anxiety disorder	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Pica	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders				
Dysuria	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nephropathy	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal colic	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary retention	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders				
Dysmenorrhoea	0 (0.00%)	1 (4.17%)	1 (4.55%)	1 (5.00%)
Polymenorrhoea	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Priapism	0 (0.00%)	2 (8.33%)	0 (0.00%)	1 (5.00%)

Respiratory, thoracic and mediastinal disorders				
Acute chest syndrome	1 (4.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Dyspnoea	0 (0.00%)	0 (0.00%)	1 (4.55%)	1 (5.00%)
Dyspnoea exertional	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Epistaxis	0 (0.00%)	1 (4.17%)	1 (4.55%)	1 (5.00%)
Oropharyngeal pain	1 (4.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Pharyngeal swelling	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)
Skin and subcutaneous tissue disorders				
Dermatitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Dermatitis contact	0 (0.00%)	1 (4.17%)	0 (0.00%)	0 (0.00%)
Eczema	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (10.00%)
Rash	1 (4.00%)	0 (0.00%)	0 (0.00%)	1 (5.00%)
Urticaria	1 (4.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Xeroderma	0 (0.00%)	1 (4.17%)	0 (0.00%)	1 (5.00%)
Vascular disorders				
Venous thrombosis	0 (0.00%)	0 (0.00%)	1 (4.55%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

- ACZ885 at 300 mg (or 4mg/kg for body weight ≤40kg) s.c. q4w for up to 48 weeks was well tolerated without any new safety findings in adolescent and young adult patients with sickle cell anemia.
- ACZ885 did not demonstrate significant pain reduction vs placebo according to pre-specified criteria for the primary endpoint.
- ACZ885 did reduce markers of inflammation.
- ACZ885 showed trends towards less fatigue, better sleep and less school/work absences.

Date of Clinical Trial Report

Sep 15, 2020