Clinical trial results:
A randomized, double-blind, placebo controlled, withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2008-005479-82
Trial protocol	ES NO FR HU BE DE SE IT GB DK AT GR Outside EU/EEA
Global end of trial date	12 September 2011

Results information

Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification

Sponsor protocol code	CACZ885G2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000060-PIP02-08
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	12 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a two-part study, the main objective of Part I was to assess the efficacy of canakinumab, in terms if it allowed tapering of maintenance dose of oral steroids in at least 25% of the study subjects and the main objective of Part II was to demonstrate that the time to flare was higher with canakinumab than with placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 July 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	United States: 10

Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Turkey: 12
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Peru: 3
Worldwide total number of subjects	177
EEA total number of subjects	114

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)	1
Children (2-11 years)	128
Adolescents (12-17 years)	42
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 63 centres in 21 countries.

Pre-assignment

Screening details:

A total of 177 subjects were enrolled into Part I open-label period and 100 subjects were enrolled into Part II double-blind withdrawal period.

Period 1

Period 1 title	Part I
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

As the Part I was an open-label period, this section was not applicable.

Arms

Arm title	ACZ885 (Part I)

Arm description:

Subjects received single dose of 4 milligram/kilogram (mg/kg) canakinumab subcutaneous (s.c.) injection every 4 weeks up to maximum of 32 weeks. Part 1 was divided into 4 sub-parts: Part Ia (4 weeks) and Part Ib (4 weeks), subjects were maintained on a stable oral steroid dose (prednisone or equivalent) followed by Part Ic (20 weeks), during which subjects received tapered doses of steroid. In Part Id (4 weeks), subjects again received stable steroid dose.

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

Dosage and administration details:

Single dose of 4 mg/kg canakinumab s.c. injection every 4 weeks up to maximum of 32 weeks.

Number of subjects in period 1	ACZ885 (Part I)
Started	177
Completed	100
Not completed	77
Adverse event, non-fatal	4
Death	1
Unsatisfactory therapeutic effect	72

Period 2

Period 2 title	Part II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

The identity of the canakinumab/placebo treatments were concealed by the use of study drugs in the form of syringes filled with reconstituted canakinumab solutions that were identical in appearance. Unblinding was allowed only in the case of subject emergencies, for Data Monitoring Committee (DMC) interim safety review and when the study was completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	ACZ885 (Part II)

Arm description:

Subjects received 4 mg/kg canakinumab s.c. injection every 4 weeks and remained on stable oral steroid dose for 24 weeks. The maximal total single dose of canakinumab allowed was 300 mg. Any subject who required a dose greater than 150 mg (body weight more than 37.5 kg), received two s.c. injections of canakinumab. Subjects with oral prednisolone dose between 0.2 mg/kg and 0.5 mg/kg and no flare for at least 24 weeks, were allowed to receive tapered doses of prednisolone. If the dose of oral prednisolone was less than or equal to (≤) 0.2 mg/kg, subjects continued to maintain their current dose for the remainder of Part II.

Arm type	Active comparator
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received single dose of 4 mg/kg canakinumab s.c. injection every 4 weeks up to maximum of 75 weeks.

Arm title	Placebo (Part II)

Arm description:

Subjects in Part II were received placebo matching to canakinumab s.c. injection every 4 weeks up to maximum of 75 weeks. Subjects with oral prednisolone dose between 0.2 mg/kg and 0.5 mg/kg and no flare for at least 24 weeks, were allowed to receive tapered doses of prednisolone. If the dose of oral prednisolone was ≤ 0.2 mg/kg, subjects continued to maintain their current dose for the remainder of Part II.

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

Dosage and administration details:

Single dose of placebo matching to canakinumab s.c injection every 4 weeks up to maximum of 75 weeks.

Number of subjects in period 2	ACZ885 (Part II)	Placebo (Part II)
Started	50	50
Completed	39	24
Not completed	11	26
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	4
Unsatisfactory therapeutic effect	11	20
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ACZ885 (Part I)

Reporting group description:

Subjects received single dose of 4 milligram/kilogram (mg/kg) canakinumab subcutaneous (s.c.) injection every 4 weeks up to maximum of 32 weeks. Part 1 was divided into 4 sub-parts: Part Ia (4 weeks) and Part Ib (4 weeks), subjects were maintained on a stable oral steroid dose (prednisone or equivalent) followed by Part Ic (20 weeks), during which subjects received tapered doses of steroid. In Part Id (4 weeks), subjects again received stable steroid dose.

Reporting group values	ACZ885 (Part I)	Total	
Number of subjects	177	177	
Age categorical Units: Subjects			
2 to < 4 years	21	21	
4 to < 6 years	32	32	
6 to < 12 years	76	76	
12 to < 20 years	48	48	
Age continuous Units: years			
arithmetic mean	8.7		
standard deviation	± 4.46	-	
Gender categorical Units: Subjects			
Female	98	98	
Male	79	79	

End points

End points reporting groups

Reporting group title	ACZ885 (Part I)

Reporting group description:

Subjects received single dose of 4 milligram/kilogram (mg/kg) canakinumab subcutaneous (s.c.) injection every 4 weeks up to maximum of 32 weeks. Part 1 was divided into 4 sub-parts: Part Ia (4 weeks) and Part Ib (4 weeks), subjects were maintained on a stable oral steroid dose (prednisone or equivalent) followed by Part Ic (20 weeks), during which subjects received tapered doses of steroid. In Part Id (4 weeks), subjects again received stable steroid dose.

Reporting group title	ACZ885 (Part II)

Reporting group description:

Subjects received 4 mg/kg canakinumab s.c. injection every 4 weeks and remained on stable oral steroid dose for 24 weeks. The maximal total single dose of canakinumab allowed was 300 mg. Any subject who required a dose greater than 150 mg (body weight more than 37.5 kg), received two s.c. injections of canakinumab. Subjects with oral prednisolone dose between 0.2 mg/kg and 0.5 mg/kg and no flare for at least 24 weeks, were allowed to receive tapered doses of prednisolone. If the dose of oral prednisolone was less than or equal to (≤) 0.2 mg/kg, subjects continued to maintain their current dose for the remainder of Part II.

Reporting group title	Placebo (Part II)

Reporting group description:

Subjects in Part II were received placebo matching to canakinumab s.c. injection every 4 weeks up to maximum of 75 weeks. Subjects with oral prednisolone dose between 0.2 mg/kg and 0.5 mg/kg and no flare for at least 24 weeks, were allowed to receive tapered doses of prednisolone. If the dose of oral prednisolone was ≤ 0.2 mg/kg, subjects continued to maintain their current dose for the remainder of Part II.

Primary: Percentage of subjects able to taper oral steroid use from the start of Part I to end of Part Ic

End point title	Percentage of subjects able to taper oral steroid use from the start of Part I to end of Part Ic[1]

End point description:

The ability to taper oral steroids was defined as if dose was reduced from start of Part I to end of Part Ic from >0.8 mg/kg/day to ≤ 0.5 mg/kg/day, or from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day by at least 0.3 mg/kg, or from any initial dose to ≤ 0.2 mg/kg/day, while maintaining a minimum adapted ACR 30 paediatric criterion (defined as improvement from baseline of ≥ 30% in at least 3 of the first 6 response variables of adapted ACR paediatric criteria; no intermittent fever in the preceding week and no more than one of the first 6 response variables worsening by more than 30%). Subjects on oral steroids at study entry who did not enter Part 1c were considered steroid tapering failures. The analysis was performed in full analysis set (FAS) population, defined as all subjects who received at least one dose of study drug in Part I.

End point type	Primary

End point timeframe:

Day 1 up to Week 28

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	128			
Units: percentage of subjects				
number (confidence interval 90%)	44.5 (37.1 to 52.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to disease flare in Part II

End point title	Time to disease flare in Part II

End point description:

Disease flare was defined if at least one of following criteria was met: 1.Reappearance of fever(>38°C,lasting for at least 2 consecutive days) not due to infections, 2.Flare according to adapted ACR paediatric criteria such as ≥ 30% worsening in at least 3 of first 6 response variables and ≥ 30% improvement in not more than 1 of first 6 response variables. The worsening of response variables was further defined as worsening of ≥20 millimetres(mm) in physician or parent global assessment, worsening in mobility of at least 2 joints and serum C-reactive protein(CRP) level to be more than 30 milligrams/litres(mg/L). Kaplan Meier estimate was used to analyze probability to experience a flare in subject. Flare Analysis was done in FAS II population, defined as all subjects who received at least one dose of study drug in Part II. Here, 99999.9 represents not estimable data becasue EudraCT system is not accepting "NA" for not available/not estimable data.

End point type	Primary

End point timeframe:

Week 32 up to Week 88 (maximum of 37 flare events)

End point values	ACZ885 (Part II)	Placebo (Part II)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[2]	50		
Units: Days				
median (confidence interval 95%)	99999.9 (99999.9 to 99999.9)	236 (141 to 449)		

Notes:

[2] - As only 11 events occurred in this arm, median and 95% confidence interval could not be estimated.

Statistical analyses

Statistical analysis title	Time to disease flare in Part II

Statistical analysis description:

Log-rank test adjusted for stratification factors prednisone (or equivalent) dose and adapted ACR 70 Paediatric response reached at the end of Part Id as covariates.

Comparison groups	Placebo (Part II) v ACZ885 (Part II)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0032 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.36

Confidence interval	
level	95 %
sides	1-sided
upper limit	0.75

Notes:

[3] - Statistically significant on onesided significance level 0.025.

Secondary: Percentage of subjects who reached a steroid dose ≤0.2 mg/kg at end of Part Ic

End point title	Percentage of subjects who reached a steroid dose ≤0.2 mg/kg at end of Part Ic

End point description:

Successful steroid tapering was achieved if dose was reduced from start of Part Ic to end of Part Ic from >0.8 mg/kg/day to ≤ 0.5 mg/kg/day, or from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day by at least 0.3 mg/kg, or from any initial dose to ≤ 0.2 mg/kg/day, while maintaining a minimum adapted ACR 30 paediatric criterion. Subjects who were steroid free or who had an oral steroid dose at a level of >0 mg/kg and ≤ 0.2 mg/kg at the end of Part Ic were determined. The analysis was performed in FAS I population.

End point type	Secondary

End point timeframe:

Day 1 up to Week 28

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	92			
Units: percentage of subjects				
number (confidence interval 95%)				
steroid free	45.7 (35.2 to 56.4)			
> 0 mg/kg and ≤ 0.2 mg/kg	26.1 (17.5 to 36.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects on steroids at the start of 1c who were able to taper steroids by the end of part 1c

End point title	Percentage of subjects on steroids at the start of 1c who were able to taper steroids by the end of part 1c

End point description:

Successful steroid tapering was achieved if dose was reduced from start of Part Ic to end of Part Ic from >0.8 mg/kg/day to ≤ 0.5 mg/kg/day, or from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day by at least 0.3 mg/kg, or from any initial dose to ≤ 0.2 mg/kg/day, while maintaining a minimum adapted ACR 30 paediatric criterion. The analysis was performed in FAS I population, where missing values were imputed using Last observation carried forward (LOCF) technique.

End point type	Secondary

End point timeframe:

Week 8 up to Week 28

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percentage of subjects				
number (not applicable)				
>0 and ≤ 0.2 mg/kg/day Steroid free	21 71.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in oral steroid dose in successful steroid taperers at end of Part Ic

End point title	Change from baseline in oral steroid dose in successful steroid taperers at end of Part Ic

End point description:

Successful steroid tapering was achieved if dose was reduced from start of Part Ic to end of Part Ic from >0.8 mg/kg/day to ≤ 0.5 mg/kg/day, or from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day by at least 0.3 mg/kg, or from any initial dose to ≤ 0.2 mg/kg/day, while maintaining a minimum adapted ACR 30 paediatric criterion. Change from baseline was calculated by using the formula = (end of Part Ic value - baseline value). The analysis was performed in FAS I population.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: mg/kg/day				
arithmetic mean (standard deviation)	-0.299 (± 0.2412)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who achieved minimum response of American College of Rheumatology (ACR) pediatric 30/50/70/90/100 criteria at the end of

Part I

End point title	Percentage of subjects who achieved minimum response of American College of Rheumatology (ACR) pediatric 30/50/70/90/100 criteria at the end of Part I

End point description:

Adapted ACR Paediatric 30/50/70/90 or 100 criteria was assessed based on following 7 variables: 1.Physician's Global Assessment on a 0-100 millimetres (mm) visual analog scale (VAS); 2.Patient Global Assessment on a 0-100 mm VAS in the Child Health Assessment Questionnaire (CHAQ); 3.Functional ability; 4.Joints count with active arthritis; 5.Joints count with limitation of motion; 6.Laboratory measure of C-reactive protein (CRP) and 7.Absence of intermittent fever due to sJIA during the preceding week. Response was defined as more than or equal to (≥) 30%/50%/70%/90% or 100% improvement in at least 3 of the response variables 1 to 6, no intermittent fever (i.e. body temperature ≤ 38°C) in the preceding week (variable 7) and with no more than one variable 1-6 worsening by more than 30%. The analysis was done in FAS I papulation. Here 'Number of subjects analysed' signifies number of subjects with an ACR assessment at the given visit.

End point type	Secondary

End point timeframe:

Week 32

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	175			
Units: percentage of subjects				
number (not applicable)				
Non-Responders	22.9			
ACR 30	77.1			
ACR 50	73.1			
ACR 70	64.6			
ACR 90	51.4			
ACR 100	34.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with normal body temperature at Day 3

End point title	Percentage of subjects with normal body temperature at Day 3

End point description:

Subjects who had body temperature of less than or equal to 38 degree Celsius were counted. Body temperature was derived from vital signs evaluation and normal body temperature indicated treatment response. The analysis was performed on FAS I population.

End point type	Secondary

End point timeframe:

Day 3

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percentage of subjects				
number (confidence interval 95%)	98.6 (95 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to adapted American College of Rheumatology (ACR) pediatric 50 criteria and normal C – Reactive Protein (CRP) during Part I

End point title	Time to adapted American College of Rheumatology (ACR) pediatric 50 criteria and normal C – Reactive Protein (CRP) during Part I

End point description:

Adapted ACR response was defined as more than or equal to (≥) 50% improvement in at least 3 of the response variables 1 to 6, no intermittent fever (i.e. body temperature ≤ 38°C) in the preceding week (variable 7) and with no more than one variable 1-6 worsening by more than 30%. Duration in days in the study to the first minimum adapted ACR Paediatric 50 criteria and a normal (<10 mg/L) CRP was determined. The analysis was performed in FAS I population.

End point type	Secondary

End point timeframe:

Day 1 up to Week 32

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: Days				
arithmetic mean (standard deviation)	20.4 (± 8.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to adapted American College of Rheumatology (ACR) pediatric 70 criteria and normal C – Reactive Protein (CRP) during Part I

End point title	Time to adapted American College of Rheumatology (ACR) pediatric 70 criteria and normal C – Reactive Protein (CRP) during Part I

End point description:

Adapted ACR response was defined as more than or equal to (≥) 70% improvement in at least 3 of the response variables 1 to 6, no intermittent fever (i.e. body temperature ≤ 38°C) in the preceding week (variable 7) and with no more than one variable 1-6 worsening by more than 30%. Duration in days in the study to the first minimum adapted ACR Paediatric 70 criteria and a normal (<10 mg/L) CRP was determined. The analysis was performed in FAS I population.

End point type	Secondary

End point timeframe:

Day 1 up to Week 32

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Days				
arithmetic mean (standard deviation)	24.5 (± 21.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in disability score assessed with the Child Health Assessment Questionnaire -Disability index (CHAQ-DI) to end of Part I

End point title	Change from baseline in disability score assessed with the Child Health Assessment Questionnaire -Disability index (CHAQ-DI) to end of Part I

End point description:

The CHAQ was used to assess physical ability and functional status of subjects as well as quality of life. The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and other "activities". Parents were choosen from four response categories, ranging from 0 (without any difficulty) to 3(unable to do). Change from baseline was calculated by using the formula = (post-baseline value – baseline value). A negative change indicates improvement. The analysis was performed in FAS I population.

End point type	Secondary

End point timeframe:

Baseline, Week 32 (End of Part 1)

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	175			
Units: Units on a scale				
median (full range (min-max))	-0.875 (-2.875 to 1.125)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Health Related Quality of Life (HRQoL) assessed by Child Health Questionnaire Parent Form (CHQ-PF50) to end of Part I

End point title	Change from baseline in Health Related Quality of Life (HRQoL) assessed by Child Health Questionnaire Parent Form (CHQ-PF50) to end of Part I

End point description:

The Child Health Questionnaire – Parent Form (CHQ-PF50) instrument was used to measure HRQoL aged 5 to 18 years from a parent's perspective. This 14-concept questionnaire measured physical and psychosocial health of the subjects on following points: physical functioning, role/social emotional, role/social behavior, role/social physical, bodily pain, general behavior, mental health, self-esteem, general health perception, change in health, parental impact – emotional, parental impact – time, family activities, and family cohesion. Total score ranged from 0-100. Increase in score represented improvement in overall well-being of subjects. Change from baseline was calculated by using the formula = (post-baseline value – baseline value). The analysis was performed in FAS I population.

End point type	Secondary

End point timeframe:

Baseline, Week 32 (End of Part 1)

End point values	ACZ885 (Part I)			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: Units on a scale				
median (full range (min-max))				
CHQ-PF50 physical health score	21.805 (-21.554 to 62.309)			
CHQ-PF50 psychosocial score	8.2223 (-21.71 to 38.854)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to a worsening in American College of Rheumatology (ACR) response during Part II

End point title	Time to a worsening in American College of Rheumatology (ACR) response during Part II

End point description:

Adapted ACR Paediatric criteria was assessed based on following 7 variables: 1.Physician's Global Assessment on a 0-100 millimetres (mm) visual analog scale (VAS); 2.Patient Global Assessment on a 0-100 mm VAS in the Child Health Assessment Questionnaire (CHAQ); 3.Functional ability; 4.Joints count with active arthritis; 5.Joints count with limitation of motion; 6.Laboratory measure of CRP and 7.Absence of intermittent fever due to sJIA during the preceding week. Kaplan Meier estimate was utilized to analyze the time in days to the probability of worsening of the ACR response in subject. The analysis was performed in FAS II population. Here, 99999.9 represents not estimable data becasue EudraCT system is not accepting "NA" for not available/not estimable data.

End point type	Secondary

End point timeframe:

Week 32 up to Week 88 (maximum of 37 flare events)

End point values	ACZ885 (Part II)	Placebo (Part II)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[4]	50		
Units: Days				
median (confidence interval 95%)	99999.9 (171 to 99999.9)	141 (85 to 281)		

Notes:

[4] - As only 18 events occurred in this arm, median and upper 95% confidence interval was not estimated.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in disability from Week 32 assessed with the Child Health Assessment Questionnaire-Disability Index (CHAQ-DI) to end of Part II

End point title	Change in disability from Week 32 assessed with the Child Health Assessment Questionnaire-Disability Index (CHAQ-DI) to end of Part II

End point description:

The CHAQ was used to assess physical ability and functional status of subjects as well as quality of life. The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and other "activities". Parents were choosen from four response categories, ranging from 0 (without any difficulty) to 3(unable to do). Change from baseline was calculated by using the formula = (post-baseline value – baseline value). A negative change indicates improvement. The analysis was performed in FAS II population.

End point type	Secondary

End point timeframe:

Week 32 (start of Part II), Week 88 (end of Part II)

End point values	ACZ885 (Part II)	Placebo (Part II)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Units on a scale				
least squares mean (standard error)	0.1184 (± 0.17592)	0.1258 (± 0.18241)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Health Related Quality of Life (HRQoL) assessed by Child Health Questionnaire Parent Form (CHQ-PF50) to end of Part II

End point title	Change from baseline in Health Related Quality of Life (HRQoL)

	assessed by Child Health Questionnaire Parent Form (CHQ-PF50) to end of Part II

End point description:

The Child Health Questionnaire – Parent Form (CHQ-PF50) instrument was used to measure HRQoL aged 5 to 18 years from a parent's perspective. This 14-concept questionnaire measured physical and psychosocial health of the subjects on following points: physical functioning, role/social emotional, role/social behavior, role/social physical, bodily pain, general behavior, mental health, self-esteem, general health perception, change in health, parental impact – emotional, parental impact – time, family activities, and family cohesion. Total score ranged from 0-100. Increase in score represented improvement in overall well-being of subjects. Change from baseline was calculated by using the formula = (post-baseline value – baseline value). The analysis was performed in FAS II population.

End point type	Secondary

End point timeframe:

Week 32 (start of Part II), Week 88 (end of Part II)

End point values	ACZ885 (Part II)	Placebo (Part II)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: Units on a scale				
least squares mean (standard error)				
CHQ-PF50 physical health score	3.9 (± 2.54)	0.3 (± 2.53)		
CHQ-PF50 psychosocial health score	2.5 (± 1.88)	0.5 (± 1.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), AEs leading to discontinuation, serious adverse events (SAEs), SAEs leading to discontinuation and death

End point title	Number of subjects with adverse events (AEs), AEs leading to discontinuation, serious adverse events (SAEs), SAEs leading to discontinuation and death

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. Treatment related AEs or SAEs were defined as AEs or SAEs that were suspected to be related to study treatment as per investigator. The analysis was performed in safety set I (SS I) population and SS II population defined as, all subject who received at least one dose of study drug and had at least one post-treatment safety assessment in Part I and Part II respecively.

End point type	Secondary

End point timeframe:

Baseline (start of study treatment) up to Week 88 (End of Part II)

End point values	ACZ885 (Part I)	ACZ885 (Part II)	Placebo (Part II)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	177	50	50	
Units: Number of subjects				
AEs	138	40	35	
SAEs	15	6	6	
Deaths	1	0	0	
Discontinuation due to any AE including SAE(s)	5	0	6	
Discontinuation due to SAEs	5	0	3	
Discontinuation due to non-serious AEs	0	0	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-ACZ885 antibodies at any visit

End point title	Number of subjects with anti-ACZ885 antibodies at any visit

End point description:

Immunogenicity was analyzed by using a bridging ELISA method. Anti-ACZ885 antibodies were captured in solution by combination of biotinylated and ruthenium-labeled forms of ACZ885. Complex formation was subsequently detected by Electro Chemi Luminescence using a Mesoscale Discovery streptavidin plate. The analysis was performed in safety set I (SS I) population and SS II population.

End point type	Secondary

End point timeframe:

Baseline up to Week 88 (End of Part II)

End point values	ACZ885 (Part I)	ACZ885 (Part II)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	50		
Units: Number of subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of Canakinumab

End point title	Serum concentrations of Canakinumab

End point description:

Canakinumab concentrations were assessed in serum. The analysis was performed in FAS I population and FAS II population.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 3, Day 15, Day 29, Day 57, Week 32, Week 88

End point values	ACZ885 (Part I)	ACZ885 (Part II)	Placebo (Part II)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	47	13	
Units: micrograms/millilitres				
arithmetic mean (standard deviation)	20.114 (± 11.3115)	35.098 (± 14.1822)	6.386 (± 6.5006)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration of total Interleukin-1 beta antibody (IL-1)

End point title	Serum concentration of total Interleukin-1 beta antibody (IL-1)

End point description:

Pharmacodynamics of canakinumab was assessed by total IL-1β (sum of free and bound canakinumab) concentration, determined in serum by means of competitive ELISA assay. The analysis was performed in FAS I population and FAS II population.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 3, Day 15, Day 29, Day 57, Week 32, Week 88

End point values	ACZ885 (Part I)	ACZ885 (Part II)	Placebo (Part II)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	46	12	
Units: picograms/millilitres				
arithmetic mean (standard deviation)	58.753 (± 58.1004)	56.99 (± 63.6162)	25.073 (± 23.5487)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Part 1 ACZ885
Reporting group description:	
Part 1 ACZ885	
Reporting group title	Part 2 Placebo
Reporting group description:	
Part 2 Placebo	
Reporting group title	Part 2 ACZ885
Reporting group description:	
Part 2 ACZ885	

Serious adverse events	Part 1 ACZ885	Part 2 Placebo	Part 2 ACZ885
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 177 (8.47%)	6 / 50 (12.00%)	6 / 50 (12.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Histiocytosis haematophagic			
subjects affected / exposed	4 / 177 (2.26%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic neoplasm malignancy unspecified			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Medical device complication			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Pyrexia			
subjects affected / exposed	3 / 177 (1.69%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperventilation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Interstitial lung disease			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung consolidation			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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

Pulmonary hypertension			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 177 (1.13%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulation test abnormal			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haptoglobin decreased			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatic enzyme increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serum ferritin increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (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

Post procedural haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Paraesthesia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Somnolence			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Lymphadenopathy			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 177 (1.13%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Diarrhoea			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Nausea			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Oral disorder			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (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
Vomiting			
subjects affected / exposed	2 / 177 (1.13%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Hepatitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (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
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Arthritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Juvenile arthritis			
subjects affected / exposed	2 / 177 (1.13%)	2 / 50 (4.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			

subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Adenovirus infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Gastroenteritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Gastrointestinal infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Gastrointestinal viral infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Lobar pneumonia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Lymph node abscess			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Measles			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (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
Otitis media			

subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 50 (0.00%)	0 / 50 (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
Pneumonia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 177 (0.00%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1 ACZ885	Part 2 Placebo	Part 2 ACZ885
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 177 (57.06%)	25 / 50 (50.00%)	36 / 50 (72.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 177 (12.43%)	3 / 50 (6.00%)	3 / 50 (6.00%)
occurrences (all)	40	22	5
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	16 / 177 (9.04%)	5 / 50 (10.00%)	7 / 50 (14.00%)
occurrences (all)	24	6	8
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 177 (0.00%)	4 / 50 (8.00%)	2 / 50 (4.00%)
occurrences (all)	0	4	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 177 (8.47%)	4 / 50 (8.00%)	6 / 50 (12.00%)
occurrences (all)	17	5	14
Diarrhoea			
subjects affected / exposed	16 / 177 (9.04%)	3 / 50 (6.00%)	1 / 50 (2.00%)
occurrences (all)	22	4	7
Nausea			
subjects affected / exposed	8 / 177 (4.52%)	1 / 50 (2.00%)	3 / 50 (6.00%)
occurrences (all)	11	1	3
Vomiting			
subjects affected / exposed	17 / 177 (9.60%)	4 / 50 (8.00%)	1 / 50 (2.00%)
occurrences (all)	21	4	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 177 (11.30%)	6 / 50 (12.00%)	8 / 50 (16.00%)
occurrences (all)	23	6	9
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	9 / 177 (5.08%)	1 / 50 (2.00%)	3 / 50 (6.00%)
occurrences (all)	9	2	3
Pruritus			
subjects affected / exposed	0 / 177 (0.00%)	3 / 50 (6.00%)	2 / 50 (4.00%)
occurrences (all)	0	3	3
Urticaria			
subjects affected / exposed	1 / 177 (0.56%)	2 / 50 (4.00%)	4 / 50 (8.00%)
occurrences (all)	1	2	4
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	9 / 177 (5.08%)	5 / 50 (10.00%)	12 / 50 (24.00%)
occurrences (all)	13	5	17
Musculoskeletal pain			
subjects affected / exposed	2 / 177 (1.13%)	0 / 50 (0.00%)	4 / 50 (8.00%)
occurrences (all)	2	0	6
Pain in extremity			
subjects affected / exposed	7 / 177 (3.95%)	4 / 50 (8.00%)	5 / 50 (10.00%)
occurrences (all)	8	4	6
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	13 / 177 (7.34%)	1 / 50 (2.00%)	1 / 50 (2.00%)
occurrences (all)	14	2	1
Nasopharyngitis			
subjects affected / exposed	27 / 177 (15.25%)	7 / 50 (14.00%)	7 / 50 (14.00%)
occurrences (all)	37	14	11
Oral herpes			
subjects affected / exposed	3 / 177 (1.69%)	0 / 50 (0.00%)	4 / 50 (8.00%)
occurrences (all)	5	0	5
Rhinitis			
subjects affected / exposed	17 / 177 (9.60%)	7 / 50 (14.00%)	5 / 50 (10.00%)
occurrences (all)	21	15	6
Tinea pedis			
subjects affected / exposed	0 / 177 (0.00%)	0 / 50 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	4
Upper respiratory tract infection			
subjects affected / exposed	18 / 177 (10.17%)	5 / 50 (10.00%)	6 / 50 (12.00%)
occurrences (all)	24	5	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2009	Modified the criteria for which a subject discontinued due to flare in Part I, to that of not achieved ACR30 response or not maintained a minimum ACR30 response and the stable steroid dose level that allowed a subject to taper off steroids after 24 weeks in Part II was lowered to a threshold of > 0.2 mg/kg/day. The entry criteria for rollover subjects from the CACZ885G2305 and CACZ885A2203 studies was changed so that the requirement of intermittent fever and CRP > 30 mg/L was not applicable.
22 September 2009	Changes done to ensure subjects from the study CACZ885A2203 could continue to receive continuous treatment in subsequent phase III studies provided that the subject did not meet the discontinuation criteria of CACZ885A2203 or the safety discontinuation criteria of CACZ885G2301.
03 November 2009	Modified the study procedures in order to replace "absence of fever" in the secondary objectives with "body temperature ≤ 38°C"; to ensure that subjects were on a stable dose of corticosteroids for at least 3 days prior to baseline; clarified the transition of CACZ885G2305 placebo subjects to the CACZ885G2301 study if they did not maintain a minimum ACR30 response between Days 15 and 29; and clarified the handling of CACZ885A2203 rollover subjects when there was a gap of at least 6 months between the subject's last dose in CACZ885A2203 and entry into CACZ885G2301.
19 January 2010	Modified the study procedures for the subjects who were doing well clinically, to avoid unnecessary exposure to higher steroid doses.
03 January 2011	Modified the criteria to describe the implementation of an adjudication committee for macrophage activation syndrome (MAS) and follow-up to be conducted on MAS cases identified during the study.
23 May 2011	Modified the criteria to introduce the possibility performing an interim analysis and adjusted the statistical hypothesis in the statistical methods section for Part I to be fully aligned with the objective.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: