Clinical trial results:
An open-label extension study of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations who participated in studies ACZ885G2301 and ACZ885G2305;and response characterization study in canakinumab treatment-naïve patients with active SJIA with and without fever

Summary

EudraCT number	2008-008008-42
Trial protocol	NO FR ES HU BE DE NL SE IT GB DK GR AT Outside EU/EEA
Global end of trial date	10 December 2014

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	CACZ885G2301E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00891046
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	10 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate long-term safety, tolerability and immunogenicity of canakinumab treated subjects with inactive Systemic Juvenile Idiopathic Arthritis (SJIA), rolled over from CACZ885G2301 (EudraCT number: 2008-005479-82) and CACZ885G2305 (EudraCT number: 2008-005476-27) and canakinumab naive subjects with active SJIA.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 September 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	Canada: 14
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Greece: 8
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Peru: 3
Country: Number of subjects enrolled	Brazil: 9

Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Russian Federation: 16
Worldwide total number of subjects	270
EEA total number of subjects	174

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)	188
Adolescents (12-17 years)	70
Adults (18-64 years)	12
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 71 centres in 20 countries.

Pre-assignment

Screening details:

A total of 147 subjects from studies CACZ885G2301 (EudraCT number: 2008-005479-82) and CACZ885G2305 (EudraCT number: 2008-005476-27) and 123 canakinumab treatment-naive subjects were enrolled into this extension study.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was open-label, and hence blinding was not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	ACZ885 treated: Group 1 (Discontinued from core study)

Arm description:

Subjects who discontinued from CACZ885G2301 study due to flares, non response or any other reason - Part II (EudraCT number: 2008-005479-82), received a subcutaneous (s.c.) injection of canakinumab 4 mg/kg every 4 weeks unless discontinuation occurs.

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

Dosage and administration details:

Canakinumab (2 mg/kg or 4 mg/kg) s.c. injection was administered every 4 weeks.

Arm title	ACZ885 treated: Group 2 (Completed core study)

Arm description:

Subjects who completed study CACZ885G2301 - Part II (EudraCT number: 2008-005479-82), received an s.c. injection of canakinumab 4 mg/kg every 4 weeks.

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

Dosage and administration details:

Canakinumab (2 mg/kg or 4 mg/kg) s.c. injection was administered every 4 weeks.

Arm title	ACZ885 treated: Group 3 (Steroid taper failures in core study)

Arm description:

Subjects who failed to taper their steroid dose in CACZ885G2301 Study - Part I (EudraCT number: 2008-005479-82); received an s.c. injection of canakinumab 4 mg/kg every 4 weeks.

Arm type	Experimental

Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Canakinumab (2 mg/kg or 4 mg/kg) s.c. injection was administered every 4 weeks.

Arm title	ACZ885 treated: Group 4 (Other criteria)

Arm description:

Subjects who previously received canakinumab treatment in Studies CACZ885G2301 (EudraCT number: 2008-005479-82) and CACZ885G2305 (EudraCT number: 2008-005476-27), but did not fulfill the criteria for Group 1, 2 or 3, received a s.c. injection of canakinumab 4 mg/kg every 4 weeks.

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

Dosage and administration details:

Canakinumab (2 mg/kg or 4 mg/kg) s.c. injection was administered every 4 weeks.

Arm title	ACZ885 treatment naive

Arm description:

Subjects who were canakinumab treatment-naïve and did not participate in previous canakinumab studies, received a s.c. injection of canakinumab 4 mg/kg every 4 weeks.

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

Dosage and administration details:

Canakinumab (2 mg/kg or 4 mg/kg) s.c. injection was administered every 4 weeks.

Number of subjects in period 1	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)
Started	33	63	40
Completed	21	54	17
Not completed	12	9	23
Consent withdrawn by subject	2	1	2
Adverse event, non-fatal	4	3	2
Unsatisfactory therapeutic effect	5	-	19
Subject's condition no longer required study drug	-	2	-
Administrative problems	-	-	-
Unsatisfatory therapeutic effect	-	2	-
Lost to follow-up	-	-	-

Protocol deviation	1	1	-

Number of subjects in period 1	ACZ885 treated: Group 4 (Other criteria)	ACZ885 treatment naive
Started	11	123
Completed	8	84
Not completed	3	39
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	14
Unsatisfactory therapeutic effect	2	20
Subject's condition no longer required study drug	-	1
Administrative problems	-	1
Unsatisfatory therapeutic effect	-	-
Lost to follow-up	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	ACZ885 treated: Group 1 (Discontinued from core study)
Reporting group description:	
Subjects who discontinued from CACZ885G2301 study due to flares, non response or any other reason - Part II (EudraCT number: 2008-005479-82), received a subcutaneous (s.c.) injection of canakinumab 4 mg/kg every 4 weeks unless discontinuation occurs.	
Reporting group title	ACZ885 treated: Group 2 (Completed core study)
Reporting group description:	
Subjects who completed study CACZ885G2301 - Part II (EudraCT number: 2008-005479-82), received an s.c. injection of canakinumab 4 mg/kg every 4 weeks.	
Reporting group title	ACZ885 treated: Group 3 (Steroid taper failures in core study)
Reporting group description:	
Subjects who failed to taper their steroid dose in CACZ885G2301 Study - Part I (EudraCT number: 2008-005479-82); received an s.c. injection of canakinumab 4 mg/kg every 4 weeks.	
Reporting group title	ACZ885 treated: Group 4 (Other criteria)
Reporting group description:	
Subjects who previously received canakinumab treatment in Studies CACZ885G2301 (EudraCT number: 2008-005479-82) and CACZ885G2305 (EudraCT number: 2008-005476-27), but did not fulfill the criteria for Group 1, 2 or 3, received a s.c. injection of canakinumab 4 mg/kg every 4 weeks.	
Reporting group title	ACZ885 treatment naive
Reporting group description:	
Subjects who were canakinumab treatment-naïve and did not participate in previous canakinumab studies, received a s.c. injection of canakinumab 4 mg/kg every 4 weeks.	

Reporting group values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)
Number of subjects	33	63	40
Age categorical Units: Subjects			
2 - <4 years	0	2	3
4 - <6 years	6	10	6
6 - <12 years	16	32	21
12 - <20 years	11	17	10
≥ 20 years	0	2	0
Age continuous Units: years			
arithmetic mean	9.8	9.9	9.1
standard deviation	± 4.25	± 4.66	± 4.35
Gender categorical Units: Subjects			
Female	19	34	23
Male	14	29	17

Reporting group values	ACZ885 treated: Group 4 (Other criteria)	ACZ885 treatment naive	Total
Number of subjects	11	123	270

Age categorical Units: Subjects			
2 - <4 years	1	18	24
4 - <6 years	5	15	42
6 - <12 years	3	50	122
12 - <20 years	2	40	80
≥ 20 years	0	0	2
Age continuous Units: years			
arithmetic mean	7.8	9	
standard deviation	± 4.77	± 4.52	-
Gender categorical Units: Subjects			
Female	5	75	156
Male	6	48	114

End points

End points reporting groups

Reporting group title	ACZ885 treated: Group 1 (Discontinued from core study)

Reporting group description:

Subjects who discontinued from CACZ885G2301 study due to flares, non response or any other reason - Part II (EudraCT number: 2008-005479-82), received a subcutaneous (s.c.) injection of canakinumab 4 mg/kg every 4 weeks unless discontinuation occurs.

Reporting group title	ACZ885 treated: Group 2 (Completed core study)

Reporting group description:

Subjects who completed study CACZ885G2301 - Part II (EudraCT number: 2008-005479-82), received an s.c. injection of canakinumab 4 mg/kg every 4 weeks.

Reporting group title	ACZ885 treated: Group 3 (Steroid taper failures in core study)

Reporting group description:

Subjects who failed to taper their steroid dose in CACZ885G2301 Study - Part I (EudraCT number: 2008-005479-82); received an s.c. injection of canakinumab 4 mg/kg every 4 weeks.

Reporting group title	ACZ885 treated: Group 4 (Other criteria)

Reporting group description:

Subjects who previously received canakinumab treatment in Studies CACZ885G2301 (EudraCT number: 2008-005479-82) and CACZ885G2305 (EudraCT number: 2008-005476-27), but did not fulfill the criteria for Group 1, 2 or 3, received a s.c. injection of canakinumab 4 mg/kg every 4 weeks.

Reporting group title	ACZ885 treatment naive

Reporting group description:

Subjects who were canakinumab treatment-naïve and did not participate in previous canakinumab studies, received a s.c. injection of canakinumab 4 mg/kg every 4 weeks.

Subject analysis set title	ACZ885 treated
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who were responsive to canakinumab in previous studies: CACZ885G2301 (EudraCT number: 2008-005479-82) and CACZ885G2305 (EudraCT number: 2008-005476-27) and entered into this extension study in Group 1, 2, 3 and 4.

Subject analysis set title	Male subjects aged 6-20 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Male subjects (age lying in following categories: 6-9 years, 9-11 years and 11-20 years) who received a s.c. injection of canakinumab 4 mg/kg every 4 weeks during the study.

Subject analysis set title	Female subjects aged 6-20 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Female subjects (age lying in following categories: 6-9 years, 9-11 years and 11-20 years) who received a s.c. injection of canakinumab 4 mg/kg every 4 weeks during the study.

Primary: Number of subjects with adverse events (AEs), treatment related AEs, AEs leading to discontinuation, AEs by severity, serious adverse events (SAEs), SAEs leading to discontinuation

End point title	Number of subjects with adverse events (AEs), treatment related AEs, AEs leading to discontinuation, AEs by severity, serious adverse events (SAEs), SAEs leading to discontinuation[1][2]

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, defined as all subjects who received at least one dose of study drug.

End point type	Primary

End point timeframe:

From start of study treatment (Day 1) to end of follow-up period (Week 271)

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 primary outcome measure.

[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: The end point is reporting pooled data for Group 1, 2, 3 and 4 in 'ACZ treated' arm.

End point values	ACZ885 treatment naive	ACZ885 treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	123	147		
Units: Subjects				
number (not applicable)				
AEs	108	137		
SAEs	40	47		
Discontinuation due to any AE	14	18		
Discontinuation due to any SAE	13	14		
Treatment Related AEs	44	57		
Treatment related SAEs	1	4		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with anti-ACZ885 antibodies at any visit during the study

End point title	Number of subjects with anti-ACZ885 antibodies at any visit during the study[3][4]

End point description:

Immunogenicity assessment included determination of anti-canakinumab (ACZ885) antibodies in serum samples using BIAcore system. The analysis was performed on the FAS population.

End point type	Primary

End point timeframe:

From start of study treatment (Day 1) to end of follow--up period (Week 271)

Notes:

[3] - 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 primary outcome measure.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The end point is reporting pooled data for Group 1, 2, 3 and 4 in 'ACZ treated' arm.

End point values	ACZ885 treatment naive	ACZ885 treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	123	147		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically significant local injection site reactions during the study

End point title	Number of subjects with clinically significant local injection site reactions during the study[5][6]

End point description:

Local injection site tolerability was assessed on the injection site. Each subject was classified into one of the following four categories: 1. no tolerability reactions at any time during the study, 2. mild reaction observed on at least one occasion but no moderate or severe reactions. 3. moderate reaction observed on at least one occasion but no severe reaction. 4. severe reaction observed on at least one occasion. The analysis was performed in SS population.

End point type	Primary

End point timeframe:

From start of study treatment (Day 1) to end of follow--up period (Week 271)

Notes:

[5] - 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: The end point is reporting pooled data for Group 1, 2, 3 and 4 in 'ACZ treated' arm.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive summary statistics was planned for this primary outcome measure.

End point values	ACZ885 treatment naive	ACZ885 treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	123	147		
Units: subjects				
No tolerability reaction	115	129		
Mild tolerability reaction	6	15		
Moderate tolerability reaction	2	3		
Severe tolerability reaction	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of non-responders at end of prior study who achieved minimum response of American College of Rheumatology (ACR) pediatric 30/50/70/90/100 criteria at end of the present study

End point title	Percentage of non-responders at end of prior study who

	achieved minimum response of American College of Rheumatology (ACR) pediatric 30/50/70/90/100 criteria at end of the present study[7]

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; 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 severe juvenile idiopathic arthritis (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 temperatureless than or equal to (≤) 38 degree celsius [°C]) in the preceding week (variable 7) and with no more than one variable 1 to -6, worsening by more than 30%. The analysis was done in FAS population. Here 'Number of subjects analysed' signifies number of subjects with an ACR assessment at the given visit.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV) or date of discontinuation, which ever occurred earlier

Notes:

[7] - 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: The ACR pediatric scores was collected for subjects who met the minimum of ACR criteria at baseline in 'ACZ treated' cohort i.e. Group 1, 2, 3 and 4.

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	0[8]	17	6
Units: percentage of subjects				
number (not applicable)				
ACR ≥30 criteria	82.4		76.5	83.3
ACR ≥ 50 criteria	82.4		70.6	83.3
ACR ≥ 70 criteria	82.4		52.9	83.3
ACR ≥ 90 criteria	76.5		23.5	50
ACR 100 criteria	58.8		17.6	50

Notes:

[8] - No subject was analyzed in this group.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with minimum adapted ACR pediatric ≥ 30 at baseline who achieved minimum response of ACR pediatric 30/50/70/90/100 criteria at last assessment of study

End point title	Percentage of subjects with minimum adapted ACR pediatric ≥ 30 at baseline who achieved minimum response of ACR pediatric 30/50/70/90/100 criteria at last assessment of study[9]

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 mm VAS; 2. Patient Global Assessment on a 0-100 mm VAS; 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. Response was defined as ≥ 30%/50%/70%/90% or 100% improvement in at least 3 of the response variables 1 to 6, no intermittent fever in the preceding week (variable 7) and with no more than one

variable 1 to 6 worsening by more than 30%. For minimum adapted ACR paediatric scores, the last measurement recorded from the subject's previous study was considered baseline for the current study. The analysis was done in FAS population. Here 'Number of subjects analysed' signifies number of subjects with an ACR assessment at the given visit.

End point type	Secondary

End point timeframe:

Baseline up to last assessment or date of discontinuation, which ever occurred earlier

Notes:

[9] - 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: The ACR pediatric scores was collected for subjects who met the minimum of ACR 30 criteria at baseline in 'ACZ treated' cohort i.e. Group 1, 2, 3 and 4.

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	63	23	5
Units: percentage of subjects				
number (not applicable)				
ACR ≥ 30	100	100	91.3	100
ACR ≥ 50	100	100	87	100
ACR ≥ 70	100	100	78.3	100
ACR ≥ 90	100	100	69.6	100
ACR 100	87.5	93.7	39.1	80

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects able to taper oral steroid use or reached steroid free regimen

End point title	Percentage of subjects able to taper oral steroid use or reached steroid free regimen

End point description:

Steroid tapering with oral steroids was allowed if the subject achieved an adapted ACR Paediatric 50 response and had no fever. A subject was considered to have tapered steroids successfully, if the steroid dose was reduced from baseline and the subject did not flare and maintained a minimum adapted ACR Paediatric 30 at the last measurement. A subject was considered to have unsuccessfully tapered steroids if the steroid dose was reduced during the study but dose at last assessment was equal to or greater than dose at baseline or; if steroid dose was reduced but the subject did not maintain a minimum adapted ACR Paediatric 30 at the last measurement. The analysis was done in FAS population. Here 'Number of subjects analysed' signifies number of subjects who were steroid users at baseline.

End point type	Secondary

End point timeframe:

Baseline up to last assessment or date of discontinuation, which ever occurred earlier

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	63	40	11
Units: percentage of subjects				
number (not applicable)				
Steroid free (n = 11,9,38,8,71)	36.4	55.6	23.7	25
Successfully tapered (n = 11,9,38,8,71)	27.3	0	21.1	25
Unsuccessfully tapered (n = 11,9,38,8,71)	18.2	22.2	18.4	25
Not tapered (n = 11,9,38,8,71)	18.2	22.2	36.8	25

End point values	ACZ885 treatment naive			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: percentage of subjects				
number (not applicable)				
Steroid free (n = 11,9,38,8,71)	33.8			
Successfully tapered (n = 11,9,38,8,71)	23.9			
Unsuccessfully tapered (n = 11,9,38,8,71)	11.3			
Not tapered (n = 11,9,38,8,71)	31			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who reduced their canakinumab dose to 2 mg/kg

End point title	Number of subjects who reduced their canakinumab dose to 2 mg/kg

End point description:

The canakinumab dose could be reduced from 4 mg/kg to 2 mg/kg in subjects who were steroid-free, if requested by the treating physician and agreed by the sponsor. For treatment naive subjects, dose reduction was allowed after the subject had received 6 months treatment with canakinumab. The analysis was done in FAS population.

End point type	Secondary

End point timeframe:

Baseline up to last assessment or date of discontinuation, which ever occurred earlier

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	63	40	11
Units: number of subjects	9	29	4	2

End point values	ACZ885 treatment naive			
Subject group type	Reporting group			
Number of subjects analysed	123			
Units: number of subjects	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with inactive disease

End point title	Percentage of subjects with inactive disease

End point description:

Inactive disease was defined as no joints with active arthritis; no fever (body temperature ≤ 38 degree Celsius); no rheumatoid rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to SJIA; normal CRP, and a rating of no disease activity on the Physician's Global Assessment of disease activity (with a best possible score ≤10 mm on the VAS). The analysis was performed in FAS population. Here 'Number of subjects analysed' signifies number of subjects with an assessment in the given visit.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV: 10-Dec-2014) or date of discontinuation, which ever occurred earlier

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	63	40	11
Units: Percentage of subjects				
number (not applicable)	39.4	79.4	12.5	36.4

End point values	ACZ885 treatment naive			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Percentage of subjects				
number (not applicable)	50.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with clinical remission

End point title	Percentage of subjects with clinical remission[10]

End point description:

Clinical remission was defined as at least 6 months of inactive disease or at least 12 months of inactive disease on medication during the extension period. Subjects with inactive disease for at least 6 months, but had loss of inactive disease before 12 months were also determined. The analysis was done in FAS population. Here 'Number of subjects analysed' signifies number of subjects with an assessment in the given visit.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV: 10-Dec-2014) or date of discontinuation, which ever occurred earlier

Notes:

[10] - 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: The end point is reporting pooled data for Group 1, 2, 3 and 4 in 'ACZ treated' arm.

End point values	ACZ885 treatment naive	ACZ885 treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	123	147		
Units: percentage of subjects				
number (not applicable)				
At least 6 consecutive months of inactive disease	42.3	52.4		
At least 12 consecutive months of inactive disease	26.8	42.9		
Loss of inactive disease after 6 months	8.9	6.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in disability, overall well-being and pain intensity scores based on Child Health Assessment Questionnaire (CHAQ) to last assessment of study

End point title	Change from baseline in disability, overall well-being and pain

	intensity scores based on Child Health Assessment Questionnaire (CHAQ) to last assessment of study

End point description:

The CHAQ was used to assess physical ability, overall well-being and pain intensity experienced by subjects. The CHAQ disability dimension consisted 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 graded the response in four categories, ranging from 0 (without any difficulty) to 3 (unable to do). Subject's pain intensity was assessed by parents and adult subjects (18-20 years old) on a VAS scale of 0-100 mm (0 mm: no pain to 100: very severe pain). Change from baseline was calculated by using the formula = (post baseline value – baseline value). A negative change from baseline indicates improvement. The analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV: 10-Dec-2014) or date of discontinuation, which ever occurred earlier

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	63	40	11
Units: Units on a scale				
median (full range (min-max))				
Disability score	-0.375 (-2 to 0.625)	0 (-1.5 to 2.125)	-0.125 (-1.25 to 2.25)	0 (-2.125 to 1.375)
Overall well-being score	-18 (-64 to 54)	0 (-36 to 81)	0 (-36 to 1)	-10 (-69 to 20)
Pain Intensity score	-13 (-69 to 39)	0 (-39 to 80)	0 (-58 to 93)	0 (-57 to 53)

End point values	ACZ885 treatment naive			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: Units on a scale				
median (full range (min-max))				
Disability score	-0.7143 (-3 to 2.5)			
Overall well-being score	-28 (-100 to 83)			
Pain Intensity score	-39 (-100 to 89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Health-Related Quality of Life (HRQoL) over time based on Child Health Questionnaire - Parent Form (CHQ-PF50) to last assessment of study

End point title	Change from baseline in Health-Related Quality of Life (HRQoL) over time based on Child Health Questionnaire - Parent Form (CHQ-PF50) to last assessment of study

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 population.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV: 10-Dec-2014) or date of discontinuation, which ever occurred earlier

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	44	29	8
Units: Units on a scale				
median (full range (min-max))				
CHQ-PF50 physical score	14.0407 (-18.289 to 38.33)	0.6959 (-14.663 to 23.833)	1.3716 (-42.009 to 41.275)	13.9255 (-3.074 to 37.083)
CHQ-PF50 psychosocial score	3.8815 (-22.516 to 22.471)	1.4004 (-14.99 to 30.982)	0.7582 (-21.674 to 22.907)	11.9798 (-5.931 to 33.497)

End point values	ACZ885 treatment naive			
Subject group type	Reporting group			
Number of subjects analysed	90			
Units: Units on a scale				
median (full range (min-max))				
CHQ-PF50 physical score	18.8758 (-38.587 to 60.661)			
CHQ-PF50 psychosocial score	9.3209 (-23.862 to 48.657)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EuroQual 5-Dimension health status questionnaire (EQ-5D) utility index and health state assessment scores to last assessment of study

End point title	Change from baseline in EuroQual 5-Dimension health status questionnaire (EQ-5D) utility index and health state assessment scores to last assessment of study

End point description:

EQ-5D HRQoL tool was employed for subjects above 12 years of age and EQ-5D proxy was employed for subjects 8 – 11 years of age). EQ-5D was not completed for subjects aged 7 years and younger. The utility based EQ-5D questionnaire was in two parts and provides a generic measure of health for clinical and economic appraisal. The health state classification part contains 5 questions each with 3 categories (no problem, moderate problem, severe problems). The visual analogue scale was measured from 0 (worst imaginable health state) to 100 (best imaginable health state). A positive change from baseline score indicated improvement. The analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV: 10-Dec-2014) or date of discontinuation, which ever occurred earlier

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	35	22	4
Units: Units on a scale				
median (full range (min-max))				
Health State Assessment	21 (-45 to 63)	0 (-17 to 49)	5 (-86 to 50)	28 (0 to 65)
EQ--5D Utility Index Score	0.204 (-0.636 to 0.945)	0 (-0.434 to 0.377)	0.069 (-1.181 to 0.508)	0.2385 (0 to 0.741)

End point values	ACZ885 treatment naive			
Subject group type	Reporting group			
Number of subjects analysed	65			
Units: Units on a scale				
median (full range (min-max))				
Health State Assessment	30 (-24 to 95)			
EQ--5D Utility Index Score	0.228 (-0.434 to 1.291)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Pediatric Daytime Sleepiness Scale (PDSS) score to last assessment of study

End point title	Change from baseline in Pediatric Daytime Sleepiness Scale (PDSS) score to last assessment of study[11]

End point description:

Sleep patterns in children and adolescents aged between 11 and 15 years were determined using PDSS instrument. Subjects were assessed for 8 items of PDSS on a scale of 0 to 4 (0 – never, 1 – seldom, 2-sometimes, 3 – frequently and 4 – always). Change from baseline was calculated by using the formula = (post-baseline value – baseline value). A positive change from baseline score indicated improvement in sleep patterns. The analysis was performed in FAS population. Here, 'Number of subjects analysed' signifies those subjects with a value at both baseline and the respective post-baseline time point.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV: 10-Dec-2014) or date of discontinuation, which ever occurred earlier

Notes:

[11] - 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: The PDSS score was collected for subjects in 'ACZ treated' cohort i.e. Group 1, 2, 3 and 4.

End point values	ACZ885 treated: Group 1 (Discontinued from core study)	ACZ885 treated: Group 2 (Completed core study)	ACZ885 treated: Group 3 (Steroid taper failures in core study)	ACZ885 treated: Group 4 (Other criteria)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	12	5	2
Units: Units on a scale				
median (full range (min-max))	1 (-9 to 4)	0.5 (-6 to 9)	0 (-4 to 6)	-4.5 (-11 to 2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in growth velocity parameters to last assessment of study

End point title	Change from baseline in growth velocity parameters to last assessment of study[12]

End point description:

Growth velocity parameters like height, weight and BMI percentiles were determined. Percentiles were based on the growth charts smoothed percentile curves released by Centers for Disease control and prevention (CDC) in 2000, by sex and age. The analysis was performed in FAS population. Here, 'Number of subjects analysed' signifies those subjects with a value at both baseline and the respective post-baseline time point.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV: 10-Dec-2014) or date of discontinuation, which ever occurred earlier

Notes:

[12] - 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: The end point is reporting pooled data for Group 1, 2, 3 and 4 in 'ACZ treated' arm.

End point values	ACZ885 treatment naive	ACZ885 treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	123	147		
Units: As defined in categories				
median (full range (min-max))				
Height (cm) percentile (n=123, 139)	-0.01 (-66.18 to 47.06)	0 (-37.94 to 37.12)		
Weight (kg) percentile (n=123, 145)	0.1 (-47.35 to 82.84)	0 (-62.49 to 56.87)		
BMI (kg/meters^2) percentile (n=123, 139)	1.08 (-66.95 to 76.3)	-0.77 (-72.88 to 88.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant changes in Tanner staging score during the study

End point title	Number of subjects with clinically significant changes in Tanner staging score during the study

End point description:

Tanner staging, a well--established scale ranging from 1 to 5, characterizes physical development and quantifies primary and secondary sex characteristics such as the size of the breasts, genitalia, and development of pubic hair in subjects aged 6-20 years. Clinically significant findings were defined as any results which were observed beyond the expected limits as per the discretion of investigator. The analysis was performed in FAS population.

End point type	Secondary

End point timeframe:

Baseline up to last assessment (LSLV: 10-Dec-2014) or date of discontinuation, which ever occurred earlier

End point values	Female subjects aged 6-20 years	Male subjects aged 6-20 years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	55		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of ACZ naive subjects at baseline who achieved minimum response of ACR pediatric 30/50/70/90/100 criteria at last assessment of study

End point title	Percentage of ACZ naive subjects at baseline who achieved minimum response of ACR pediatric 30/50/70/90/100 criteria at last assessment of study[13]

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 mm VAS; 2. Patient Global Assessment on a 0--100 mm VAS; 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. Response was defined as ≥ 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 to -6, worsening by more than 30%. The analysis was done in FAS population. Here 'Number of subjects analysed' signifies number of subjects with an ACR assessment at the given visit.

End point type	Secondary

End point timeframe:

Baseline up to last assessment or date of discontinuation, which ever occurred earlier

Notes:

[13] - 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: The end point is reporting only ACZ naive data.

End point values	ACZ885 treatment naive			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: Percentage of subjects				
number (not applicable)				
ACR ≥30 criteria	92.6			
ACR ≥50 criteria	90.9			
ACR ≥70 criteria	87.6			
ACR ≥90 criteria	78.5			
ACR ≥100 criteria	66.1			

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	17.1

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Cohort 1	
Reporting group title	Cohort 2
Reporting group description:	
Cohort 2	

Serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 147 (31.97%)	40 / 123 (32.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic large cell lymphoma T- and null-cell types			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Drug ineffective			
subjects affected / exposed	1 / 147 (0.68%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury associated with device			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 147 (3.40%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	1 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vulvovaginal pain			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal pruritus			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute interstitial pneumonitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 147 (0.68%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Liver function test abnormal			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serum ferritin increased			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Road traffic accident			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion-related acute lung injury			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Superior sagittal sinus thrombosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Abdominal lymphadenopathy			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	10 / 147 (6.80%)	6 / 123 (4.88%)	
occurrences causally related to treatment / all	8 / 12	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 147 (0.68%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 147 (0.00%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 147 (0.68%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenomegaly			

subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 147 (0.68%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 147 (1.36%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	2 / 147 (1.36%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatomegaly			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 147 (0.68%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and			

systemic symptoms			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ingrowing nail			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 147 (1.36%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	1 / 147 (0.68%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Juvenile idiopathic arthritis			
subjects affected / exposed	14 / 147 (9.52%)	13 / 123 (10.57%)	
occurrences causally related to treatment / all	4 / 22	1 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 147 (1.36%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal disorder			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			

subjects affected / exposed	0 / 147 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus hepatitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 147 (0.68%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	4 / 147 (2.72%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	1 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis yersinia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 147 (0.68%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bites			

subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 147 (1.36%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudocroup			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scarlet fever			
subjects affected / exposed	1 / 147 (0.68%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 147 (1.36%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis streptococcal			
subjects affected / exposed	2 / 147 (1.36%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxoplasmosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	3 / 147 (2.04%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 147 (0.68%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	124 / 147 (84.35%)	91 / 123 (73.98%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 147 (5.44%)	5 / 123 (4.07%)	
occurrences (all)	14	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	14 / 147 (9.52%)	4 / 123 (3.25%)	
occurrences (all)	16	4	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	9 / 147 (6.12%)	12 / 123 (9.76%)	
occurrences (all)	12	12	
Contusion			
subjects affected / exposed	11 / 147 (7.48%)	0 / 123 (0.00%)	
occurrences (all)	14	0	
Fall			
subjects affected / exposed	11 / 147 (7.48%)	7 / 123 (5.69%)	
occurrences (all)	18	7	
Ligament sprain			
subjects affected / exposed	11 / 147 (7.48%)	5 / 123 (4.07%)	
occurrences (all)	21	7	
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 147 (20.41%)	24 / 123 (19.51%)	
occurrences (all)	110	84	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	10 / 147 (6.80%)	3 / 123 (2.44%)	
occurrences (all)	16	7	
Pyrexia			
subjects affected / exposed	38 / 147 (25.85%)	27 / 123 (21.95%)	
occurrences (all)	72	48	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	10 / 147 (6.80%)	7 / 123 (5.69%)	
occurrences (all)	16	8	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	21 / 147 (14.29%)	22 / 123 (17.89%)	
occurrences (all)	35	56	
Abdominal pain upper			
subjects affected / exposed	18 / 147 (12.24%)	13 / 123 (10.57%)	
occurrences (all)	66	31	
Nausea			
subjects affected / exposed	17 / 147 (11.56%)	11 / 123 (8.94%)	
occurrences (all)	30	27	
Diarrhoea			
subjects affected / exposed	30 / 147 (20.41%)	16 / 123 (13.01%)	
occurrences (all)	53	25	
Vomiting			
subjects affected / exposed	35 / 147 (23.81%)	18 / 123 (14.63%)	
occurrences (all)	66	24	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 147 (25.17%)	28 / 123 (22.76%)	
occurrences (all)	102	49	
Epistaxis			
subjects affected / exposed	10 / 147 (6.80%)	5 / 123 (4.07%)	
occurrences (all)	24	7	
Oropharyngeal pain			
subjects affected / exposed	36 / 147 (24.49%)	17 / 123 (13.82%)	
occurrences (all)	98	30	

Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	12 / 147 (8.16%)	16 / 123 (13.01%)	
occurrences (all)	15	22	
Urticaria			
subjects affected / exposed	7 / 147 (4.76%)	7 / 123 (5.69%)	
occurrences (all)	12	9	
Rash			
subjects affected / exposed	15 / 147 (10.20%)	13 / 123 (10.57%)	
occurrences (all)	26	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 147 (24.49%)	25 / 123 (20.33%)	
occurrences (all)	79	56	
Arthritis			
subjects affected / exposed	9 / 147 (6.12%)	7 / 123 (5.69%)	
occurrences (all)	11	10	
Back pain			
subjects affected / exposed	11 / 147 (7.48%)	9 / 123 (7.32%)	
occurrences (all)	18	13	
Joint swelling			
subjects affected / exposed	9 / 147 (6.12%)	5 / 123 (4.07%)	
occurrences (all)	21	10	
Juvenile idiopathic arthritis			
subjects affected / exposed	23 / 147 (15.65%)	27 / 123 (21.95%)	
occurrences (all)	46	65	
Myalgia			
subjects affected / exposed	9 / 147 (6.12%)	6 / 123 (4.88%)	
occurrences (all)	15	6	
Neck pain			
subjects affected / exposed	8 / 147 (5.44%)	7 / 123 (5.69%)	
occurrences (all)	18	7	
Pain in extremity			
subjects affected / exposed	19 / 147 (12.93%)	12 / 123 (9.76%)	
occurrences (all)	43	13	
Infections and infestations			

Bronchitis			
subjects affected / exposed	13 / 147 (8.84%)	6 / 123 (4.88%)	
occurrences (all)	15	6	
Conjunctivitis			
subjects affected / exposed	8 / 147 (5.44%)	6 / 123 (4.88%)	
occurrences (all)	9	7	
Influenza			
subjects affected / exposed	14 / 147 (9.52%)	4 / 123 (3.25%)	
occurrences (all)	19	4	
Gastroenteritis			
subjects affected / exposed	28 / 147 (19.05%)	19 / 123 (15.45%)	
occurrences (all)	39	29	
Nasopharyngitis			
subjects affected / exposed	47 / 147 (31.97%)	32 / 123 (26.02%)	
occurrences (all)	121	56	
Otitis media			
subjects affected / exposed	11 / 147 (7.48%)	7 / 123 (5.69%)	
occurrences (all)	12	7	
Oral herpes			
subjects affected / exposed	11 / 147 (7.48%)	1 / 123 (0.81%)	
occurrences (all)	22	1	
Pharyngitis			
subjects affected / exposed	15 / 147 (10.20%)	15 / 123 (12.20%)	
occurrences (all)	22	18	
Respiratory tract infection			
subjects affected / exposed	7 / 147 (4.76%)	13 / 123 (10.57%)	
occurrences (all)	10	21	
Tonsillitis			
subjects affected / exposed	10 / 147 (6.80%)	7 / 123 (5.69%)	
occurrences (all)	14	9	
Rhinitis			
subjects affected / exposed	35 / 147 (23.81%)	26 / 123 (21.14%)	
occurrences (all)	81	45	
Upper respiratory tract infection			
subjects affected / exposed	36 / 147 (24.49%)	24 / 123 (19.51%)	
occurrences (all)	100	54	

Urinary tract infection			
subjects affected / exposed	8 / 147 (5.44%)	4 / 123 (3.25%)	
occurrences (all)	11	4	
Viral upper respiratory tract infection			
subjects affected / exposed	10 / 147 (6.80%)	4 / 123 (3.25%)	
occurrences (all)	12	5	
Viral infection			
subjects affected / exposed	6 / 147 (4.08%)	11 / 123 (8.94%)	
occurrences (all)	6	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2009	The amendment was written to change criteria for which a subject would discontinue due to flare, to that of an unmet ACR30 response. Steroid tapering guidelines were also updated to take into account a loss of ACR 30 response.
03 November 2009	The main purpose of this amendment was to clarify the eligibility criteria for subjects who rolled over from Study CACZ885G2301 (EudraCT number: 2008-005479-82) and CACZ885G2305 (EudraCT number: 2008-005476-27); to clarify the ACR response calculation and align it with the CAC885G2305 and CACZ885G2301 studies; and to indicate the planned end of study visit date.
19 January 2010	The main purpose of this amendment was to allow subjects with elevated CRP levels to initiate and continue tapering their corticosteroid dose. Additional inclusion criteria were added to allow responders from CACZ885G2301 (EudraCT number: 2008-005479-82) Part I who flared in Part II to be eligible for study entry.
03 January 2011	The amendment described the implementation of an adjudication committee for macrophage activation syndrome (MAS) and the follow-up procedures for MAS cases identified in the study.
26 October 2011	A new canakinumab treatment-naive subject cohort with active SJIA with and without fever was included in the study. The addition of this cohort aimed to i) increase the safety database by capturing key data on infections, genetic biomarkers and risk of MAS; ii) provide safety and efficacy information on the subset of subjects without fever who were not enrolled in the core Studies CACZ885G2301 (EudraCT number: 2008-005479-82) and CACZ885G2305 (EudraCT number: 2008-005476-27); iii) provide an alternative, albeit experimental, treatment option to subjects; and iv) enhance the biomarker database for investigation of response characterization.
28 March 2012	The exclusion criteria were amended to be in alignment with the canakinumab summary of product characteristics (approved canakinumab label in European Union). Subjects were required to maintain contraception use for 3 months after study drug discontinuation and neutropenic subjects at screening were excluded from participating in the study. The study end date was extended to March 2013 to allow time for subjects to roll-over into Study CACZ885G2306 (EudraCT number: 2013-004867-29).
01 November 2012	This amendment was written to include two independent adjudication committees into the study, to comply with canakinumab Risk Management Plan (RMP). The study end date was extended to December 2014 to allow additional time for subjects to rollover into Study CACZ885G2306 (EudraCT number: 2013-004867-29)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported