



## Clinical trial results:

**A one-year open-label, multicenter trial to assess efficacy, safety and tolerability of canakinumab (ACZ885) and the efficacy and safety of childhood vaccinations in patients aged 4 years or younger with Cryopyrin Associated Periodic Syndromes (CAPS)**

### Summary

EudraCT number	2009-016859-22
Trial protocol	FR DE ES GB BE Outside EU/EEA IE
Global end of trial date	19 November 2014

### Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	08 August 2015

### Trial information

#### Trial identification

Sponsor protocol code	CACZ885D2307
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01302860
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)	EMA-000060-PIP01-07
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	19 November 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 November 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 assess the efficacy of canakinumab with respect to the treatment response in subjects aged 4 years and younger.

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. Subjects who did not achieve a complete response following canakinumab subcutaneous (s.c.) injection, or who experienced a relapse before the next planned administration, were eligible for a dose up-titration as rescue medication.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	17
EEA total number of subjects	14

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	6
Children (2-11 years)	11
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 14 centres in 7 countries.

### Pre-assignment

Screening details:

A total of 17 subjects were enrolled into the study.

### Period 1

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

Blinding implementation details:

This was an open-label, single-treatment arm study. Hence, blinding was not applicable.

### Arms

Arm title	Canakinumab
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Arm description:

Subjects received body weight stratified dose of canakinumab 2 mg/kg s.c. injection every 8 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 s.c. injection (2 mg/kg) was administered every 8 weeks.

<b>Number of subjects in period 1</b>	Canakinumab
Started	17
Completed	17

## Baseline characteristics

### Reporting groups

Reporting group title	Canakinumab
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Reporting group description:

Subjects received body weight stratified dose of canakinumab 2 mg/kg s.c. injection every 8 weeks.

Reporting group values	Canakinumab	Total	
Number of subjects	17	17	
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	6	6	
Children (2-11 years)	11	11	
Age continuous			
Units: years			
arithmetic mean	1.9		
standard deviation	± 1.39	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	12	12	

## End points

### End points reporting groups

Reporting group title	Canakinumab
Reporting group description:	
Subjects received body weight stratified dose of canakinumab 2 mg/kg s.c. injection every 8 weeks.	

### Primary: Percentage of subjects aged 4 years or younger with at least one complete response at Week 56

End point title	Percentage of subjects aged 4 years or younger with at least one complete response at Week 56 <sup>[1]</sup>
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End point description:

Complete response was defined as clinical remission and serological remission. Clinical remission was defined as Physician global assessment of auto-inflammatory disease activity as absent or minimal (using a 5-point scale ranging from absent to severe) and assessment of skin disease as absent or minimal (using a 5-point scale ranging from absent to severe). Serological remission was defined as C reactive protein (CRP) or Serum amyloid A protein (SAA) to be less than (<) 15 milligram per litre (mg/L) and <10 mg/L respectively. The analysis was performed in Full analysis set (FAS), defined as all subjects who received at least one dose of study drug under this study protocol.

End point type	Primary
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End point timeframe:

Week 56

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.

<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Percentage of subjects				
number (not applicable)	94.1			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of subjects aged 2 years or younger with at least one complete response at Week 56

End point title	Percentage of subjects aged 2 years or younger with at least one complete response at Week 56
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End point description:

Complete response was defined as clinical remission and serological remission. Clinical remission was defined as Physician global assessment of autoinflammatory disease activity as absent or minimal (using a 5-point scale ranging from absent to severe) and assessment of skin disease as absent or minimal (using a 5-point scale ranging from absent to severe). Serological remission was defined as CRP or SAA to be <15 mg/L and <10 mg/L respectively. The analysis was performed in FAS population.

End point type	Secondary
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End point timeframe:

Week 56

<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	10 <sup>[2]</sup>			
Units: Percentage of subjects				
number (not applicable)	90			

Notes:

[2] - Subjects aged 2 years or younger

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects assessed for auto inflammatory disease activity by using physician's global assessment score at Week 56

End point title	Percentage of subjects assessed for auto inflammatory disease activity by using physician's global assessment score at Week 56
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End point description:

Subjects were assessed based by physician on Physician's Global Assessment measured on a 5--point scale for auto inflammatory disease activity as: 0 = None/absent; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Severe. The analysis was performed in FAS population. "Number of Subject analyzed" is the total number of patients with non-missing assessment at the time point.

End point type	Secondary
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End point timeframe:

Week 56

<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Percentage of subjects				
number (not applicable)				
Absent	70.6			
Minimal	23.5			
Mild	0			
Moderate	5.9			
Severe	0			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects with assessment of skin disease by using physician's global assessment score at Week 56

End point title	Percentage of subjects with assessment of skin disease by using physician's global assessment score at Week 56
End point description: Subjects were assessed by physician for skin disease (urticarial skin rash) on a 5--point scale as: 0 = None/absent; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Severe. The analysis was performed in FAS population. "Number of Subject analyzed" is the total number of patients with non-missing assessment at the time point.	
End point type	Secondary
End point timeframe: Week 56	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Percentage of subjects				
number (not applicable)				
Absent	82.4			
Minimal	5.9			
Mild	11.8			
Moderate	0			
Severe	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in C--Reactive Protein (CRP) and Serum Amyloid A (SAA) concentrations at Week 56

End point title	Change from baseline in C--Reactive Protein (CRP) and Serum Amyloid A (SAA) concentrations at Week 56
End point description: The CRP and SAA were used as inflammatory markers. The target level concentrations for CRP and SAA was ≤15 mg/L and ≤10 mg/L, respectively. Negative change in concentration of inflammatory markers indicated improvement. The analysis was performed in FAS population. Here 'n' signifies those subjects with evaluable measurements at both baseline and the post-baseline visit.	
End point type	Secondary
End point timeframe: Baseline, Week 56	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: mg/L				
arithmetic mean (standard deviation)				
CRP (n=14)	-5.4 (± 6.28)			



SAA (n=16)	-54.4 (± 133.81)			
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of subjects with adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of subjects with adverse events (AEs) and serious adverse events (SAEs)
End point description:	
Adverse events (AEs) were defined as any unfavourable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events (SAEs) were defined as any untoward medical occurrences that result in death, are life threatening, require (or prolong) hospitalisation, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgement of investigators represent significant hazards. The analysis was performed in the safety set population defined as subjects who received at least one dose of study drug. Here, 'n' signifies subjects evaluable for this measure at specified time points for each group, respectively.	
End point type	Secondary
End point timeframe:	
Day 1 (start of study treatment) up to Week 56 (end of study)	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Subjects				
number (not applicable)				
AEs (Overall, n=17)	17			
SAEs (Overall, n=17)	4			
AEs (Subjects ≤2 years, n=10)	10			
SAEs (Subjects ≤2 years, n=10)	3			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects receiving a concomitant vaccination during the study

End point title	Percentage of subjects receiving a concomitant vaccination during the study
End point description:	
Subjects receiving any one of the following inactivated vaccines as per the immunization program: Corynebacterium diphtheria, Bordetella pertussis, Neisseria meningitidis, Clostridium tetani, Influenza	

type A, Influenza type B, Haemophilus influenza B, Streptococcus pneumoniae, or Hepatitis B were determined. The analysis was performed in the FAS population.

End point type	Secondary
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End point timeframe:

Day 1 (start of study treatment) to Week 56 (end of study)

<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Percentage of subjects				
number (not applicable)	41.2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of vaccination cases with protective antibody levels following immunization with inactivated vaccines

End point title	Number of vaccination cases with protective antibody levels following immunization with inactivated vaccines
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End point description:

Subjects who received any inactivated vaccines during the study were assessed for their ability to attain protective antibody levels against the vaccine (antigen) post immunization. Subject vaccinations were not assessed for a response if the antibody titre was already sufficient at pre-dose and maintained during the study. The analysis was performed in the FAS population. The data reported in the table based on antibody levels are reporting number of vaccination cases in the respective categories.

End point type	Secondary
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End point timeframe:

Day -14 (prior-vaccination), Day 0 (vaccination), Day 28, Day 57 (post-vaccination)

<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	7 <sup>[3]</sup>			
Units: vaccination cases				
number (not applicable)				
Positive response for antibody levels	18			
No pre-dose antibody levels	13			

Notes:

[3] - Evaluable subjects who had total 31 vaccinations during study.

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of subjects with anti-canakinumab antibodies at Week 56**

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End point title	Number of subjects with anti-canakinumab antibodies at Week 56
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End point description:

Immunogenicity assessment included determination of anti-canakinumab (ACZ885) antibodies in serum samples using BIAcore system, with detection based on surface plasmon resonance technique. The analysis was performed in the safety set population. Here, 'Number of subjects analysed' signifies subjects who had immunogenicity samples taken and analyzed during the study.

End point type	Secondary
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End point timeframe:

Week 56 (end of study)

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<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects				
number (not applicable)	0			

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until Last Subject Last Visit.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

### Reporting groups

Reporting group title	Canakinumab
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Reporting group description:

Subjects received body weight stratified dose of canakinumab 2 mg/kg s.c. injection every 8 weeks.

Serious adverse events	Canakinumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cryopyrin associated periodic syndrome			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cryptorchism			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection staphylococcal			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Canakinumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)		
Surgical and medical procedures			
Hearing aid therapy			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed occurrences (all)	6 / 17 (35.29%) 13		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)  Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2  4 / 17 (23.53%) 7  1 / 17 (5.88%) 1		
Investigations CSF white blood cell count increased subjects affected / exposed occurrences (all)  Transaminases increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1  1 / 17 (5.88%) 1		
Injury, poisoning and procedural complications Skin abrasion subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Congenital, familial and genetic disorders Cryopyrin associated periodic syndrome subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 4		
Nervous system disorders Speech disorder developmental subjects affected / exposed occurrences (all)  Motor developmental delay	1 / 17 (5.88%) 1		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 17 (5.88%)</p> <p>1</p> <p>4 / 17 (23.53%)</p> <p>15</p>		
<p>Blood and lymphatic system disorders</p> <p>Eosinophilia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 17 (5.88%)</p> <p>1</p>		
<p>Ear and labyrinth disorders</p> <p>Conductive deafness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 17 (5.88%)</p> <p>1</p>		
<p>Eye disorders</p> <p>Iridocyclitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Papilloedema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 17 (5.88%)</p> <p>2</p> <p>1 / 17 (5.88%)</p> <p>1</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Toothache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Stomatitis</p>	<p>3 / 17 (17.65%)</p> <p>7</p> <p>4 / 17 (23.53%)</p> <p>6</p> <p>1 / 17 (5.88%)</p> <p>1</p> <p>4 / 17 (23.53%)</p> <p>16</p> <p>1 / 17 (5.88%)</p> <p>1</p>		

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Skin lesion			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Bronchitis			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		
Ear infection			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	6		
Eczema infected			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastroenteritis			



subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Gastritis viral			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Escherichia urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Enterobiasis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	8		
Molluscum contagiosum			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Laryngitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oral fungal infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	11		
Pharyngitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Otitis externa			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oral herpes			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Tinea pedis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Tonsillitis bacterial			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	11		
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Varicella			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2010	<ol style="list-style-type: none"><li>1. Dose rationale for the dosing regimen for the study was outlined</li><li>2. Exclusion criteria related to live vaccinations was corrected</li><li>3. Paediatric subjects with neutropenia were excluded from receiving canakinumab treatment</li><li>4. Periodic assessment of neutrophil counts was introduced to monitor and detect neutropenia in subjects while receiving canakinumab treatment</li></ol>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported