



## Clinical trial results:

### A Multi-Center, Open label, Repeated Dose Range Finding Study to Evaluate the Safety, Tolerability, Immunogenicity, Pharmacokinetics and Efficacy of an Anti-IL-1; Monoclonal Antibody ACZ885 Given Subcutaneously in Pediatric Subjects with Active Systemic Juvenile Idiopathic Arthritis (SJIA)

#### Summary

EudraCT number	2006-001834-42
Trial protocol	FR IT GB
Global end of trial date	09 March 2010

#### Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	05 August 2015

#### Trial information

##### Trial identification

Sponsor protocol code	CACZ885A2203
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 March 2010
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 March 2010
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 the safety and efficacy of canakinumab after subcutaneous (s.c.) administration in paediatric subjects with active Systemic Juvenile Idiopathic Arthritis (SJIA) according to American College of Rheumatology (ACR). The study also assessed the pharmacokinetics (PK) and the relationship between PK and pharmacodynamics (PD) to derive a dosage regimen for phase III studies.

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 defined as non-responder were provided with rescue medication. A rescue dose of increased prednisone, methotrexate, cyclosporine, or other disease-modifying antirheumatic drugs (DMARDs), possibly anakinra on which the subjects agreed, was initiated at the discretion of the investigator.

Background therapy:

Subjects remained on their current medication and non-drug therapies during the study. Treatment with any biologics was not allowed during the entire study.

Evidence for comparator: -

Actual start date of recruitment	07 December 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	19
Adolescents (12-17 years)	6
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 4 centres in 4 countries.

### Pre-assignment

Screening details:

A total of 26 subjects were enrolled into Stage I of the study, out of which 3 subjects entered the study twice. So, in actual 23 subjects were enrolled. Out of 23, 11 subjects who responded during Stage I were enrolled into Stage II.

### Period 1

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

Blinding implementation details:

The study was open label, hence no blinding was performed.

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Canakinumab 0.5 mg/kg
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Arm description:

Subjects were injected with canakinumab as 0.5 milligrams/kilograms (mg/kg). Subjects were re-dosed up to a maximum dose of 1 mg/kg if no measurable improvement was observed within 48 hours of first dose 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:

Subjects received canakinumab s.c. injections (0.5 mg/kg, or 1.5 mg/kg, or 4.5 mg/kg) and re-dosed up to maximum of 1 mg/kg, 3 mg/kg and 9 mg/kg respectively based on the cohort.

<b>Arm title</b>	Canakinumab 1.5 mg/kg
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Arm description:

Subjects were injected with canakinumab as 1.5 mg/kg. Subjects were re-dosed up to a maximum dose of 3 mg/kg if no measurable improvement was observed within 48 hours of first dose 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:

Subjects received canakinumab s.c. injection of 1.5 mg/kg and re-dosed up to maximum of 3 mg/kg.

<b>Arm title</b>	Canakinumab 4.5 mg/kg
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Arm description:

Subjects were injected with canakinumab as 4.5 mg/kg. Subjects were re-dosed up to a maximum dose of 9 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.

Arm type	Experimental
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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:

Subjects received canakinumab s.c. injection of 4.5 mg/kg and re-dosed up to maximum of 9 mg/kg.

Number of subjects in period 1	Canakinumab 0.5 mg/kg	Canakinumab 1.5 mg/kg	Canakinumab 4.5 mg/kg
Started	5	10	11
Completed	4	7	9
Not completed	1	3	2
Consent withdrawn by subject	-	-	1
Unsatisfactory therapeutic effect	-	3	1
'Unsatisfactory therapeutic effect '	1	-	-

## Period 2

Period 2 title	Stage II
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was open label, hence no blinding was performed.

## Arms

Arm title	Canakinumab (Stage II)
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Arm description:

All subjects who responded in Stage I were included in Stage II. Subjects received a fixed dose of 4 mg/kg, up to a maximum single dose of 300 mg s.c of canakinumab 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:

Subjects received canakinumab s.c. fixed dose of 4 mg/kg, up to a maximum single dose of 300 mg every 4 weeks.

Number of subjects in period 2 <sup>[1]</sup>	Canakinumab (Stage II)
Started	11
Completed	11

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of 17 subjects who completed the Stage I, only 11 subjects were enrolled in Stage II.

## Baseline characteristics

### Reporting groups

Reporting group title	Canakinumab 0.5 mg/kg
Reporting group description: Subjects were injected with canakinumab as 0.5 milligrams/kilograms (mg/kg). Subjects were re-dosed up to a maximum dose of 1 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.	
Reporting group title	Canakinumab 1.5 mg/kg
Reporting group description: Subjects were injected with canakinumab as 1.5 mg/kg. Subjects were re-dosed up to a maximum dose of 3 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.	
Reporting group title	Canakinumab 4.5 mg/kg
Reporting group description: Subjects were injected with canakinumab as 4.5 mg/kg. Subjects were re-dosed up to a maximum dose of 9 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.	

Reporting group values	Canakinumab 0.5 mg/kg	Canakinumab 1.5 mg/kg	Canakinumab 4.5 mg/kg
Number of subjects	5	10	11
Age categorical Units: Subjects			
4 - 19 years	5	10	11
Age continuous Units: years arithmetic mean standard deviation	11 ± 2.2	10 ± 4.7	9 ± 3.9
Gender categorical Units: Subjects			
Female	4	4	6
Male	1	6	5

Reporting group values	Total		
Number of subjects	26		
Age categorical Units: Subjects			
4 - 19 years	26		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	14		
Male	12		

## End points

### End points reporting groups

Reporting group title	Canakinumab 0.5 mg/kg
Reporting group description: Subjects were injected with canakinumab as 0.5 milligrams/kilograms (mg/kg). Subjects were re-dosed up to a maximum dose of 1 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.	
Reporting group title	Canakinumab 1.5 mg/kg
Reporting group description: Subjects were injected with canakinumab as 1.5 mg/kg. Subjects were re-dosed up to a maximum dose of 3 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.	
Reporting group title	Canakinumab 4.5 mg/kg
Reporting group description: Subjects were injected with canakinumab as 4.5 mg/kg. Subjects were re-dosed up to a maximum dose of 9 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.	
Reporting group title	Canakinumab (Stage II)
Reporting group description: All subjects who responded in Stage I were included in Stage II. Subjects received a fixed dose of 4 mg/kg, up to a maximum single dose of 300 mg s.c of canakinumab every 4 weeks.	
Subject analysis set title	Canakinumab (Stage I)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects during Stage I were injected with canakinumab in 3 cohorts; Cohort I as 0.5 mg/kg, Cohort II as 1.5 mg/kg, Cohort III 4.5 mg/kg. Subjects were re-dosed up to a maximum dose of 1 mg/kg, 3 mg/kg and 9 mg/kg in Cohort I, II and III, respectively if no measurable improvement was observed within 48 hours of first dose every 4 weeks.	

### Primary: Number of subjects with adverse events and serious adverse events

End point title	Number of subjects with adverse events and serious adverse events <sup>[1]</sup>
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 (SAF) population, defined as all subjects who received at least one dose of study drug with at least one post-baseline safety assessment.	
End point type	Primary
End point timeframe: Day 1 up to Day 928 (End of study)	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.



End point values	Canakinumab 0.5 mg/kg	Canakinumab 1.5 mg/kg	Canakinumab 4.5 mg/kg	Canakinumab (Stage II)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	10	11	11
Units: Number of subjects				
AEs	5	10	10	11
SAEs	0	6	4	3

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of subjects with anti-canakinumab antibodies at any visit

End point title	Number of subjects with anti-canakinumab antibodies at any visit <sup>[2]</sup>
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End point description:

Immunogenicity assessment included determination of anti-canakinumab (ACZ885) antibodies in serum samples using BIAcore system. The analysis was performed in all subjects who received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Day 1 up to Day 918 (End of study)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	Canakinumab 0.5 mg/kg	Canakinumab 1.5 mg/kg	Canakinumab 4.5 mg/kg	Canakinumab (Stage II)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	10	11	11
Units: Number of subjects	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of responders to treatment in Stage I

End point title	Percentage of responders to treatment in Stage I <sup>[3]</sup>
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End point description:

Adapted ACR Paediatric 30/50/70/90/100 criteria was assessed based on following 7 variables: 1. Physician's Global Assessment on a 0-100 millimetres (mm) visual analog scale (VAS); 2. Patient Global Assessment on a 0-100 mm VAS in the Child Health Assessment Questionnaire (CHAQ); 3. Functional ability; 4. Joints count with active arthritis; 5. Joints count with limitation of motion; 6. Laboratory measure of C-reactive protein (CRP) and 7. Absence of intermittent fever (i.e. body temperature  $\leq 38^{\circ}\text{C}$ ) due to SJIA during the preceding week. Response was defined as more than or equal to ( $\geq$ ) 30%/50%/70%/90% or 100% improvement in at least 3 of the response variables 1 to 7, with no more than one variable 1-6 worsening by more than 30%. The analysis was performed on Full analysis set (FAS), defined as all randomized subjects who received at least one dose of study drug. The 'n' signifies those subject evaluable for this measure at specified time point for each group, respectively.

End point type	Primary
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End point timeframe:

Day 15

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 outcome measure.

End point values	Canakinumab 0.5 mg/kg	Canakinumab 1.5 mg/kg	Canakinumab 4.5 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	10	11	
Units: Percentage of subjects				
number (not applicable)	40	80	46	

## Statistical analyses

No statistical analyses for this end point

### Primary: Time to relapse after last dose of canakinumab

End point title	Time to relapse after last dose of canakinumab <sup>[4]</sup>
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End point description:

Relapse according to the modified ACR paediatric criteria for flare was defined as subjects with more than or equal to ( $\geq$ ) 30% worsening in at least 3 of 6 variables,  $\geq$  30% improvement in not more than 1 of the 6 variables,  $\geq$  2 cm of worsening in Physician or Parent Global Assessment, worsening in  $\geq$  2 joints and CRP  $>$  30 mg/L in responders. Time to relapse was defined as reappearance of fever not due to infection and/or symptoms that are expression of systemic manifestation, and increase of CRP more than 30 mg/L. Subjects who withdrew before the end of Stage I or before the end of Stage II and subjects who had not relapsed before the end of the study were not included for analysis. The analysis was performed in all subjects who received at least one dose of study drug.

End point type	Primary
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End point timeframe:

Day 43 up to Day 928 (End of study)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	Canakinumab (Stage I)			
Subject group type	Subject analysis set			
Number of subjects analysed	23			
Units: Days				
median (confidence interval 95%)				
Dose group $<3$ mg/kg	56.11 (31.46 to 100.49)			
Dose group 3 mg/kg	99.98 (58.1 to 172.03)			
Dose group 4 mg/kg	90.47 (54.74 to 149.52)			
Dose group $>4$ mg/kg	71.52 (41 to 124.75)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Area under the concentration-time curve from time zero to infinity (AUC 0-inf) of canakinumab

End point title	Area under the concentration-time curve from time zero to infinity (AUC 0-inf) of canakinumab <sup>[5]</sup>
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End point description:

The area under the concentration-time curve from time zero to infinity (AUC 0-inf) was used to measure the total drug exposure over time. The analysis was performed in all subjects with evaluable/complete PK data.

End point type	Primary
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End point timeframe:

Pre-dose, Day 2 (Periods 1 and 2), Day 3 (Periods 1 and 2), Day 8 (Periods 1 and 2), Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, Day 113, Day 127, Day 141 and Day 155

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: Only descriptive summary statistics was planned for this outcome measure.

<b>End point values</b>	Canakinumab (Stage I)			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Day*microgram/millilitre/milligram				
arithmetic mean (standard deviation)	4.395 (± 1.4363)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Maximum Plasma Concentration (Cmax) of canakinumab

End point title	Maximum Plasma Concentration (Cmax) of canakinumab <sup>[6]</sup>
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End point description:

Maximum plasma concentration (Cmax) was defined as the peak plasma level of canakinumab, derived from plasma concentration-time data of canakinumab. The analysis was performed in all subjects with evaluable/complete PK data.

End point type	Primary
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End point timeframe:

Pre-dose, Day 2 (Periods 1 and 2), Day 3 (Periods 1 and 2), Day 8 (Periods 1 and 2), Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, Day 113, Day 127, Day 141 and Day 155

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	Canakinumab (Stage I)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Microgram/millilite/milligram				
arithmetic mean (standard deviation)	0.1678 ( $\pm$ 0.03056)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Time to maximum plasma concentration (Tmax) of canakinumab

End point title	Time to maximum plasma concentration (Tmax) of canakinumab <sup>[7]</sup>
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End point description:

Tmax was defined as the time taken to reach the maximum plasma concentration of canakinumab. The analysis was performed in all subjects with evaluable/complete PK data.

End point type	Primary
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End point timeframe:

Pre-dose, Day 2 (Periods 1 and 2), Day 3 (Periods 1 and 2), Day 8 (Periods 1 and 2), Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, Day 113, Day 127, Day 141 and Day 155

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	Canakinumab (Stage I)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Day				
arithmetic mean (standard deviation)	2.62 ( $\pm$ 2.0797)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Total body clearance (CL/F) of canakinumab from serum

End point title	Total body clearance (CL/F) of canakinumab from serum <sup>[8]</sup>
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End point description:

Clearance from serum (CL/F) was defined as the apparent body clearance of canakinumab from the serum when the systemic availability was unknown. The analysis was performed in all subjects with evaluable/complete PK data.

End point type	Primary
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End point timeframe:

Pre-dose, Day 2 (Periods 1 and 2), Day 3 (Periods 1 and 2), Day 8 (Periods 1 and 2), Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, Day 113, Day 127, Day 141 and Day 155

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.

<b>End point values</b>	Canakinumab (Stage I)			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Millilitre(s)/day				
arithmetic mean (standard deviation)	256.4 (± 99.374)			

## Statistical analyses

No statistical analyses for this end point

## Primary: Apparent volume of distribution (V<sub>z</sub>/F) of canakinumab during terminal phase

End point title	Apparent volume of distribution (V <sub>z</sub> /F) of canakinumab during terminal phase <sup>[9]</sup>
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End point description:

The volume of distribution was defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. The analysis was performed in all subjects with evaluable/complete PK data.

End point type	Primary
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End point timeframe:

Pre-dose, Day 2 (Periods 1 and 2), Day 3 (Periods 1 and 2), Day 8 (Periods 1 and 2), Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99, Day 113, Day 127, Day 141 and Day 155

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.

<b>End point values</b>	Canakinumab (Stage I)			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Millilitre(s)				
arithmetic mean (standard deviation)	5941 (± 2541.3)			

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of subjects with inactive disease at Day 15**

End point title	Percentage of subjects with inactive disease at Day 15
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End point description:

Inactive disease was defined as absence of active joints arthritis, no fever (body temperature  $\leq 37.5^{\circ}\text{C}$ ), absence of rheumatoid rash, serositis, splenomegaly, hepatomegaly or lymphadenopathy; normal ESR and CRP; and no disease activity (value  $\leq 10$  mm) for Physician's Global Assessment on a 10 cm VAS (0 cm = no disease activity to 10 cm = very severe disease activity). The analysis was performed in all subjects who received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Day 15

End point values	Canakinumab (Stage I)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Percentage of subjects				
number (not applicable)	18.2			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of subjects able to taper or discontinue steroids from baseline to end of study**

End point title	Percentage of subjects able to taper or discontinue steroids from baseline to end of study
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End point description:

The ability to taper oral steroids was defined as if dose was reduced from start of baseline to end of study, while maintaining a minimum adapted ACR 30 paediatric criterion (defined as improvement from baseline of  $\geq 30\%$  in at least 3 of the 6 response variables of adapted ACR paediatric criteria; no intermittent fever in the preceding week and no more than one of the first 6 response variables worsening by more than 30%). The analysis was performed in all subjects who received at least one dose of study drug. Here, "Number of subjects analysed" were subjects who were responders at the end of study.

End point type	Secondary
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End point timeframe:

Baseline to Day 928 (End of study)

End point values	Canakinumab 0.5 mg/kg	Canakinumab 1.5 mg/kg	Canakinumab 4.5 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	7	10	
Units: Percentage of subjects				
number (not applicable)				
Steroids tapered	1	3	7	
Steroids discontinued	0	2	3	

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

### Reporting groups

Reporting group title	Canakinumab 0.5 mg/kg
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Reporting group description:

Subjects were injected with canakinumab as 0.5 milligrams/kilograms (mg/kg). Subjects were re-dosed up to a maximum dose of 1 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.

Reporting group title	Canakinumab (Stage II)
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Reporting group description:

All subjects who responded in Stage I were included in Stage II. Subjects received a fixed dose of 4 mg/kg, up to a maximum single dose of 300 mg s.c of canakinumab every 4 weeks.

Reporting group title	Canakinumab (Stage I)
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Reporting group description:

Subjects during Stage I were injected with canakinumab in 3 cohorts; Cohort I as 0.5 mg/kg, Cohort II as 1.5 mg/kg, Cohort III 4.5 mg/kg. Subjects were re-dosed up to a maximum dose of 1 mg/kg, 3 mg/kg and 9 mg/kg in Cohort I, II and III, respectively if no measurable improvement was observed within 48 hours of first dose every 4 weeks.

Reporting group title	Canakinumab 1.5 mg/kg
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Reporting group description:

Subjects were injected with canakinumab as 1.5 mg/kg. Subjects were re-dosed up to a maximum dose of 3 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.

Reporting group title	Canakinumab 4.5 mg/kg
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Reporting group description:

Subjects were injected with canakinumab as 4.5 mg/kg. Subjects were re-dosed up to a maximum dose of 9 mg/kg if no measurable improvement was observed within 48 hours of first dose every 4 weeks.

Serious adverse events	Canakinumab 0.5 mg/kg	Canakinumab (Stage II)	Canakinumab (Stage I)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	3 / 11 (27.27%)	10 / 23 (43.48%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0



Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal erosion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Juvenile arthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenosynovitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Epstein-Barr virus infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Canakinumab 1.5 mg/kg	Canakinumab 4.5 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	4 / 11 (36.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (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			
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	
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	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal erosion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (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 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Juvenile arthritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Epstein-Barr virus infection			

subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Canakinumab 0.5 mg/kg	Canakinumab (Stage II)	Canakinumab (Stage I)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	11 / 11 (100.00%)	20 / 23 (86.96%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Histiocytosis haematophagic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Melanocytic naevus			



subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Skin papilloma subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Vascular disorders			
Hot flush subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Raynaud's phenomenon subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Drug intolerance subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Feeling hot subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Injection site urticaria subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Influenza like illness subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 11 (0.00%) 0	2 / 23 (8.70%) 2
Irritability subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Pyrexia			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	2 / 11 (18.18%) 3	6 / 23 (26.09%) 8
Thirst subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Vessel puncture site haematoma subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Penis disorder subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	4 / 11 (36.36%) 4	5 / 23 (21.74%) 5
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Painful respiration subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Pharyngeal erythema subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	1 / 11 (9.09%) 2	3 / 23 (13.04%) 6
Pharyngeal hypertrophy			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 4	1 / 23 (4.35%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Tonsillar disorder subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	2 / 23 (8.70%) 7
Psychiatric disorders Fear subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Insomnia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Investigations Blood pressure systolic increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 2
Excoriation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Joint sprain			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Scratch subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 2
Cardiac disorders Extrasystoles subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	6 / 23 (26.09%) 11
Hypersomnia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Presyncope subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 11 (0.00%) 0	2 / 23 (8.70%) 3
Eye disorders			

Eye pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Eye pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Myopia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	8 / 23 (34.78%)
occurrences (all)	0	4	14
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	2 / 11 (18.18%)	3 / 23 (13.04%)
occurrences (all)	1	2	3
Anal fissure			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	3 / 11 (27.27%)	4 / 23 (17.39%)
occurrences (all)	1	3	6
Gingivitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Haematochezia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	1 / 23 (4.35%)
occurrences (all)	0	1	2
Nausea			

subjects affected / exposed	1 / 5 (20.00%)	1 / 11 (9.09%)	4 / 23 (17.39%)
occurrences (all)	1	1	4
Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	2 / 11 (18.18%)	8 / 23 (34.78%)
occurrences (all)	1	6	12
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	3
Dermatitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Heat rash			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Periorbital oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	4
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

Skin exfoliation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Urticaria subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	3 / 23 (13.04%) 4
Renal and urinary disorders Enuresis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	1 / 23 (4.35%) 1
Arthralgia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 4	2 / 23 (8.70%) 2
Back pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Muscle contracture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 1	0 / 23 (0.00%) 0
Bone pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 11 (9.09%) 2	0 / 23 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Myalgia intercostal subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 11 (0.00%) 0	1 / 23 (4.35%) 1
Neck pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Osteoporosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Tenosynovitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	1 / 23 (4.35%)
occurrences (all)	0	1	2
Acute tonsillitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Dermatophytosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	4 / 23 (17.39%)
occurrences (all)	0	2	4



Gastroenteritis viral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	2 / 11 (18.18%)	0 / 23 (0.00%)
occurrences (all)	0	3	0
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	3 / 23 (13.04%)
occurrences (all)	0	1	3
Molluscum contagiosum			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	3
Oral candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 11 (9.09%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Otitis media			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Pertussis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Pharyngotonsillitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Rash pustular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	5
Rhinitis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 11 (9.09%)	6 / 23 (26.09%)
occurrences (all)	2	1	10
Rhinotracheitis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 11 (9.09%)	1 / 23 (4.35%)
occurrences (all)	1	1	1

Tonsillitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Tooth abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	3 / 23 (13.04%)
occurrences (all)	0	0	3
Varicella			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 11 (0.00%)	2 / 23 (8.70%)
occurrences (all)	1	0	2
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 11 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

<b>Non-serious adverse events</b>	Canakinumab 1.5 mg/kg	Canakinumab 4.5 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	9 / 11 (81.82%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Histiocytosis haematophagic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Melanocytic naevus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			

Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Raynaud's phenomenon			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Drug intolerance			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Feeling hot			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Injection site urticaria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)	3 / 11 (27.27%)	
occurrences (all)	4	3	
Thirst			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vessel puncture site haematoma			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 11 (9.09%) 1	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)  Penis disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1  0 / 10 (0.00%) 0	0 / 11 (0.00%) 0  1 / 11 (9.09%) 1	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)  Painful respiration subjects affected / exposed occurrences (all)  Pharyngeal erythema subjects affected / exposed occurrences (all)  Pharyngeal hypertrophy subjects affected / exposed occurrences (all)  Rhinorrhoea subjects affected / exposed occurrences (all)  Tonsillar disorder	0 / 10 (0.00%) 0  2 / 10 (20.00%) 2  0 / 10 (0.00%) 0  1 / 10 (10.00%) 1  1 / 10 (10.00%) 4  1 / 10 (10.00%) 1  0 / 10 (0.00%) 0	0 / 11 (0.00%) 0  1 / 11 (9.09%) 1  0 / 11 (0.00%) 0  0 / 11 (0.00%) 0  0 / 11 (0.00%) 0  0 / 11 (0.00%) 0	

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	
Tonsillar hypertrophy subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 7	0 / 11 (0.00%) 0	
Psychiatric disorders Fear subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	
Investigations Blood pressure systolic increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 11 (9.09%) 1	
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	
Contusion subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 11 (0.00%) 0	
Excoriation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	
Joint sprain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 11 (0.00%) 0	
Limb injury subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 11 (0.00%) 0	
Scratch			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 11 (0.00%) 0	
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 10 (40.00%)	2 / 11 (18.18%)	
occurrences (all)	8	3	
Hypersomnia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Lymphadenopathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

Myopia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 10 (50.00%)	4 / 11 (36.36%)	
occurrences (all)	8	6	
Abdominal discomfort			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Anal fissure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
Gingivitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Haematochezia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Rectal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Vomiting			

subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4	4 / 11 (36.36%) 7	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	3	
Dermatitis allergic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Heat rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Periorbital oedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Rash pruritic			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin exfoliation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	3 / 10 (30.00%)	0 / 11 (0.00%)	
occurrences (all)	4	0	



Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Muscle contracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Bone pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Myalgia intercostal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Osteoporosis			

subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tendonitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tenosynovitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Bronchitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Acute tonsillitis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Cystitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Dermatophytosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	
Ear infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	3 / 10 (30.00%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Gastroenteritis viral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)	
occurrences (all)	0	0	

Nasopharyngitis		
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)
occurrences (all)	2	1
Molluscum contagiosum		
subjects affected / exposed	0 / 10 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	3
Oral candidiasis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	1
Pertussis		
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	1
Pharyngotonsillitis		
subjects affected / exposed	2 / 10 (20.00%)	0 / 11 (0.00%)
occurrences (all)	2	0
Rash pustular		
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	1	0
Pharyngitis		
subjects affected / exposed	3 / 10 (30.00%)	0 / 11 (0.00%)
occurrences (all)	5	0
Rhinitis		
subjects affected / exposed	4 / 10 (40.00%)	1 / 11 (9.09%)
occurrences (all)	7	1
Rhinotracheitis		
subjects affected / exposed	0 / 10 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0
Tonsillitis		
subjects affected / exposed	1 / 10 (10.00%)	1 / 11 (9.09%)
occurrences (all)	1	1
Tooth abscess		
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)
occurrences (all)	1	0

Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 10 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Varicella			
subjects affected / exposed	1 / 10 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2006	The amount of blood to be collected for pharmacodynamic (PD) determinations was reduced by using the same samples for the planned fibrinogen determinations and the PD-soluble marker determinations. The maximum total amount of blood that was going to be obtained in the first study month was also specified.
24 October 2007	This amendment was issued to decrease the number of visits and invasive procedures on study population.
17 December 2008	Minimized the burden on the subjects and simplified the study logistics, as sufficient information was available from the collected PK, PD, soluble markers, immunogenicity and PG data. The number of blood samplings was reduced and the visits schedule was simplified. Namely, the visits previously planned for days 2, 3 and 8 were skipped. After day 1 dosing the subjects were monitored with clinical visits on day 15, from then on every month or until a clear relapse was diagnosed. Blood samples were collected on day 1 and 15 for safety laboratory evaluations (blood chemistry, hematology and CRP) only and all the other blood samplings (PK, PD, PG, soluble markers and immunogenicity) were not required any longer. Only PK and immunogenicity assessments planned at follow-up and study completion were kept.
13 January 2009	All the subjects included in the study, were sampled for one more time for the newly planned pharmacogenetic exploratory assessments. The blood was collected into EDTA tubes. This amendment increased the total amount of blood sampled from each patient. Relevant Ethics committees reviewed and approved the amendment before implementation.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported