



## Clinical trial results:

**A three-part multi-center study, with a randomized, double-blind, placebo controlled, withdrawal design in Part II to assess efficacy, safety and tolerability of ACZ885 (antiinterleukin-1 monoclonal antibody) in patients with Muckle-Wells Syndrome**

### Summary

EudraCT number	2006-005455-15
Trial protocol	DE ES FR GB Outside EU/EEA
Global end of trial date	29 October 2008

### Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

### Trial information

#### Trial identification

Sponsor protocol code	CACZ885D2304
-----------------------	--------------

#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00465985
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	29 October 2008
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 October 2008
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 efficacy of canakinumab (percentage of subjects who experienced disease flare) compared with placebo as determined by the Physician's global assessment of auto-inflammatory disease activity, assessment of skin disease and inflammation markers (C-reactive protein (CRP) and/or serum amyloid A (SAA)).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 June 2007
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	United Kingdom: 9
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	India: 1
Worldwide total number of subjects	35
EEA total number of subjects	29

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)	1

Adolescents (12-17 years)	4
Adults (18-64 years)	29
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 11 centres in 5 countries.

### Pre-assignment

Screening details:

A total of 41 subjects were screened and 35 entered the study. Remaining 6 subjects were screening failures.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

The study was conducted in 3 parts, Part 1 (Open-label treatment period 1), Part 2 (double-blind treatment period) and Part 3 (open-label treatment period 2). In Part 2 of the study, randomization data were kept strictly confidential until the time of unblinding, and was accessible only to an independent, unblinded qualified study person at the investigator's site who prepared the study medication. During Part 1 and Part 3, blinding was not performed.

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Canakinumab - Part I

Arm description:

Subjects received body-weight stratified dose of canakinumab (150 milligrams (mg) or 2 mg/kilograms[kg]) subcutaneous (s.c.) injection. Subjects with body weight more than (>) 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks.

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

Dosage and administration details:

Body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c. injection was administered every 8 weeks.

<b>Arm title</b>	Canakinumab - Part II
------------------	-----------------------

Arm description:

Subjects received body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c injection. Subjects with body weight > 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks. The maximum duration of Part II was 24 weeks.

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

Dosage and administration details:

Body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c. injection was administered every

8 weeks.

<b>Arm title</b>	Placebo - Part II
------------------	-------------------

Arm description:

Placebo s.c. injection was administered every 8 weeks. The maximum duration of Part II was 24 weeks.

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

Dosage and administration details:

Placebo s.c. injection was administered every 8 weeks.

<b>Arm title</b>	Canakinumab - Part III
------------------	------------------------

Arm description:

Subjects received body- weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c. injection. Subjects with body weight > 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks. The maximum duration of Part III was 16 weeks.

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

Dosage and administration details:

Body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c. injection was administered every 8 weeks.

<b>Number of subjects in period 1</b>	Canakinumab - Part I	Canakinumab - Part II	Placebo - Part II
Started	35	15	16
Completed	31	15	4
Not completed	4	0	12
Adverse event, non-fatal	-	-	-
Unsatisfactory therapeutic effect	4	-	12

<b>Number of subjects in period 1</b>	Canakinumab - Part III
Started	31
Completed	29
Not completed	2
Adverse event, non-fatal	1
Unsatisfactory therapeutic effect	1



## Baseline characteristics

### Reporting groups

Reporting group title	Overall Study
-----------------------	---------------

Reporting group description:

All subjects who received at least one dose of study drug in open-label treatment period (Part I).

Reporting group values	Overall Study	Total	
Number of subjects	35	35	
Age categorical			
Units: Subjects			
≥4 - <17	4	4	
≥17 - <41	17	17	
≥41 - <75	14	14	
Age continuous			
Units: years			
arithmetic mean	34		
standard deviation	± 14.89	-	
Gender categorical			
Units: Subjects			
Female	25	25	
Male	10	10	

## End points

### End points reporting groups

Reporting group title	Canakinumab - Part I
Reporting group description: Subjects received body-weight stratified dose of canakinumab (150 milligrams (mg) or 2 mg/kilograms[kg]) subcutaneous (s.c.) injection. Subjects with body weight more than (>) 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks.	
Reporting group title	Canakinumab - Part II
Reporting group description: Subjects received body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c injection. Subjects with body weight > 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks. The maximum duration of Part II was 24 weeks.	
Reporting group title	Placebo - Part II
Reporting group description: Placebo s.c. injection was administered every 8 weeks. The maximum duration of Part II was 24 weeks.	
Reporting group title	Canakinumab - Part III
Reporting group description: Subjects received body- weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c. injection. Subjects with body weight > 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks. The maximum duration of Part III was 16 weeks.	
Subject analysis set title	Canakinumab (Part I and Part II)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects who received at least one dose of canakinumab in Part I and Part II were evaluated for pharmacokinetic parameters.	

### Primary: Percentage of subjects with disease flare at Week 32 (Part II)

End point title	Percentage of subjects with disease flare at Week 32 (Part II) <sup>[1]</sup>
End point description: Disease relapse in subjects was defined as a CRP and/or SAA value >30 mg/L and either a Physician's global assessment of autoinflammatory disease activity greater than minimal on a 5-point scale (0: absent to 5: severe), or a Physician's global assessment of autoinflammatory disease activity equal to minimal in conjunction with an assessment of skin disease greater than minimal using a 5-point scale (0: absent to 5: severe), or discontinued prematurely in Part II due to any reason. The analysis was performed in Intent to treat (ITT) population, defined as all subjects who received at least one dose of study drug in double-blind treatment period (Part II).	
End point type	Primary
End point timeframe: Week 32	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: The evaluation was planned for selected arm (Part II) only.

End point values	Canakinumab - Part II	Placebo - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: Percentage of subjects				
number (not applicable)	0	0.81		



## Statistical analyses

<b>Statistical analysis title</b>	Odds ratio of treatment responders
Statistical analysis description: Common odds ratio was used for test statistics and corresponding 95% confidence intervals. Null hypothesis suggested that common odds ratio was 1, i.e. the probability of having disease flare was same for both groups. Common odds ratio < 1 favored canakinumab.	
Comparison groups	Canakinumab - Part II v Placebo - Part II
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.14

## Secondary: Number of subjects with treatment response at Week 8 (Part I)

End point title	Number of subjects with treatment response at Week 8 (Part I)
End point description: Treatment response was graded as complete response (CR), partial response (PR), disease flare based on Physician's global assessment of auto-inflammatory disease activity, assessment of skin disease and serum values of CRP and/or SAA. CR was defined as physician global assessment and skin disease to be minimal ( $\leq 1$ ) using a 5-point scale (0: absent to 5: severe) and normal CRP and/or SAA. PR was defined as reduction of CRP and/or SAA from baseline by >30% but not reaching normal values and physician global assessment score improvement from baseline by at least one category. Disease flare was characterized by CRP and/or SAA > 30 mg/L and either physician global assessment score > minimal or physician global assessment score = minimal and skin disease > minimal. Non-responders were determined as subjects without PR by Day 8 or no CR by Day 15. The analysis was performed in ITT population, defined as all subjects who received at least one dose of study drug in open-label period (Part I).	
End point type	Secondary
End point timeframe: Week 8	

### Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The evaluation was planned for selected arm (Part I) only.

End point values	Canakinumab - Part I			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Number of subjects				
number (not applicable)				
Complete Response	34			
Partial Response	0			
Disease flare	1			
Non-responders	0			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Week 8 in serum concentrations of C-reactive protein and Serum Amyloid A protein at Week 32 (Part II)

End point title	Change from Week 8 in serum concentrations of C-reactive protein and Serum Amyloid A protein at Week 32 (Part II) <sup>[3]</sup>
-----------------	--

End point description:

The CRP and SAA were used as inflammatory markers. The normal level concentration was < 10 mg/L. Reduced change in concentration of CRP or SAA indicated improvement. The analysis was performed on ITT population in double-blind treatment period (Part II). Missing values were imputed using last observation carried forward (LOCF) technique.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 8 to Week 32

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The evaluation was planned for selected arm (Part II) only.

End point values	Canakinumab - Part II	Placebo - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: mg/L				
arithmetic mean (standard deviation)				
CRP	1.1 (± 3.086)	19.93 (± 24.175)		
SAA	2.27 (± 8.064)	71.09 (± 136.637)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects with defined grades of physician global assessment of autoinflammatory disease activity at Week 32 (Part II)

End point title	Percentage of subjects with defined grades of physician global
-----------------	--

## End point description:

Physician global assessment of autoinflammatory disease activity grades were based on a 5-point scale: 0=absent, 1= minimal, 2= mild, 3= moderate and 4: severe. The physician performed the assessment of following disease activities or symptoms: skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, and other symptoms related or not related to autoinflammatory syndrome. Lower scores indicated improvement. The analysis was performed on ITT population in double-blind treatment period (Part II). Missing values were imputed using LOCF technique.

End point type	Secondary
----------------	-----------

## End point timeframe:

Week 32

## Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The evaluation was planned for selected arm (Part II) only.

End point values	Canakinumab - Part II	Placebo - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: percentage of subjects				
number (not applicable)				
Absent	53.3	0		
Minimal	46.7	25		
Mild	0	50		
Moderate	0	25		
Severe	0	0		

## Statistical analyses

No statistical analyses for this end point

**Secondary: Percentage of subjects with defined grades of Subject's global assessment of symptoms total score at Week 32 (Part II)**

End point title	Percentage of subjects with defined grades of Subject's global assessment of symptoms total score at Week 32 (Part II) <sup>[5]</sup>
-----------------	---

## End point description:

Subject's or parent's rated the disease symptoms on a 5-point scale for assessing disease symptoms as 0=absent, 1= minimal, 2= mild, 3= moderate and 4: severe. The total score was sum of scores of 7-items like fever or chills, skin rash, joint or muscle pain, eye discomfort or redness, fatigue, headaches, and other symptoms. Lower scores indicated improvement. The analysis was performed on ITT population in double-blind treatment period (Part II). Missing values were imputed using LOCF technique.

End point type	Secondary
----------------	-----------

## End point timeframe:

Week 32

## Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The evaluation was planned for selected arm (Part II) only.

End point values	Canakinumab - Part II	Placebo - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: percentage of subjects				
number (not applicable)				
Absent	40	0		
Minimal	26.7	31.3		
Mild	6.7	25		
Moderate	0	37.5		
Severe	26.7	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clearance of canakinumab (Part I and Part II)

End point title	Clearance of canakinumab (Part I and Part II)
End point description:	Clearance from serum of canakinumab was obtained using NONMEM software for population pharmacokinetic modeling. The serum concentration data was obtained from subjects who received at least one dose of canakinumab from Day 1 to Day 225.
End point type	Secondary
End point timeframe:	Day 1 (pre-dose), 8 hours post-dose, Days 8, 29, 57, 85, Day 113 (pre-dose), Day 141, Day 169 (pre-dose), Day 197, 225

End point values	Canakinumab (Part I and Part II)			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Litres/day				
arithmetic mean (standard deviation)	0.177 (± 0.085)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Serum concentration of total interleukin-1beta antibody (IL-1β) (Part I, Part II and Part III)

End point title	Serum concentration of total interleukin-1beta antibody (IL-1β) (Part I, Part II and Part III)
End point description:	Pharmacodynamics of canakinumab was assessed by total IL-1β (sum of free and bound canakinumab) concentration, determined in serum by means of competitive enzyme linked immunosorbent assay

(ELISA) with limit of detection at 0.25 picograms/millilitre (pg/mL). The analysis was performed in ITT population in respective parts of the study (Part I, II and III).

End point type	Secondary
End point timeframe:	
Day 1 (pre-dose), 8 hours post-dose, Days 8, 29, 57, 85, Day 113 (pre-dose), Day 141, Day 169 (pre-dose), Day 197, 225, 253, Day 281 (pre-dose), Day 309, 337	

End point values	Canakinumab - Part I	Canakinumab - Part II	Placebo - Part II	Canakinumab - Part III
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34 <sup>[6]</sup>	15 <sup>[7]</sup>	5 <sup>[8]</sup>	31 <sup>[9]</sup>
Units: pg/mL				
arithmetic mean (standard deviation)	19.047 (± 17.6609)	21.943 (± 10.3698)	0.596 (± 0.7289)	23.018 (± 16.5193)

Notes:

[6] - Evaluable subjects in Part I for this measure at Day 57

[7] - Evaluable subjects in Part II at Day 169

[8] - Evaluable subjects in Part II at Day 169

[9] - Evaluable subjects in Part III at Day 337

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of subjects with skin disease at Week 32 (Part II)

End point title	Percentage of subjects with skin disease at Week 32 (Part
-----------------	---

End point description:

Physician assessed the skin disease (urticarial skin rash) in subjects based on 5-point scale: 0=absent, 1= minimal, 2= mild, 3= moderate and 4: severe. Lower scores indicated improvement. The analysis was performed in ITT population of double blind treatment period (Part II), imputed using LOCF technique.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 8, Week 32

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The evaluation was planned for selected arm (Part II) only.

End point values	Canakinumab - Part II	Placebo - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: percentage of subjects				
number (not applicable)				
Absent	93.3	31.3		
Minimal	6.7	18.8		
Mild	0	31.3		
Moderate	0	18.8		
Severe	0	0		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with clinically significant findings in audiogram, neurological and ophthalmological assessments at Week 32 (Part II)

End point title	Number of subjects with clinically significant findings in audiogram, neurological and ophthalmological assessments at Week 32 (Part II) <sup>[11]</sup>
-----------------	--

#### End point description:

Audiologic examination evaluated the status of hearing in subjects and included air-conduction thresholds for pure tone frequencies, bone conduction thresholds when indicated and possible, tympanometry, and distortion product otoacoustic emissions. A structured neurological assessment was conducted on each subject, with attention to signs of chronic meningitis, chronic headaches, fever, and vomiting. A standardized ophthalmologic evaluation was performed by an ophthalmology consultant focusing on visual changes that are sensitive in documenting optic nerve function. The overall interpretation of these assessments was categorized as normal, clinically insignificant abnormality, clinically significant abnormality when compared to baseline. The analysis was performed in safety population, defined as subjects who received at least one dose of study drug and had at least one post-baseline safety assessment.

End point type	Secondary
----------------	-----------

#### End point timeframe:

Week 32

#### Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The evaluation was planned for selected arm (Part II) only.

End point values	Canakinumab - Part II	Placebo - Part II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	16		
Units: number of subjects				
number (not applicable)				
Clinically significant audiogram assessment	7	11		
Clinically significant neurological assessment	6	1		
Clinically significant ophthalmological assessment	2	1		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with anti-canakinumab antibodies (Part I, Part II and Part III)

End point title	Number of subjects with anti-canakinumab antibodies (Part I, Part II and Part III)
End point description:	
Immunogenicity assessment included determination of anti-canakinumab (ACZ885) antibodies in serum samples when canakinumab was administered through subcutaneous route into the body. The immune response (presence of antibodies) was detected using BIAcore system based on a validated surface plasmon resonance spectroscopy assay method. The analysis was performed in safety population, defined as subjects who received at least one dose of study drug and had at least one post--baseline immunogenicity assessment.	
End point type	Secondary
End point timeframe:	
Baseline, Day 1, 57, 113, 169, 225, 281, 337	

<b>End point values</b>	Canakinumab - Part I	Canakinumab - Part II	Placebo - Part II	Canakinumab - Part III
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	15	16	31
Units: Number of subjects				
number (not applicable)	0	0	0	0

### Statistical analyses

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
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

### Reporting groups

Reporting group title	Canakinumab - Part II
-----------------------	-----------------------

Reporting group description:

Subjects received body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c injection. Subjects with body weight > 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks.

Reporting group title	Canakinumab - Part I
-----------------------	----------------------

Reporting group description:

Subjects received body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c injection. Subjects with body weight > 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks.

Reporting group title	Placebo - Part II
-----------------------	-------------------

Reporting group description:

Subjects received placebo s.c. injection matching to canakinumab every 8 weeks.

Reporting group title	Canakinumab - Part III
-----------------------	------------------------

Reporting group description:

Subjects received body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c injection. Subjects with body weight > 40 kg received one injection of canakinumab 150 mg s.c. while subjects with a body weight between 15 kg to 40 kg received an equivalent of 2 mg/kg s.c. every 8 weeks.

Reporting group title	Canakinumab Treated (Total)
-----------------------	-----------------------------

Reporting group description:

Subjects who received body-weight stratified dose of canakinumab (150 mg or 2 mg/kg) s.c injection during the study (Part I, II and III).

Serious adverse events	Canakinumab - Part II	Canakinumab - Part I	Placebo - Part II
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Intraocular pressure increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			



complications			
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Canakinumab - Part III	Canakinumab Treated (Total)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Canakinumab - Part II	Canakinumab - Part I	Placebo - Part II
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	27 / 35 (77.14%)	14 / 16 (87.50%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 15 (0.00%)	1 / 35 (2.86%)	1 / 16 (6.25%)
occurrences (all)	0	1	1

Hot flush			
subjects affected / exposed	1 / 15 (6.67%)	1 / 35 (2.86%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Orthostatic hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 35 (5.71%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hangover			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 35 (2.86%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
House dust allergy subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Allergic cough subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Cough subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 3	1 / 35 (2.86%) 1	0 / 16 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 35 (2.86%) 1	1 / 16 (6.25%) 1
Respiratory tract congestion subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 35 (2.86%) 1	0 / 16 (0.00%) 0
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 35 (2.86%) 1	0 / 16 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Depression subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Stress			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Investigations			
Liver function test abnormal subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Weight increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	3 / 35 (8.57%) 3	0 / 16 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 3	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Face injury subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Joint sprain subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Traumatic haematoma subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Complex regional pain syndrome subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Memory impairment subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Nystagmus			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Sciatica subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	1 / 35 (2.86%) 1	0 / 16 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Tension headache subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 35 (2.86%) 1	0 / 16 (0.00%) 0
Blood and lymphatic system disorders Lymphocytosis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Neutropenia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Tinnitus subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Vertigo subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 35 (2.86%) 1	0 / 16 (0.00%) 0
Eye disorders Erythema of eyelid subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	2 / 35 (5.71%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Aphthous stomatitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	2 / 16 (12.50%)
occurrences (all)	1	0	2
Haemorrhoids			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	3 / 35 (8.57%)	1 / 16 (6.25%)
occurrences (all)	1	3	2
Stomach discomfort			
subjects affected / exposed	1 / 15 (6.67%)	1 / 35 (2.86%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Tooth impacted			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 35 (2.86%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)	1 / 35 (2.86%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 35 (2.86%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Groin pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Muscle contracture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 15 (0.00%)	2 / 35 (5.71%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Pain in extremity			



subjects affected / exposed	0 / 15 (0.00%)	1 / 35 (2.86%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Tendonitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)	3 / 35 (8.57%)	1 / 16 (6.25%)
occurrences (all)	1	5	1
Herpes zoster			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Influenza			
subjects affected / exposed	2 / 15 (13.33%)	1 / 35 (2.86%)	3 / 16 (18.75%)
occurrences (all)	2	1	3
Nasopharyngitis			
subjects affected / exposed	4 / 15 (26.67%)	4 / 35 (11.43%)	2 / 16 (12.50%)
occurrences (all)	4	4	2
Oral herpes			
subjects affected / exposed	0 / 15 (0.00%)	1 / 35 (2.86%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	4 / 35 (11.43%)	2 / 16 (12.50%)
occurrences (all)	1	4	2
Pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Tinea pedis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 35 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Tooth infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Tooth abscess subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 35 (0.00%) 0	1 / 16 (6.25%) 3
Viral infection subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3	0 / 35 (0.00%) 0	0 / 16 (0.00%) 0
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 35 (0.00%) 0	1 / 16 (6.25%) 1

<b>Non-serious adverse events</b>	Canakinumab - Part III	Canakinumab Treated (Total)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 31 (77.42%)	35 / 35 (100.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Hot flush			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Orthostatic hypotension			

subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hangover			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Non-cardiac chest pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Seasonal allergy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
House dust allergy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Allergic cough			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Oropharyngeal pain			
subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences (all)	1	5	
Epistaxis			
subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Respiratory tract congestion			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Rhinitis allergic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	2	
Rhinorrhoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Depression			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Stress			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Weight increased			

subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	4 / 35 (11.43%) 4	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	3	
Face injury			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Joint sprain			
subjects affected / exposed	0 / 31 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Traumatic haematoma			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 31 (9.68%)	5 / 35 (14.29%)	
occurrences (all)	3	6	
Complex regional pain syndrome			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Nystagmus			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Sciatica			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences (all)	2	4	
Paraesthesia			

subjects affected / exposed occurrences (all)  Tension headache subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0  1 / 31 (3.23%) 1	1 / 35 (2.86%) 1  2 / 35 (5.71%) 2	
Blood and lymphatic system disorders Lymphocytosis subjects affected / exposed occurrences (all)  Neutropenia subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0  0 / 31 (0.00%) 0	1 / 35 (2.86%) 1  1 / 35 (2.86%) 1	
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all)  Tinnitus subjects affected / exposed occurrences (all)  Vertigo subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0  1 / 31 (3.23%) 1  2 / 31 (6.45%) 4	1 / 35 (2.86%) 1  2 / 35 (5.71%) 2  3 / 35 (8.57%) 5	
Eye disorders Erythema of eyelid subjects affected / exposed occurrences (all)  Eye pain subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0  0 / 31 (0.00%) 0	1 / 35 (2.86%) 1  1 / 35 (2.86%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Abdominal discomfort subjects affected / exposed occurrences (all)  Abdominal pain upper	2 / 31 (6.45%) 3  0 / 31 (0.00%) 0	2 / 35 (5.71%) 3  1 / 35 (2.86%) 1	

subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Aphthous stomatitis			
subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	5 / 31 (16.13%)	7 / 35 (20.00%)	
occurrences (all)	7	10	
Haemorrhoids			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	1 / 31 (3.23%)	5 / 35 (14.29%)	
occurrences (all)	1	7	
Stomach discomfort			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Rectal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Tooth impacted			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Erythema			
subjects affected / exposed	2 / 31 (6.45%)	3 / 35 (8.57%)	
occurrences (all)	2	3	

Hyperhidrosis			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Pruritus			
subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 31 (6.45%)	3 / 35 (8.57%)	
occurrences (all)	2	3	
Arthralgia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Groin pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Muscle contracture			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Muscle spasms			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences (all)	2	4	
Pain in extremity			
subjects affected / exposed	2 / 31 (6.45%)	3 / 35 (8.57%)	
occurrences (all)	2	3	
Musculoskeletal pain			
subjects affected / exposed	2 / 31 (6.45%)	4 / 35 (11.43%)	
occurrences (all)	2	4	
Tendonitis			



subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 31 (0.00%)	4 / 35 (11.43%)	
occurrences (all)	0	7	
Herpes zoster			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	2 / 31 (6.45%)	4 / 35 (11.43%)	
occurrences (all)	2	5	
Influenza			
subjects affected / exposed	0 / 31 (0.00%)	6 / 35 (17.14%)	
occurrences (all)	0	6	
Nasopharyngitis			
subjects affected / exposed	4 / 31 (12.90%)	12 / 35 (34.29%)	
occurrences (all)	4	14	
Oral herpes			
subjects affected / exposed	0 / 31 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Rhinitis			
subjects affected / exposed	0 / 31 (0.00%)	6 / 35 (17.14%)	
occurrences (all)	0	7	
Pharyngitis			
subjects affected / exposed	2 / 31 (6.45%)	4 / 35 (11.43%)	
occurrences (all)	2	4	
Tinea pedis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	3 / 35 (8.57%) 5	
Viral infection subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	2 / 35 (5.71%) 3	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	2 / 35 (5.71%) 4	
Metabolism and nutrition disorders			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 35 (2.86%) 1	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported