



Clinical trial results:

A randomized, double-blind, placebo controlled study of canakinumab in patients with Hereditary Periodic Fevers (TRAPS, HIDS, or crFMF), with subsequent randomized withdrawal/dosing frequency reduction and open-label long-term treatment epochs

Summary

EudraCT number	2013-004291-35
Trial protocol	IT ES IE DE BE HU NL GR
Global end of trial date	04 July 2017

Results information

Result version number	v1 (current)
This version publication date	23 December 2017
First version publication date	23 December 2017

Trial information

Trial identification

Sponsor protocol code	CACZ885N2301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02059291
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-PIP04-14, EMA-000060-PIP05-14
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	04 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the randomized treatment epoch and of the overall study was to demonstrate that canakinumab treatment at a dose of 150 mg (or 2 mg/kg in patients weighing ≤ 40 kg) sc q4w is superior to placebo in achieving a clinically meaningful reduction of disease activity, defined as resolution of the index flare at Day 15 and no new disease flares over 16 weeks of treatment.

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	27 June 2014
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	Belgium: 14
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Turkey: 20
Country: Number of subjects enrolled	United States: 2

Worldwide total number of subjects	203
EEA total number of subjects	137

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)	2
Children (2-11 years)	67
Adolescents (12-17 years)	45
Adults (18-64 years)	86
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study consists of 4 study epochs. A total of 203 participants ((181 randomized + 4 non-randomized open-label participants who entered in Epoch 2 (E2)) + (18 TRAPS roll-over participants from ACZ885D2203 (NCT01242813) and ACZ885D2207M who entered in Epoch 3 (E3))) have been enrolled into this study.

Pre-assignment

Screening details:

Of the 181 E2 randomized patients 41 were re-randomized to canakinumab or placebo, and 126 patients were not re-randomized and switched to open-label (OL) treatment in E3. 2 re-randomized and 6 OL patients discontinued E3. 178 patients from E2 and E3 received OL treatment in E4.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Epoch 2 crFMF: 150 mg

Arm description:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing \leq 40kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded up-titration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing \leq 40 kg) q4w and re-flared (PGA \geq 2 and CRP \geq 30 mg/L) were not eligible for further up-titration.

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

Dosage and administration details:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing \leq 40kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded up-titration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing \leq 40 kg) q4w and re-flared (PGA \geq 2 and CRP \geq 30 mg/L) were not eligible for further up-titration.

Arm title	Epoch 2: crCMF: placebo
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Arm description:

During epoch 2, participants received matching placebo to canakinumab 150 mg. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab. 150mg, participants were up-titrated to open-label canakinumab 300 mg

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

Dosage and administration details:

During epoch 2, participants received matching placebo to canakinumab 150 mg. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between day 8 and day 28, and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were uptitrated to open-label canakinumab 300 mg.

Arm title	Epoch 2: HIDS/MKD: 150 mg
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Arm description:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing ≤ 40 kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between day 8 and day 28, and then received blinded uptitration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q4w and re-flared (PGA ≥ 2 and CRP ≥ 30 mg/L) were not eligible for further up-titration.

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Investigational medicinal product name	Canakinumab
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Dosage and administration details:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing ≤ 40 kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between day 8 and day 28, and then received blinded uptitration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q4w and re-flared (PGA ≥ 2 and CRP ≥ 30 mg/L) were not eligible for further up-titration.

Arm title	Epoch 2: HIDS/MKD: placebo
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Arm description:

During epoch 2, participants received matching placebo to canakinumab 150 mg qw4. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between day 8 and day 28 and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were uptitrated to open-label canakinumab 300 mg.

Arm type	Experimental
Investigational medicinal product name	Canakinumab
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Routes of administration	Subcutaneous use

Dosage and administration details:

During epoch 2, participants received matching placebo to canakinumab 150 mg qw4. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between day 8 and day 28 and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were uptitrated to open-label canakinumab 300 mg.

Arm title	Epoch 2: TRAPS: 150 mg
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Arm description:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing ≤ 40 kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on

dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between day 8 and day 28, and then received blinded up-titration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q4w and re-flared (PGA ≥ 2 and CRP ≥ 30 mg/L) were not eligible for further up-titration

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

Dosage and administration details:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing ≤ 40 kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between day 8 and day 28, and then received blinded up-titration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q4w and re-flared (PGA ≥ 2 and CRP ≥ 30 mg/L) were not eligible for further up-titration

Arm title	Epoch 2: TRAPS: placebo
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Arm description:

During epoch 2, participants received matching placebo to canakinumab 150 mg qw4. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between Day 8 and 28 and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were up-titrated to open-label canakinumab 300 mg.

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

Dosage and administration details:

During epoch 2, participants received matching placebo to canakinumab 150 mg qw4. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing ≤ 40 kg) between Day 8 and 28 and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were up-titrated to open-label canakinumab 300 mg.

Arm title	Epoch 2: Non-randomized open label treatment - crFMF
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Arm description:

Canakinumab-naïve Japanese patients with non-exon 10 mutations received open-label canakinumab 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) q4w .

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

Dosage and administration details:

Canakinumab-naïve Japanese patients with non-exon 10 mutations received open-label canakinumab 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) q4w

Arm title	Epoch 2: Non-randomized open label HIDS/MKD
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Arm description:

Participants in the 28 days to less than 2 years old cohort who received open-label canakinumab 150 mg (or 2mg/kg for patients weighing ≤ 40 kg) q4w.

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

Dosage and administration details:

Participants in the 28 days to less than 2 years old cohort who received open-label canakinumab 150 mg (or 2mg/kg for patients weighing ≤ 40 kg) q4w.

Arm title	Epoch 2 (Epoch 3) - non-randomized open label TRAPS
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Arm description:

Open-label treatment in Epoch 3 was initiated for TRAPS patients who rolled over from CACZ885D2203 or CACZ885D2207M.

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

Dosage and administration details:

Open-label treatment in Epoch 3 was initiated for TRAPS patients who rolled over from CACZ885D2203 or CACZ885D2207M.

Number of subjects in period 1	Epoch 2 crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg
Started	31	32	37
Completed	31	31	36
Not completed	0	1	1
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	1
Lack of efficacy	-	-	-

Number of subjects in period 1	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo
Started	35	22	24
Completed	33	22	22
Not completed	2	0	2
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	-	-
Lack of efficacy	1	-	1

Number of subjects in period 1	Epoch 2: Non-randomized open label treatment - crFMF	Epoch 2: Non-randomized open label HIDS/MKD	Epoch 2 (Epoch 3) - non-randomized open label TRAPS
Started	2	2	18
Completed	2	1	16
Not completed	0	1	2
Consent withdrawn by subject	-	-	1

Adverse event, non-fatal	-	1	1
Lack of efficacy	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	Epoch 2 crFMF: 150 mg
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Reporting group description:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing \leq 40kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded up-titration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing \leq 40 kg) q4w and re-flared (PGA \geq 2 and CRP \geq 30 mg/L) were not eligible for further up-titration.

Reporting group title	Epoch 2: crCMF: placebo
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Reporting group description:

During epoch 2, participants received matching placebo to canakinumab 150 mg. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were up-titrated to open-label canakinumab 300 mg.

Reporting group title	Epoch 2: HIDS/MKD: 150 mg
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Reporting group description:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing \leq 40kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded up-titration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing \leq 40 kg) q4w and re-flared (PGA \geq 2 and CRP \geq 30 mg/L) were not eligible for further up-titration.

Reporting group title	Epoch 2: HIDS/MKD: placebo
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Reporting group description:

During epoch 2, participants received matching placebo to canakinumab 150 mg qw4. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28 and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were up-titrated to open-label canakinumab 300 mg.

Reporting group title	Epoch 2: TRAPS: 150 mg
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Reporting group description:

During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing \leq 40kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded up-titration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing \leq 40 kg) q4w and re-flared (PGA \geq 2 and CRP \geq 30 mg/L) were not eligible for further up-titration.

Reporting group title	Epoch 2: TRAPS: placebo
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Reporting group description:

During epoch 2, participants received matching placebo to canakinumab 150 mg qw4. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between Day 8 and 28 and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were up-titrated to open-label canakinumab 300 mg.

Reporting group title	Epoch 2: Non-randomized open label treatment - crFMF
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Reporting group description:

Canakinumab-naïve Japanese patients with non-exon 10 mutations received open-label canakinumab 150 mg (or 2 mg/kg for patients weighing \leq 40 kg) q4w.

Reporting group title	Epoch 2: Non-randomized open label HIDS/MKD
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Reporting group description:

Participants in the 28 days to less than 2 years old cohort who received open-label canakinumab 150 mg (or 2mg/kg for patients weighing \leq 40 kg) q4w.

Reporting group title	Epoch 2 (Epoch 3) - non-randomized open label TRAPS
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Reporting group description:

Open-label treatment in Epoch 3 was initiated for TRAPS patients who rolled over from CACZ885D2203 or CACZ885D2207M.

Reporting group values	Epoch 2 crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg
Number of subjects	31	32	37
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	9	4	18
Adolescents (12-17 years)	5	11	9
Adults (18-64 years)	17	16	10
From 65-84 years	0	1	0
85 years and over	0	0	0
Gender, Male/Female Units: Subjects			
Female	14	15	24
Male	17	17	13
Race Units: Subjects			
Asian	0	1	0
White	27	27	34
Other	4	4	3

Reporting group values	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo
Number of subjects	35	22	24
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	19	9	8
Adolescents (12-17 years)	7	5	5
Adults (18-64 years)	9	7	11
From 65-84 years	0	1	0
85 years and over	0	0	0
Gender, Male/Female Units: Subjects			
Female	19	10	13
Male	16	12	11

Race			
Units: Subjects			
Asian	1	2	4
White	31	20	18
Other	3	0	2

Reporting group values	Epoch 2: Non-randomized open label treatment - crFMF	Epoch 2: Non-randomized open label HIDS/MKD	Epoch 2 (Epoch 3) - non-randomized open label TRAPS
Number of subjects	2	2	18
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	2	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	2
Adults (18-64 years)	2	0	15
From 65-84 years	0	0	1
85 years and over	0	0	0
Gender, Male/Female			
Units: Subjects			
Female	2	0	7
Male	0	2	11
Race			
Units: Subjects			
Asian	2	1	0
White	0	1	16
Other	0	0	2

Reporting group values	Total		
Number of subjects	203		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	2		
Children (2-11 years)	67		
Adolescents (12-17 years)	44		
Adults (18-64 years)	87		
From 65-84 years	3		
85 years and over	0		
Gender, Male/Female			
Units: Subjects			
Female	104		
Male	99		

Race			
Units: Subjects			
Asian	11		
White	174		
Other	18		

End points

End points reporting groups

Reporting group title	Epoch 2 crFMF: 150 mg
Reporting group description: During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing \leq 40kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded uptitration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing \leq 40 kg) q4w and re-flared (PGA \geq 2 and CRP \geq 30 mg/L) were not eligible for further up-titration.	
Reporting group title	Epoch 2: crCMF: placebo
Reporting group description: During epoch 2, participants received matching placebo to canakinumab 150 mg. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were uptitrated to open-label canakinumab 300 mg.	
Reporting group title	Epoch 2: HIDS/MKD: 150 mg
Reporting group description: During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing \leq 40kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded uptitration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing \leq 40 kg) q4w and re-flared (PGA \geq 2 and CRP \geq 30 mg/L) were not eligible for further up-titration.	
Reporting group title	Epoch 2: HIDS/MKD: placebo
Reporting group description: During epoch 2, participants received matching placebo to canakinumab 150 mg qw4. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28 and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were uptitrated to open-label canakinumab 300 mg.	
Reporting group title	Epoch 2: TRAPS: 150 mg
Reporting group description: During Epoch 2, participants received canakinumab 150mg (or 2mg/kg for participants weighing \leq 40kg) q4w for 16 weeks. If participants were eligible for blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between day 8 and day 28, and then received blinded uptitration to canakinumab 300 mg q4w from day 29 through day 112. If patients on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing \leq 40 kg) q4w and re-flared (PGA \geq 2 and CRP \geq 30 mg/L) were not eligible for further up-titration.	
Reporting group title	Epoch 2: TRAPS: placebo
Reporting group description: During epoch 2, participants received matching placebo to canakinumab 150 mg qw4. Participants who required blinded escape, they received a single add-on dose of canakinumab (150 mg or 2mg/kg for participants weighing \leq 40kg) between Day 8 and 28 and then received blinded one dose of placebo and one dose of canakinumab q4w from day 29 through day 112. If flare or re-flare still occurred after receipt of canakinumab 150mg, participants were uptitrated to open-label canakinumab 300 mg.	
Reporting group title	Epoch 2: Non-randomized open label treatment - crFMF
Reporting group description: Canakinumab-naïve Japanese patients with non-exon 10 mutations received open-label canakinumab 150 mg (or 2 mg/kg for patients weighing \leq 40 kg) q4w .	
Reporting group title	Epoch 2: Non-randomized open label HIDS/MKD
Reporting group description: Participants in the 28 days to less than 2 years old cohort who received open-label canakinumab 150 mg (or 2mg/kg for patients weighing \leq 40 kg) q4w.	
Reporting group title	Epoch 2 (Epoch 3) - non-randomized open label TRAPS

Primary: Percentage of participants with resolution of initial flare and absence of new flares up to the end of the randomized treatment epoch (16 weeks)

End point title	Percentage of participants with resolution of initial flare and absence of new flares up to the end of the randomized treatment epoch (16 weeks) ^[1]
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End point description:

Resolution of the initial disease flare is defined as: Physician's Global Assessment of Disease activity (PGA) <2 and C-reactive protein (CRP) within normal range (≤ 10 mg/L) or reduction by at least 70% from baseline. The PGA was evaluated by the investigator based on a 5-point scale: 0 = None (no) disease associated with clinical signs and symptoms; 1 = minimal disease associated signs and symptoms; 2 = mild disease associated signs and symptoms; 3 = moderate disease associated signs and symptoms; and 5 = severe disease associated signs and symptoms.

End point type	Primary
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End point timeframe:

16 weeks

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: Statistics do not apply to all arms.

End point values	Epoch 2 crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	37	35
Units: Percentage of participants				
number (not applicable)	61.29	6.25	35.14	5.71

End point values	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Percentage of participants				
number (not applicable)	45.45	8.33		

Statistical analyses

Statistical analysis title	Resolution of initial flare/absence of new flares
Comparison groups	Epoch 2 crFMF: 150 mg v Epoch 2: crCMF: placebo

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Fisher's exact test

Statistical analysis title	Resolution of initial flare/absence of new flares
Comparison groups	Epoch 2: TRAPS: 150 mg v Epoch 2: TRAPS: placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.005
Method	Fisher's exact test

Statistical analysis title	Resolution of initial flare/absence of new flares
Comparison groups	Epoch 2: HIDS/MKD: 150 mg v Epoch 2: HIDS/MKD: placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002
Method	Fisher's exact test

Secondary: Percentage of participants who achieve Physician's global assessment < 2

End point title	Percentage of participants who achieve Physician's global assessment < 2 ^[2]
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End point description:

The PGA was evaluated by the investigator based on a 5-point scale: 0 = None (no) disease associated with clinical signs and symptoms; 1 = minimal disease associated signs and symptoms; 2 = mild disease associated signs and symptoms; 3 = moderate disease associated signs and symptoms; and 5 = severe disease associated signs and symptoms.

End point type	Secondary
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End point timeframe:

16 weeks

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: Statistics do not apply to all arms.

End point values	Epoch 2 crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	37	35
Units: Percentage of participants				
number (not applicable)	64.52	9.38	45.95	5.71

End point values	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Percentage of participants				
number (not applicable)	45.45	4.17		

Statistical analyses

Statistical analysis title	Participnats who achieve PGA < 2
Comparison groups	Epoch 2 crFMF: 150 mg v Epoch 2: crCMF: placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.15
upper limit	69.21

Statistical analysis title	Participnats who achieve PGA < 2
Comparison groups	Epoch 2: HIDS/MKD: 150 mg v Epoch 2: HIDS/MKD: placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	13.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.83
upper limit	65.59

Statistical analysis title	Participnats who achieve PGA < 2
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Comparison groups	Epoch 2: TRAPS: 150 mg v Epoch 2: TRAPS: placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0028
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	23.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.52
upper limit	224.86

Secondary: Percentage of participants with the serologic remission

End point title	Percentage of participants with the serologic remission ^[3]
End point description:	Serologic remission was defined as C-reactive protein ≤ 10 mg/L.
End point type	Secondary
End point timeframe:	16 weeks

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: Statistics do not apply to all arms.

End point values	Epoch 2 crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	37	35
Units: Percentage of participants				
number (not applicable)	67.74	6.25	40.54	5.71

End point values	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Percentage of participants				
number (not applicable)	36.36	8.33		

Statistical analyses

Statistical analysis title	Participants with the serologic remission
Comparison groups	Epoch 2 crFMF: 150 mg v Epoch 2: crCMF: placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	29.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.86
upper limit	151.31

Statistical analysis title	Participants with the serologic remission
Comparison groups	Epoch 2: HIDS/MKD: 150 mg v Epoch 2: HIDS/MKD: placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.53
upper limit	63.89

Statistical analysis title	Participants with the serologic remission
Comparison groups	Epoch 2: TRAPS: 150 mg v Epoch 2: TRAPS: placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0149
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	36.57

Secondary: Percentage of participants with normalized Serum Amyloid A (SAA) level

End point title	Percentage of participants with normalized Serum Amyloid A (SAA) level ^[4]
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End point description:

Normalized SAA was defined as SAA ≤ 10 mg/L.

End point type	Secondary
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End point timeframe:

16 weeks

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: Statistics do not apply to all arms.

End point values	Epoch 2 crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	37	35
Units: Percentage of participants				
number (not applicable)	25.81	0.00	13.51	2.86

End point values	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: Percentage of participants				
number (not applicable)	27.27	0.00		

Statistical analyses

Statistical analysis title	Participants with normalized SAA level
Comparison groups	Epoch 2 crFMF: 150 mg v Epoch 2: crCMF: placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0286
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	17.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	332.92

Statistical analysis title	Participants with normalized SAA level
Comparison groups	Epoch 2: HIDS/MKD: 150 mg v Epoch 2: HIDS/MKD: placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0778
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	51.97

Statistical analysis title	Participants with normalized SAA level
Comparison groups	Epoch 2: TRAPS: 150 mg v Epoch 2: TRAPS: placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0235
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	268.5

Secondary: Percentage of participants of canakinumab responders from epoch 2 who maintained a clinically meaningful response (absence of new flares) (40 weeks)

End point title	Percentage of participants of canakinumab responders from epoch 2 who maintained a clinically meaningful response (absence of new flares) (40 weeks) ^[5]
End point description:	
A responder was defined as a participant who had no flare between week 16 and week 40.	
End point type	Secondary
End point timeframe:	
40 weeks	

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: Statistics do not apply to all arms.

End point values	Epoch 2 crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	6	7
Units: Percentage of participants				
number (not applicable)	77.8	30.0	50.0	14.3

End point values	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	5		
Units: Percentage of participants				
number (not applicable)	75.0	40.0		

Statistical analyses

Statistical analysis title	Absence of new flares from weeks 16 to 40
Comparison groups	Epoch 2 crFMF: 150 mg v Epoch 2: crCMF: placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0513
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	113.44

Statistical analysis title	Absence of new flares from weeks 16 to 40
Comparison groups	Epoch 2: HIDS/MKD: 150 mg v Epoch 2: HIDS/MKD: placebo

Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2168
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	366.24

Statistical analysis title	Absence of new flares from weeks 16 to 40
Comparison groups	Epoch 2: TRAPS: 150 mg v Epoch 2: TRAPS: placebo
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3571
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	313.49

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	20.0

Reporting groups

Reporting group title	Non-randomized open@label group at the@beginning of epoch 2
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Reporting group description:

Non-randomized open@label group at the@beginning of epoch 2

Reporting group title	Roll over subjects
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Reporting group description:

Roll over subjects

Reporting group title	Randomized at the@beginning of epoch 2
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Reporting group description:

Randomized at the@beginning of epoch 2

Reporting group title	Any ACZ group
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Reporting group description:

Any ACZ group

Serious adverse events	Non-randomized open@label group at the@beginning of epoch 2	Roll over subjects	Randomized at the@beginning of epoch 2
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	1 / 18 (5.56%)	47 / 181 (25.97%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Hyperpyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyserositis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
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 / 4 (0.00%)	1 / 18 (5.56%)	7 / 181 (3.87%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal stenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord polyp			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
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			
Depression			

subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional self-injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Scar			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Familial mediterranean fever			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	4 / 181 (2.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyper IgD syndrome			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	4 / 181 (2.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tumour necrosis factor receptor-associated periodic syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	4 / 181 (2.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
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 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
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			
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
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 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal ulcer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulomatous liver disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulomatous rosacea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyoderma gangrenosum			

subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	0 / 181 (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
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
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			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
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 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	5 / 181 (2.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval abscess			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	0 / 181 (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
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Any ACZ group		
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 193 (24.35%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Hyperpyrexia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyserositis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngeal stenosis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal pain			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vocal cord polyp			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intentional self-injury			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Schizophrenia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Scar			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Familial mediterranean fever			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Hyper IgD syndrome			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 0		
Tumour necrosis factor receptor-associated periodic syndrome			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			

subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Ascites				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileal ulcer				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 193 (1.04%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Bile duct stone			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Granulomatous liver disease			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic cirrhosis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Granulomatous rosacea			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyoderma gangrenosum			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Endocrine disorders			
Thyroiditis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	0 / 193 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Conjunctivitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes virus infection			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infectious colitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			

subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orchitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngotonsillitis				
subjects affected / exposed	1 / 193 (0.52%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 193 (2.59%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vulval abscess			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obesity			

subjects affected / exposed	1 / 193 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Non-randomized open@label group at the@beginning of epoch 2	Roll over subjects	Randomized at the@beginning of epoch 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	18 / 18 (100.00%)	176 / 181 (97.24%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pyogenic granuloma			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	2 / 18 (11.11%)	1 / 181 (0.55%)
occurrences (all)	0	2	1
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	0 / 181 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	11 / 181 (6.08%)
occurrences (all)	0	1	17
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	12 / 181 (6.63%)
occurrences (all)	0	0	13
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	12 / 181 (6.63%)
occurrences (all)	0	0	15
Injection site reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	28 / 181 (15.47%)
occurrences (all)	0	1	78
Malaise			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 18 (5.56%) 1	5 / 181 (2.76%) 7
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 18 (0.00%) 0	14 / 181 (7.73%) 16
Pyrexia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 14	5 / 18 (27.78%) 6	71 / 181 (39.23%) 276
Reproductive system and breast disorders Breast mass subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	0 / 181 (0.00%) 0
Polycystic ovaries subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	1 / 181 (0.55%) 1
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	0 / 181 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	3 / 18 (16.67%) 3	38 / 181 (20.99%) 62
Epistaxis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 18 (0.00%) 0	11 / 181 (6.08%) 15
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	40 / 181 (22.10%) 60
Pleuritic pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	0 / 181 (0.00%) 0
Pneumonitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	0 / 181 (0.00%) 0
Rhinitis allergic			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 2	3 / 181 (1.66%) 3
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 4	1 / 18 (5.56%) 1	3 / 181 (1.66%) 3
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 18 (0.00%) 0	1 / 181 (0.55%) 1
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	5 / 181 (2.76%) 6
C-reactive protein increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 18 (0.00%) 0	2 / 181 (1.10%) 2
Eosinophil count increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	0 / 181 (0.00%) 0
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	0 / 181 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 18 (0.00%) 0	1 / 181 (0.55%) 1
Neutrophil count increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 18 (5.56%) 1	2 / 181 (1.10%) 2
Serum amyloid A protein increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 5	3 / 18 (16.67%) 3	6 / 181 (3.31%) 9
White blood cell count increased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 18 (5.56%) 1	2 / 181 (1.10%) 2
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	2 / 181 (1.10%) 2
Skin abrasion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	1 / 181 (0.55%) 1
Thermal burn subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 2	2 / 181 (1.10%) 2
Wound subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 2	0 / 181 (0.00%) 0
Congenital, familial and genetic disorders Familial mediterranean fever subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 18 (0.00%) 0	29 / 181 (16.02%) 92
Hyper IgD syndrome subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 18 (0.00%) 0	21 / 181 (11.60%) 82
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	0 / 181 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	2 / 181 (1.10%) 2
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 7	2 / 18 (11.11%) 6	64 / 181 (35.36%) 130
Somnolence subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 18 (0.00%) 0	0 / 181 (0.00%) 0
Blood and lymphatic system disorders Anaemia			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	8 / 181 (4.42%) 9
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 18 (0.00%) 0	27 / 181 (14.92%) 41
Neutropenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 18 (0.00%) 0	11 / 181 (6.08%) 13
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 18 (0.00%) 0	13 / 181 (7.18%) 19
Eye disorders Eye allergy subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 18 (0.00%) 0	0 / 181 (0.00%) 0
Eye pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 18 (0.00%) 0	4 / 181 (2.21%) 5
Scleritis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 4	0 / 18 (0.00%) 0	0 / 181 (0.00%) 0
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	3 / 18 (16.67%) 3	2 / 181 (1.10%) 2
Abdominal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	4 / 18 (22.22%) 5	59 / 181 (32.60%) 91
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	28 / 181 (15.47%) 45
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 6	0 / 18 (0.00%) 0	18 / 181 (9.94%) 33
Constipation			

subjects affected / exposed	1 / 4 (25.00%)	1 / 18 (5.56%)	12 / 181 (6.63%)
occurrences (all)	1	1	13
Dental caries			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	3 / 181 (1.66%)
occurrences (all)	1	0	3
Diarrhoea			
subjects affected / exposed	2 / 4 (50.00%)	4 / 18 (22.22%)	45 / 181 (24.86%)
occurrences (all)	7	4	71
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 18 (11.11%)	5 / 181 (2.76%)
occurrences (all)	0	2	5
Gastric dilatation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	0 / 181 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	5 / 181 (2.76%)
occurrences (all)	1	0	7
Haemorrhoids			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences (all)	1	0	2
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	17 / 181 (9.39%)
occurrences (all)	1	0	21
Proctitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	0 / 181 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	3 / 181 (1.66%)
occurrences (all)	7	0	4
Teething			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	7 / 181 (3.87%)
occurrences (all)	0	1	7
Vomiting			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 18 (5.56%) 1	27 / 181 (14.92%) 37
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences (all)	1	0	1
Drug eruption			
subjects affected / exposed	2 / 4 (50.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	2	0	0
Eczema			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	10 / 181 (5.52%)
occurrences (all)	1	0	11
Keloid scar			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	1	0	0
Pain of skin			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	1	0	0
Pyoderma gangrenosum			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	19 / 181 (10.50%)
occurrences (all)	0	0	24
Rash pruritic			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences (all)	1	0	1
Skin ulcer			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	9 / 181 (4.97%)
occurrences (all)	2	0	11
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	0 / 181 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	5 / 18 (27.78%)	39 / 181 (21.55%)
occurrences (all)	1	10	60
Arthritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	2 / 181 (1.10%)
occurrences (all)	0	1	2
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 18 (11.11%)	29 / 181 (16.02%)
occurrences (all)	1	3	38
Intervertebral disc disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	0 / 181 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	1 / 181 (0.55%)
occurrences (all)	0	1	1
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 18 (11.11%)	17 / 181 (9.39%)
occurrences (all)	0	2	18
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 18 (16.67%)	19 / 181 (10.50%)
occurrences (all)	0	4	27
Pain in extremity			
subjects affected / exposed	1 / 4 (25.00%)	3 / 18 (16.67%)	23 / 181 (12.71%)
occurrences (all)	1	3	35
Spinal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	2 / 181 (1.10%)
occurrences (all)	0	1	2
Tendon pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	0 / 181 (0.00%)
occurrences (all)	0	1	0
Tenosynovitis stenosans			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 18 (5.56%) 1	0 / 181 (0.00%) 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 4 (50.00%)	1 / 18 (5.56%)	13 / 181 (7.18%)
occurrences (all)	4	1	15
Conjunctivitis			
subjects affected / exposed	2 / 4 (50.00%)	1 / 18 (5.56%)	8 / 181 (4.42%)
occurrences (all)	4	1	9
Cystitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	3 / 181 (1.66%)
occurrences (all)	0	1	5
Ear infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 18 (5.56%)	10 / 181 (5.52%)
occurrences (all)	2	2	11
Gastroenteritis			
subjects affected / exposed	2 / 4 (50.00%)	1 / 18 (5.56%)	24 / 181 (13.26%)
occurrences (all)	2	1	30
Influenza			
subjects affected / exposed	1 / 4 (25.00%)	2 / 18 (11.11%)	31 / 181 (17.13%)
occurrences (all)	1	2	51
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	5 / 181 (2.76%)
occurrences (all)	0	1	7
Nasopharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	8 / 181 (4.42%)
occurrences (all)	3	0	18
Oral herpes			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	12 / 181 (6.63%)
occurrences (all)	0	2	18
Otitis media			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	13 / 181 (7.18%)
occurrences (all)	0	0	16
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	16 / 181 (8.84%)
occurrences (all)	0	0	19

Pilonidal cyst			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	1 / 181 (0.55%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	11 / 181 (6.08%)
occurrences (all)	0	1	25
Rhinitis			
subjects affected / exposed	1 / 4 (25.00%)	2 / 18 (11.11%)	25 / 181 (13.81%)
occurrences (all)	1	4	47
Sialoadenitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	7 / 181 (3.87%)
occurrences (all)	0	1	7
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	15 / 181 (8.29%)
occurrences (all)	0	1	18
Tonsillitis bacterial			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	0 / 181 (0.00%)
occurrences (all)	1	0	0
Tracheitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 18 (11.11%)	0 / 181 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	3 / 18 (16.67%)	47 / 181 (25.97%)
occurrences (all)	0	3	81
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 18 (0.00%)	16 / 181 (8.84%)
occurrences (all)	0	0	19
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 18 (5.56%)	15 / 181 (8.29%)
occurrences (all)	0	1	31
Viral tonsillitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 18 (0.00%)	1 / 181 (0.55%)
occurrences (all)	2	0	1

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	5 / 18 (27.78%) 11	38 / 181 (20.99%) 82
Metabolism and nutrition disorders			
Dehydration subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 18 (0.00%) 0	1 / 181 (0.55%) 1
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 18 (0.00%) 0	0 / 181 (0.00%) 0
Hypophosphataemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 18 (0.00%) 0	0 / 181 (0.00%) 0

Non-serious adverse events	Any ACZ group		
Total subjects affected by non-serious adverse events subjects affected / exposed	188 / 193 (97.41%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Pyogenic granuloma subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 1		
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	3 / 193 (1.55%) 3		
Hypotension subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 1		
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	12 / 193 (6.22%) 18		
Fatigue subjects affected / exposed occurrences (all)	11 / 193 (5.70%) 12		
Influenza like illness			

subjects affected / exposed	10 / 193 (5.18%)		
occurrences (all)	12		
Injection site reaction			
subjects affected / exposed	28 / 193 (14.51%)		
occurrences (all)	78		
Malaise			
subjects affected / exposed	7 / 193 (3.63%)		
occurrences (all)	9		
Non-cardiac chest pain			
subjects affected / exposed	14 / 193 (7.25%)		
occurrences (all)	16		
Pyrexia			
subjects affected / exposed	74 / 193 (38.34%)		
occurrences (all)	282		
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Polycystic ovaries			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Vaginal haemorrhage			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	40 / 193 (20.73%)		
occurrences (all)	62		
Epistaxis			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	15		
Oropharyngeal pain			
subjects affected / exposed	39 / 193 (20.21%)		
occurrences (all)	59		
Pleuritic pain			

subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	5		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 193 (2.59%)		
occurrences (all)	8		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Blood creatine phosphokinase increased			
subjects affected / exposed	6 / 193 (3.11%)		
occurrences (all)	7		
C-reactive protein increased			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	4		
Eosinophil count increased			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Neutrophil count increased			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Serum amyloid A protein increased			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>White blood cell count increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>9 / 193 (4.66%)</p> <p>15</p> <p>3 / 193 (1.55%)</p> <p>3</p>		
<p>Injury, poisoning and procedural complications</p> <p>Contusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin abrasion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thermal burn</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Wound</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 193 (1.55%)</p> <p>3</p> <p>2 / 193 (1.04%)</p> <p>2</p> <p>2 / 193 (1.04%)</p> <p>3</p> <p>1 / 193 (0.52%)</p> <p>2</p>		
<p>Congenital, familial and genetic disorders</p> <p>Familial mediterranean fever</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hyper IgD syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>25 / 193 (12.95%)</p> <p>79</p> <p>21 / 193 (10.88%)</p> <p>80</p>		
<p>Cardiac disorders</p> <p>Atrial fibrillation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tachycardia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 193 (0.52%)</p> <p>1</p> <p>3 / 193 (1.55%)</p> <p>3</p>		
<p>Nervous system disorders</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>62 / 193 (32.12%)</p> <p>136</p>		

Somnolence subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	8 / 193 (4.15%) 8		
Lymphadenopathy subjects affected / exposed occurrences (all)	27 / 193 (13.99%) 39		
Neutropenia subjects affected / exposed occurrences (all)	10 / 193 (5.18%) 12		
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	13 / 193 (6.74%) 19		
Eye disorders			
Eye allergy subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 1		
Eye pain subjects affected / exposed occurrences (all)	5 / 193 (2.59%) 6		
Scleritis subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 4		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 4		
Abdominal pain subjects affected / exposed occurrences (all)	61 / 193 (31.61%) 89		
Abdominal pain upper subjects affected / exposed occurrences (all)	27 / 193 (13.99%) 44		

Aphthous ulcer			
subjects affected / exposed	19 / 193 (9.84%)		
occurrences (all)	39		
Constipation			
subjects affected / exposed	13 / 193 (6.74%)		
occurrences (all)	14		
Dental caries			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	49 / 193 (25.39%)		
occurrences (all)	78		
Dyspepsia			
subjects affected / exposed	7 / 193 (3.63%)		
occurrences (all)	7		
Gastric dilatation			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	6 / 193 (3.11%)		
occurrences (all)	8		
Haemorrhoids			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	18 / 193 (9.33%)		
occurrences (all)	22		
Proctitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	11		
Teething			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		

Toothache			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	26 / 193 (13.47%)		
occurrences (all)	36		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Drug eruption			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Eczema			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	12		
Keloid scar			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Pyoderma gangrenosum			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	21		
Rash pruritic			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Skin ulcer			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Urticaria			

subjects affected / exposed	9 / 193 (4.66%)		
occurrences (all)	12		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	42 / 193 (21.76%)		
occurrences (all)	68		
Arthritis			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	32 / 193 (16.58%)		
occurrences (all)	42		
Intervertebral disc disorder			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	17		
Myalgia			
subjects affected / exposed	21 / 193 (10.88%)		
occurrences (all)	30		
Pain in extremity			
subjects affected / exposed	25 / 193 (12.95%)		
occurrences (all)	37		
Spinal pain			
subjects affected / exposed	3 / 193 (1.55%)		
occurrences (all)	3		
Tendon pain			

subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Tenosynovitis stenosans			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	20		
Conjunctivitis			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	14		
Cystitis			
subjects affected / exposed	4 / 193 (2.07%)		
occurrences (all)	6		
Ear infection			
subjects affected / exposed	12 / 193 (6.22%)		
occurrences (all)	15		
Gastroenteritis			
subjects affected / exposed	27 / 193 (13.99%)		
occurrences (all)	33		
Influenza			
subjects affected / exposed	33 / 193 (17.10%)		
occurrences (all)	52		
Lower respiratory tract infection			
subjects affected / exposed	6 / 193 (3.11%)		
occurrences (all)	8		
Nasopharyngitis			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	20		
Oral herpes			
subjects affected / exposed	11 / 193 (5.70%)		
occurrences (all)	18		
Otitis media			
subjects affected / exposed	13 / 193 (6.74%)		
occurrences (all)	16		

Pharyngitis			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	19		
Pilonidal cyst			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	12 / 193 (6.22%)		
occurrences (all)	25		
Rhinitis			
subjects affected / exposed	28 / 193 (14.51%)		
occurrences (all)	51		
Sialoadenitis			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	8 / 193 (4.15%)		
occurrences (all)	8		
Tonsillitis			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	19		
Tonsillitis bacterial			
subjects affected / exposed	1 / 193 (0.52%)		
occurrences (all)	1		
Tracheitis			
subjects affected / exposed	2 / 193 (1.04%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	49 / 193 (25.39%)		
occurrences (all)	80		
Urinary tract infection			
subjects affected / exposed	15 / 193 (7.77%)		
occurrences (all)	18		
Viral infection			
subjects affected / exposed	16 / 193 (8.29%)		
occurrences (all)	32		

Viral tonsillitis	subjects affected / exposed	2 / 193 (1.04%)		
	occurrences (all)	3		
	Viral upper respiratory tract infection			
	subjects affected / exposed	44 / 193 (22.80%)		
	occurrences (all)	94		
Metabolism and nutrition disorders				
Dehydration	subjects affected / exposed	2 / 193 (1.04%)		
	occurrences (all)	2		
Hypocalcaemia	subjects affected / exposed	1 / 193 (0.52%)		
	occurrences (all)	1		
Hypophosphataemia	subjects affected / exposed	1 / 193 (0.52%)		
	occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2014	Changed pregnancy and assessments of fertility section to reference the use of effective contraception in accordance with locally approved prescribing information
22 October 2014	Updated exploratory objectives to reflect the request from the Paediatric Committee at the European Medicines Agency to include patients > 28 days but < 2 years of age in addition to patients ≥ 2 years of age; Clarified how patients in the randomized and non-randomized groups were managed: study entry time and treatment was harmonized between the patients who were > 28 days but < 2 years of age and Japanese crFMF patients with non-exon 10 mutations; clarified the definition of the resolution of index flare; and clarified the blinded escape criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported