Clinical trial results:
A Multi-Centre, Placebo-Controlled Phase II Study of Canakinumab for the Treatment of Adult-onset Still's disease (AOSD) Including an Open-Label Long Term Extension.

Summary

EudraCT number	2011-001027-20
Trial protocol	DE
Global end of trial date	05 May 2018

Results information

Result version number	v1 (current)
This version publication date	01 August 2020
First version publication date	01 August 2020

Trial information

Trial identification

Sponsor protocol code	CACZ885GDE01T

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02204293
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Chariteplatz 1, Berlin, Germany, 10117
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the efficacy of canakinumab treatment for subjects with adult-onset Still's disease (AOSD) and active joint involvement according to the proportion of subjects with a significant reduction of disease activity (DAS 28 [>1.2]) after 12 week treatment period and to evaluate the long-term safety of canakinumab in subjects with AOSD and articular involvement.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 May 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	27 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	34
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with adult-onset Still's disease (AOSD) took part in the study from June 21, 2012 to May 5, 2018 at 14 investigative sites located in Germany to participate in two double-blind parts - Part I (Up to Week 12) and Part II (Up to Week 24) and one open-label Long-Term Extension (LTE) phase (Up to Month 27).

Pre-assignment

Screening details:

A total of 36 subjects entered in Part I to receive canakinumab/placebo. Out of 31, 5 subjects from the canakinumab group and 3 from placebo group did not enter Part II, 23 subjects entered Part II, and received canakinumab or placebo up to Week 24. 7 subjects who achieved clinical remission entered LTE Phase to receive canakinumab.

Pre-assignment period milestones

Number of subjects started	36
Number of subjects completed	35

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Subject Met One or More Exclusion Criteria: 1

Period 1

Period 1 title	Core Study Part I
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Canakinumab

Arm description:

Subjects received canakinumab 4 mg/kg up to a 300 mg maximum, subcutaneous (SC) injection, once in morning at Baseline (Day 0), Weeks 4, 8, and 12.

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	EU/1/09/564/004
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Canakinumab, single-dose 4 mg/kg up to 300 mg administered subcutaneously.

Arm title	Placebo

Arm description:

Subjects received placebo, SC injection, once in morning at Baseline (Day 0), Weeks 4, 8, and 12.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matched placebo, administered subcutaneously.

Number of subjects in period 1[1]	Canakinumab	Placebo
Started	18	17
Completed	17	14
Not completed	1	3
Physician decision	-	3
Adverse event, non-fatal	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One subject left the study before the start of the treatment as he/she did not meet or more exclusion criteria and was excluded from the efficacy analysis set.

Period 2

Period 2 title	Core Study Part II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Canakinumab Responders

Arm description:

Subjects with response (change in DAS score > 1.2 at Week 12) continued to receive canakinumab 4 mg/kg up to 300 mg maximum, SC injection, once in the morning for Weeks 12, 16, and 20.

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	EU/1/09/564/004
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Canakinumab, single-dose 4 mg/kg up to 300 mg administered subcutaneously.

Arm title	Placebo Responders

Arm description:

Subjects with response (change in DAS score > 1.2 at Week 12) continued to receive placebo, SC injection, once in morning for Weeks 12, 16, and 20.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matched placebo, administered subcutaneously.

Arm title	Placebo Non-responders

Arm description:

Non-responders (change in DAS score ≤ 1.2 at Week 12) who switched to canakinumab were unblinded to receive canakinumab 4 mg/kg up to 300 mg maximum, SC injection, once in the morning at Weeks 12, 16, and 20.

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	EU/1/09/564/004
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Canakinumab, single-dose 4 mg/kg up to 300 mg administered subcutaneously.

Number of subjects in period 2[2]	Canakinumab Responders	Placebo Responders	Placebo Non-responders
Started	12	4	7
Completed	12	4	7

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Out of 31, 5 subjects from the canakinumab group and 3 from placebo group did not enter Part II of the study.

Period 3

Period 3 title	LTE Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Canakinumab

Arm description:

Subjects with remission (change in DAS score > 1.2 and no signs of systemic activity for adult-onset Still's disease at Week 20) received canakinumab 4 mg/kg up to 300 mg maximum, SC injection at Weeks 24 and 28, which was down titrated to 2 mg/kg up to 150 mg maximum if applicable after Week 28 up to Month 27 (Week 117).

Arm type	Experimental

Investigational medicinal product name	Canakinumab
Investigational medicinal product code	EU/1/09/564/004
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Canakinumab, single-dose 4 mg/kg up to 300 mg administered subcutaneously.

Number of subjects in period 3[3]	Canakinumab
Started	7
Completed	0
Not completed	7
Study Suspended	7

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who achieved remission only entered LTE Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Canakinumab
Reporting group description:	
Subjects received canakinumab 4 mg/kg up to a 300 mg maximum, subcutaneous (SC) injection, once in morning at Baseline (Day 0), Weeks 4, 8, and 12.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo, SC injection, once in morning at Baseline (Day 0), Weeks 4, 8, and 12.	

Reporting group values	Canakinumab	Placebo	Total
Number of subjects	18	17	35
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)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	41.06	40.53	
standard deviation	± 13.2	± 13.2	-
Gender categorical			
Units: Subjects			
Female	10	13	23
Male	8	4	12

End points

End points reporting groups

Reporting group title	Canakinumab
Reporting group description:	
Subjects received canakinumab 4 mg/kg up to a 300 mg maximum, subcutaneous (SC) injection, once in morning at Baseline (Day 0), Weeks 4, 8, and 12.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo, SC injection, once in morning at Baseline (Day 0), Weeks 4, 8, and 12.	
Reporting group title	Canakinumab Responders
Reporting group description:	
Subjects with response (change in DAS score > 1.2 at Week 12) continued to receive canakinumab 4 mg/kg up to 300 mg maximum, SC injection, once in the morning for Weeks 12, 16, and 20.	
Reporting group title	Placebo Responders
Reporting group description:	
Subjects with response (change in DAS score > 1.2 at Week 12) continued to receive placebo, SC injection, once in morning for Weeks 12, 16, and 20.	
Reporting group title	Placebo Non-responders
Reporting group description:	
Non-responders (change in DAS score ≤ 1.2 at Week 12) who switched to canakinumab were unblinded to receive canakinumab 4 mg/kg up to 300 mg maximum, SC injection, once in the morning at Weeks 12, 16, and 20.	
Reporting group title	Canakinumab
Reporting group description:	
Subjects with remission (change in DAS score > 1.2 and no signs of systemic activity for adult-onset Still's disease at Week 20) received canakinumab 4 mg/kg up to 300 mg maximum, SC injection at Weeks 24 and 28, which was down titrated to 2 mg/kg up to 150 mg maximum if applicable after Week 28 up to Month 27 (Week 117).	

Subject analysis set title	Part I: Canakinumab
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
2 subjects of the placebo group received canakinumab at Week 4, as protocol violation, thus, Safety Analysis Set included those additional 2 subjects in the canakinumab group.	
Subject analysis set title	Part I: Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
2 subjects of the placebo group received canakinumab at Week 4, as protocol violation, thus, Safety Analysis Set included those additional 2 subjects in the canakinumab group.	
Subject analysis set title	Part II: Canakinumab Responders
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
2 subjects of the placebo group received canakinumab at Week 4, as protocol violation, thus, Safety Analysis Set included those additional 2 subjects in the canakinumab group.	
Subject analysis set title	Part II: Placebo Responders
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
2 subjects of the placebo group received canakinumab at Week 4, as protocol violation, thus, Safety Analysis Set included those additional 2 subjects in the canakinumab group.	

Primary: Core Study Part I: Percentage of Responders as Assessed Disease Activity Score 28 Joints (DAS28) Score at Week 12

End point title	Core Study Part I: Percentage of Responders as Assessed Disease Activity Score 28 Joints (DAS28) Score at Week 12

End point description:

Responders included subjects with change in DAS28 score > 1.2. The DAS28 index is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, patient global assessment of disease activity score, and the erythrocyte sedimentation rate (ESR) value. Total score ranged between 0-10. A DAS28-ESR score of 5.1 or above = high disease activity, a value between 3.2 and 5.1 = moderate disease activity and value between 2.6 and 3.2 = low disease activity, value < 2.6 = disease remission. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset still's disease and disease activity based on DAS28 of greater than or equal to 3.2 at Screening.

End point type	Primary

End point timeframe:

Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)	66.7 (43.1 to 85.2)	41.2 (20.1 to 65.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.1811
Method	Fisher exact

Notes:

[1] - Fisher's exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Change From Baseline (CFB) in Disease Activity Score 28 Joints Erythrocyte Sedimentation Rate (DAS28 [ESR]) Score

End point title	Core Study Part I: Change From Baseline (CFB) in Disease Activity Score 28 Joints Erythrocyte Sedimentation Rate (DAS28 [ESR]) Score

End point description:

The DAS28 index is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, patient global assessment of disease activity score, and ESR value. Total score ranged between 0-10. A DAS28-ESR score of 5.1 or above = high disease activity, a value between 3.2 and 5.1 = moderate disease activity and value between 2.6 and 3.2 = low disease activity, value < 2.6 = disease remission. A positive change in score indicates worsening, and a negative change indicates improvement. Least squares (LS) mean was calculated by mixed linear model for repeated measures (MMRM) analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data

available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	5.37 (4.7 to 6.0)	5.3 (4.6 to 6.0)		
CFB at Week 4 (n=16, 14)	3.56 (2.9 to 4.3)	4.27 (3.5 to 5.0)		
CFB at Week 8 (n=16, 12)	2.86 (2.2 to 3.6)	3.92 (3.1 to 4.7)		
CFB at Week 12 (n=16, 14)	3.1 (2.4 to 3.8)	4.0 (3.3 to 4.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in DAS28 C-reactive Protein (CRP) Score

End point title	Core Study Part I: CFB in DAS28 C-reactive Protein (CRP) Score

End point description:

The DAS28 index is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, patient global assessment of disease activity score, and CRP value. Total score ranged between 0-10. A DAS28-CRP score of 5.1 or above = high disease activity, a value between 3.2 and 5.1 = moderate disease activity and value between 2.6 and 3.2 = low disease activity, value < 2.6 = disease remission. A positive change in score indicates worsening, and a negative change indicates improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed "n" is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: score on a scale				
least squares mean (confidence interval 95%)				

Baseline	5.0 (4.4 to 5.6)	5.07 (4.4 to 5.7)		
CFB at Week 4 (n=17, 14)	3.4 (2.8 to 4.0)	4.01 (3.3 to 4.7)		
CFB at Week 8 (n=17, 13)	2.8 (2.2 to 3.4)	3.81 (3.1 to 4.5)		
CFB at Week 12 (n=17, 14)	3.31 (2.7 to 3.9)	4.01 (3.3 to 4.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in American College of Rheumatology (ACR) Component: 68 Tender Joint Count (TJC)

End point title	Core Study Part I: CFB in American College of Rheumatology (ACR) Component: 68 Tender Joint Count (TJC)

End point description:

The 68 TJC included the 8 distal interphalangeal (IP), 10 proximal IP and 10 metacarpophalangeal (MTP) joints of hands, the 10 MTP and 10 proximal IP joints of feet, the 2 wrists, 2 elbows, 2 shoulders, 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 hip, 2 knee, 2 talo-tibial, and 2 mid-tarsal joints. Joint tenderness was graded present (1) or absent (0). Total score is calculated by adding the scores, which range from 0 (no tender joint) to 68 (all tender joints). Lower scores indicate no tender joint and higher scores indicate worsening tender joints. A negative change from Baseline indicates improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: tender joints				
least squares mean (confidence interval 95%)				
Baseline	8.89 (4.9 to 12.9)	11.18 (7.1 to 15.3)		
CFB at Week 4 (n=18, 14)	5.33 (1.3 to 9.3)	5.85 (1.5 to 10.2)		
CFB at Week 8 (n=18, 13)	3.72 (-0.3 to 7.7)	5.1 (0.6 to 9.6)		
CFB at Week 12 (n=17, 14)	4.66 (0.6 to 8.7)	6.9 (2.6 to 11.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in ACR Component: 66 Swollen Joint Count (SJC)

End point title	Core Study Part I: CFB in ACR Component: 66 Swollen Joint Count (SJC)

End point description:

The 66 SJC included the 8 distal interphalangeal (IP), 10 proximal IP and 10 metacarpophalangeal (MTP) joints of hands, the 10 MTP and 10 proximal IP joints of feet, the 2 wrists, 2 elbows, 2 shoulders, 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 knee, 2 talo-tibial, and 2 mid-tarsal joints. Swelling was graded present (1) or absent (0). Total score is calculated by adding the scores, which range from 0 (no swollen joint) to 66 (all swollen joints). Lower scores indicate no swollen joint and higher scores indicate worsening swollen joints. A negative change in Baseline indicates improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: swollen joints				
least squares mean (confidence interval 95%)				
Baseline	5.78 (3.6 to 7.9)	8.0 (5.8 to 10.2)		
CFB at Week 4 (n=18, 14)	2.5 (0.4 to 4.6)	2.5 (0.1 to 4.9)		
CFB at Week 8 (n=18, 13)	1.33 (-0.8 to 3.5)	2.65 (0.2 to 5.0)		
CFB at Week 12 (n=17, 12)	2.89 (0.7 to 5.1)	4.71 (2.4 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in the 28 TJC

End point title	Core Study Part I: CFB in the 28 TJC

End point description:

A total of 28 joints were assessed for tenderness. The number of tender joints could range from 0 to 28, where higher values represented more tender joints. The change from Baseline to any time points was averaged among all subjects, where negative changes indicated an improvement in disease activity. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: tender joints				
least squares mean (confidence interval 95%)				
Baseline	6.78 (4.6 to 9.0)	7.24 (5.0 to 9.5)		
CFB at Week 4 (n=18, 14)	3.67 (1.5 to 5.9)	4.29 (1.9 to 6.7)		
CFB at Week 8 (n=18, 13)	2.39 (0.2 to 4.6)	3.85 (1.4 to 6.3)		
CFB at Week 12 (n=17, 14)	3.47 (1.2 to 5.7)	4.43 (2.1 to 6.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in the 28 SJC

End point title	Core Study Part I: CFB in the 28 SJC

End point description:

A total of 28 joints were assessed for swelling. The number of swollen joints could range from 0 to 28, where higher values represented more swollen joints. The change from Baseline to any time point was averaged among all subjects, where negative changes indicated an improvement in disease activity. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: swollen joints				
least squares mean (confidence interval 95%)				
Baseline	4.97 (3.4 to 6.6)	6.29 (4.6 to 8.0)		
CFB at Week 4 (n=18, 14)	2.11 (0.5 to 3.7)	2.47 (0.7 to 4.2)		
CFB at Week 8 (n=18, 13)	0.83 (-0.8 to 2.5)	2.79 (1.0 to 4.6)		
CFB at Week 12 (n=17, 14)	2.28 (0.6 to 3.9)	4.51 (2.8 to 6.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in ACR Component: Acute Phase Reactant CRP

End point title	Core Study Part I: CFB in ACR Component: Acute Phase Reactant CRP

End point description:

A negative change from Baseline in CRP level indicates an improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: milligrams per liter (mg/L)				
least squares mean (confidence interval 95%)				
Baseline	45.55 (26.1 to 65.0)	57.26 (37.3 to 77.2)		
CFB at Week 4 (n=17, 14)	17.53 (-2.1 to 37.1)	36.74 (15.8 to 57.7)		
CFB at Week 8 (n=18, 13)	14.61 (-4.8 to 34.0)	32.51 (11.2 to 53.8)		
CFB at Week 12 (n=17, 14)	17.05 (-2.6 to 36.7)	28.52 (7.0 to 50.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in ACR Component: Acute Phase Reactant ESR

End point title	Core Study Part I: CFB in ACR Component: Acute Phase Reactant ESR

End point description:

A negative change from Baseline in ESR level indicates an improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for

analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: millimeter per hour (mm/h)				
least squares mean (confidence interval 95%)				
Baseline	44.11 (33.8 to 54.4)	38.82 (28.3 to 49.4)		
CFB at Week 4 (n=16, 14)	24.28 (13.8 to 34.7)	38.6 (27.5 to 49.7)		
CFB at Week 8 (n=17, 12)	25.4 (15.0 to 35.8)	25.25 (13.6 to 36.9)		
CFB at Week 12 (n=16, 14)	15.85 (5.3 to 26.4)	22.41 (10.8 to 34.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in Serum Ferritin Level at Week 12

End point title	Core Study Part I: CFB in Serum Ferritin Level at Week 12

End point description:

LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Overall number of subjects analysed signifies the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	14		
Units: nanograms per milliliter (ng/mL)				
least squares mean (confidence interval 95%)	466.9 (16.0 to 918.0)	634.71 (170.0 to 1099.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: Percentage of Responders With Fever Episodes

End point title	Core Study Part I: Percentage of Responders With Fever Episodes

End point description:

Fever is defined as an oral or rectal body temperature greater than 38 degrees Celsius (°C). ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	0[2]		
Units: percentage of subjects				
number (not applicable)	8.3			

Notes:

[2] - No subjects were reported under the placebo group for fever episodes post-baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in ACR Component: Physician's Global Assessment of Disease Activity Score

End point title	Core Study Part I: CFB in ACR Component: Physician's Global Assessment of Disease Activity Score

End point description:

The physician's global assessment of disease activity was assessed using a numerical rating scale of 0-10 where 0= no disease activity and 10= activity to maximal disease activity. A negative change from Baseline indicates improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	5.5 (4.5 to 6.5)	6.0 (4.9 to 7.1)		

CFB at Week 4 (n= 18, 14)	3.06 (2.0 to 4.1)	3.67 (2.5 to 4.8)		
CFB at Week 4 (n= 18, 13)	2.72 (1.7 to 3.8)	3.56 (2.4 to 4.7)		
CFB at Week 12 (n= 17, 14)	2.86 (1.8 to 3.9)	4.26 (3.1 to 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in ACR Component: Subject's Global Assessment of Disease Activity Score

End point title	Core Study Part I: CFB in ACR Component: Subject's Global Assessment of Disease Activity Score

End point description:

The subject's global assessment of disease activity was assessed using a numerical rating scale of 0-10, where 0= no disease activity and 10= maximal disease activity. A negative change from Baseline indicates improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	6.08 (4.9 to 7.3)	5.85 (4.6 to 7.1)		
CFB at Week 4 (n=18, 14)	3.78 (2.6 to 5.0)	4.74 (3.4 to 6.0)		
CFB at Week 8 (n=17, 13)	2.84 (1.6 to 4.0)	4.58 (3.2 to 5.9)		
CFB at Week 12 (n=17, 14)	3.63 (2.4 to 4.8)	4.32 (3.0 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in ACR Component: Subject's Global Assessment of Pain Score

End point title	Core Study Part I: CFB in ACR Component: Subject's Global

	Assessment of Pain Score

End point description:

The subject’s global assessment of pain was assessed using a numerical rating scale of 0-10, where 0= no disease activity and 10= maximal disease activity. A negative change from Baseline indicates improvement. A negative change from baseline indicates improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8 and 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	6.61 (5.3 to 7.9)	6.35 (5.0 to 7.7)		
CFB at Week 4 (n=18, 14)	3.61 (2.3 to 4.9)	4.85 (3.5 to 6.2)		
CFB at Week 8 (n=17, 13)	2.73 (1.4 to 4.0)	4.18 (2.7 to 5.6)		
CFB at Week 12 (n=17, 14)	3.71 (2.4 to 5.0)	4.25 (2.8 to 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score

End point title	Core Study Part I: CFB in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score

End point description:

The HAQ measures physical disability and functional status. It has 4 dimensions: disability, pain, drug side effects and dollar costs. The HAQ score is calculated by summing the computed scores for each category and dividing by the number of categories answered. It ranges from 0 (without any difficulty) to 3 (unable to do). A negative change from Baseline indicates improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Baseline	1.31 (0.9 to 1.7)	1.29 (0.9 to 1.7)		
CFB at Week 12 (n=17, 14)	0.69 (0.3 to 1.1)	0.9 (0.6 to 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: Percentage of Responders With American College of Rheumatology Response of 20 (ACR20)

End point title	Core Study Part I: Percentage of Responders With American College of Rheumatology Response of 20 (ACR20)

End point description:

ACR20 response was defined as a ≥ 20% improvement (reduction) compared with Baseline for both 68 TJC and 66 SJC, as well as for three of the additional five ACR core set variables: Subject's Assessment of Pain over the previous 24 hours: using a NRS left end of the line 0=no pain to right end of the line 10=unbearable pain; Subject's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a NRS where left end of the line 0=no disease activity to right end of the line 10=maximum disease activity; HAQ-DI 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant ESR. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)	61.1 (37.7 to 81.1)	41.2 (20.1 to 65.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Canakinumab

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.3175
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	19.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	51.3

Notes:

[3] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Percentage of Responders With ACR30

End point title	Core Study Part I: Percentage of Responders With ACR30

End point description:

ACR30 response was defined as a ≥ 30% improvement (reduction) compared with Baseline for both 68 TJC and 66 SJC, as well as for three of the additional five ACR core set variables: Subject’s Assessment of Pain over the previous 24 hours: using a NRS left end of the line 0=no pain to right end of the line 10=unbearable pain; Subject’s Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a NRS where left end of the line 0=no disease activity to right end of the line 10=maximum disease activity; HAQ 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant ESR. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)	61.1 (37.7 to 81.1)	29.4 (11.7 to 53.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Canakinumab

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0922
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	31.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	61.8

Notes:

[4] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Percentage of Responders With Modified ACR30

End point title	Core Study Part I: Percentage of Responders With Modified ACR30

End point description:

ACR30 response: ≥ 30% improvement compared with baseline for both TJC68 and SJC66, and for 3 of the additional 5 ACR core set variables: Assessment of Pain over last 24 hours using NRS (0=no pain - 10=unbearable pain); Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over last 24 hours on NRS (0=no disease activity -10=maximum disease activity); Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant ESR. Modified ACR 30% response calculated using above definition and requiring no intermittent fever and no more than 1 variable worsening by 30% in the preceding week. ITT population: all subjects who did not violate any of following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)	55.6 (32.7 to 76.8)	23.5 (8.0 to 47.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Canakinumab

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0858
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	61.1

Notes:

[5] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Percentage of Responders With ACR50

End point title	Core Study Part I: Percentage of Responders With ACR50

End point description:

ACR50 response was defined as a ≥ 50% improvement (reduction) compared with Baseline for both 68 TJC and 66 SJC, as well as for three of the additional five ACR core set variables: Subject’s Assessment of Pain over the previous 24 hours: using a NRS left end of the line 0=no pain to right end of the line 10=unbearable pain; Subject’s Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a NRS where left end of the line 0=no disease activity to right end of the line 10=maximum disease activity; HAQ-DI 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant ESR. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)	50.0 (27.8 to 72.2)	17.6 (4.7 to 40.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.075
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	32.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	60.5

Notes:

[6] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Percentage of Responders With ACR70

End point title	Core Study Part I: Percentage of Responders With ACR70

End point description:

ACR70 response was defined as a ≥ 70% improvement (reduction) compared with Baseline for both 68 TJC and 66 SJC, as well as for three of the additional five ACR core set variables: Subject’s Assessment of Pain over the previous 24 hours: using a NRS left end of the line 0=no pain to right end of the line 10=unbearable pain; Subject’s Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a NRS where left end of the line 0=no disease activity to right end of the line 10=maximum disease activity; HAQ-DI 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant ESR. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)	27.8 (11.0 to 51.3)	11.8 (2.0 to 33.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.4018
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	43.4

Notes:

[7] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Percentage of Responders With ACR90

End point title	Core Study Part I: Percentage of Responders With ACR90

End point description:

ACR90 response was defined as a ≥ 90% improvement (reduction) compared with Baseline for both 68 TJC and 66 SJC, as well as for three of the additional five ACR core set variables: Subject’s Assessment of Pain over the previous 24 hours: using a NRS left end of the line 0=no pain to right end of the line 10=unbearable pain; Subject’s Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a NRS where left end of the line 0=no disease activity to right end of the line 10=maximum disease activity; HAQ-DI 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant ESR. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)	11.1 (1.9 to 32.1)	5.9 (0.3 to 25.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 1
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.8
upper limit	29.2

Notes:

[8] - Fisher's exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Percentage of Responders With European League Against Rheumatism (EULAR) Response

End point title	Core Study Part I: Percentage of Responders With European League Against Rheumatism (EULAR) Response

End point description:

EULAR response is based on DAS28-ESR and DAS28-CRP scores. The DAS28 index is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, subject global assessment of disease activity score, and ESR or CRP value. A DAS28-CRP or ESR score of 5.1 or above = high disease activity, a value between 3.2 and 5.1 = moderate disease activity and value between 2.6 and 3.2 = low disease activity, value < 2.6 = disease remission. EULAR response has 3 categories: EULAR Good response: DAS28 ≤ 3.2 and a change from Baseline < -1.2. EULAR Moderate response: DAS28 >3.2 to ≤ 5.1 or a change from Baseline < -0.6 to ≥ -1.2 or EULAR No response: DAS28 >5.1 or a change from Baseline < -0.6 to ≤ -1.2. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still's disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)				
EULAR DAS28-ESR Response	77.8 (54.7 to 92.5)	52.9 (29.7 to 75.2)		
EULAR DAS28-CRP Response	72.2 (48.7 to 89.0)	47.1 (24.8 to 70.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

EULAR DAS28-ESR Response

Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.1642
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	24.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	54.2

Notes:

[9] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
EULAR DAS28-CRP Response	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.1756
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	25.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	55.1

Notes:

[10] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Percentage of Responders Achieving Low Disease Activity (LDA)

End point title	Core Study Part I: Percentage of Responders Achieving Low Disease Activity (LDA)

End point description:

Percentage of responders were defined as the subjects who achieved LDA (DAS28 score < 3.2) at Week 12. The DAS28 index is a composite score of weighted components including tender joint counts of 28, swollen joint counts of 28, subject global assessment of disease activity score, and ESR or CRP value. Total score ranged between 0-10. A DAS28 score greater than 5.1 implies high disease activity, equal to or less than 3.2 low disease activity, and less than 2.6 remissions. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)				
DAS28 (ESR) LDA	33.3 (14.8 to 56.9)	29.4 (11.7 to 53.7)		
DAS28 (CRP) LDA	50.0 (27.8 to 72.2)	23.5 (8.0 to 47.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: DAS28 (ESR) LDA	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 1
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.7
upper limit	35

Notes:

[11] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: DAS28 (CRP) LDA	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.1642
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	26.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	56

Notes:

[12] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Percentage of Responders Achieving Disease Remission and Extended Disease Remission

End point title	Core Study Part I: Percentage of Responders Achieving Disease Remission and Extended Disease Remission

End point description:

Subjects with disease remission: LDA (DAS28 score< 2.6). The DAS28 index is a composite score of weighted components including both 28 TJC an SJC, subject global assessment of disease activity score, and ESR or CRP value. A DAS28 score greater than 5.1: high disease activity, ≤ 3.2: low disease activity, and less than 2.6: remission. Extended remission criteria included DAS28 < 2.6 and no signs of systemic activity for up to two consecutive study visits till Week 12 defined as any of Yamaguchi´s primary classification criteria for AOSD which included fever attacks at 39 °C for more than a week, arthralgia, salmon red, maculate, urticarial or maculo-papular rash and leukocytosis (white blood cells increase) of > 10000/cubic millimeters (mm^3) with > 80% neutrophils. ITT population: subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening.

End point type	Secondary

End point timeframe:

Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: percentage of subjects				
number (confidence interval 95%)				
DAS28 (ESR) Remission	33.3 (14.8 to 56.9)	11.8 (2.0 to 33.7)		
DAS28 (CRP) Remission	38.9 (18.9 to 62.3)	11.8 (2.0 to 33.7)		
Extended Remission	27.8 (11.0 to 51.3)	11.8 (2.0 to 33.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

DAS28 (ESR) remission

Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.2285
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	21.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	49.9

Notes:

[13] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
DAS28 (CRP) Remission	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.1212
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	27.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	54.6

Notes:

[14] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Extended Remission	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.4018
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	43.4

Notes:

[15] - Fisher’s exact test with a two-tailed level of significance of α = 0.05.

Secondary: Core Study Part I: Change in Joint Mobility (Degrees of Motion) Assessed by Neutral Zero Method

End point title	Core Study Part I: Change in Joint Mobility (Degrees of Motion) Assessed by Neutral Zero Method

End point description:

Number of joints with limitation of motion according to neutral zero method was assessed which included mobility of joints (elbows, wrists, shoulder joints, hip joints, knee joints, and upper ankle joints) within the reference range/degree. Response is defined as an improvement of ≥ 30%, 50%, 70% and 90% from Baseline. A negative change score indicates improvement. LS mean was calculated by MMRM analyses. ITT population included all subjects who did not violate any of the following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of greater than or equal to 3.2 at Screening. Number analysed is the number of subjects with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: degrees				
least squares mean (confidence interval 95%)				
Baseline	4.94 (3.0 to 6.9)	6.29 (4.3 to 8.3)		
Week 12 (n=17, 14)	5.37 (3.4 to 7.3)	6.05 (4.0 to 8.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study Part I: CFB in Medical Outcome Short Form (SF-36) Health Survey Score

End point title	Core Study Part I: CFB in Medical Outcome Short Form (SF-36) Health Survey Score

End point description:

The SF-36 determines overall quality of life assessing 1) limitations in physical functioning due to health problems; 2) limitations in usual role because of physical health problems; 3) bodily pain; 4) general health perceptions; 5) vitality; 6) limitations in social functioning because of physical or emotional problems; 7) limitations in usual role due to emotional problems; and 8) general mental health. Items 1-4 contribute to physical component summary score (PCS). Items 5-8 contribute to mental component summary score (MCS). Scores on each item are summed and averaged (range = 0 "worst"-100 "best"). Positive numbers indicate improvement from Baseline. LS mean was calculated by MMRM analyses. ITT population: subjects who did not violate any of following inclusion criteria: diagnosis of adult-onset Still’s disease and disease activity based on DAS28 score of ≥ 1.2 at Screening. Number analysed is number of subjects with data available for analyses at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: score on a scale				
least squares mean (confidence interval 95%)				
SF-36 Physical: Baseline	29.39 (24.5 to 34.3)	28.73 (23.7 to 33.8)		
SF-36 Physical: CFB at Week 12 (n=17, 14)	41.03 (36.0 to 46.1)	33.45 (27.9 to 39.0)		
SF-36 Mental: Baseline	37.8 (32.0 to 43.6)	46.31 (40.4 to 52.2)		
SF-36 Mental: Week 12 (n=17, 14)	43.47 (37.6 to 49.3)	49.82 (43.6 to 56.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is an adverse medical event which occurs in a subject of the study and which is not necessarily in a causal relationship with the treatment the subject receives. AEs include symptoms of illnesses, as well as every unfavourable and unintended reaction. SAEs are AEs leading to death, are life-threatening, require hospitalizations or prolongation of hospitalizations, represent an innate malformation or a congenital abnormality. Safety Analysis Set included all subjects randomized who received at least one dose of the study drug.

End point type	Secondary

End point timeframe:

Up to Month 27

End point values	Canakinumab	Placebo Non-responders	Part I: Canakinumab	Part I: Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	7	7	20	15
Units: subjects				
AEs	13	6	16	10
SAEs	1	1	2	0

End point values	Part II: Canakinumab Responders	Part II: Placebo Responders		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	2		
Units: subjects				
AEs	1	2		
SAEs	1	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Month 27

Adverse event reporting additional description:

Safety Analysis Set included all subjects randomized who received at least one dose of the study drug. 2 subjects of the placebo group in Part I received canakinumab at Week 4, as protocol violation, thus, Safety Analysis Set included those additional 2 subjects in the canakinumab group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Core Study Part I: Canakinumab

Reporting group description:

Subjects received canakinumab 4 mg/kg up to 300 mg maximum, subcutaneous (SC) injection, once in morning at Baseline (Day 0), Weeks 4, 8, and 12.

Reporting group title	Core Study Part I: Placebo

Reporting group description:

Subjects received placebo, SC injection, once in morning at Baseline (Day 0), Weeks 4, 8, and 12.

Reporting group title	Core Study Part II: Canakinumab Responders

Reporting group description:

Subjects with response (change in DAS score > 1.2 at Week 12) continued to receive canakinumab 4 mg/kg up to 300 mg maximum, SC injection, once in the morning for Weeks 12, 16, and 20.

Reporting group title	Core Study Part II: Placebo Responders

Reporting group description:

SUbjects with response (change in DAS score > 1.2 at Week 12) continued to receive placebo, SC injection, once in morning for Weeks 12, 16, and 20.

Reporting group title	Core Study Part II: Placebo Non-responder

Reporting group description:

Non-responders (change in DAS score ≤ 1.2 at Week 12) who switched to canakinumab were unblinded to receive canakinumab 4 mg/kg up to 300 mg maximum, SC injection, once in the morning at Weeks 12, 16, and 20.

Reporting group title	LTE Phase: Canakinumab

Reporting group description:

Subjects with remission (change in DAS score > 1.2 and no signs of systemic activity for adult-onset Still's disease at Week 20) received canakinumab 4 mg/kg up to 300 mg maximum, SC injection at Weeks 24 and 28, which was down titrated to 2 mg/kg up to 150 mg maximum if applicable after Week 28 up to Month 27 (Week 117).

Serious adverse events	Core Study Part I: Canakinumab	Core Study Part I: Placebo	Core Study Part II: Canakinumab Responders
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			

Fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Medical device removal			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hypotonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 15 (0.00%)	0 / 14 (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
Musculoskeletal and connective tissue disorders			
Chondromalacia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 15 (0.00%)	0 / 14 (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
Patellofemoral pain syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 15 (0.00%)	0 / 14 (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

Serious adverse events	Core Study Part II: Placebo Responders	Core Study Part II: Placebo Non-responder	LTE Phase: Canakinumab
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 7 (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
Hand fracture			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 7 (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
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Medical device removal			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 7 (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
Nervous system disorders			
Hypotonia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
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			
Cholecystitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Chondromalacia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Core Study Part I: Canakinumab	Core Study Part I: Placebo	Core Study Part II: Canakinumab Responders
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	10 / 15 (66.67%)	13 / 14 (92.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	2 / 15 (13.33%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	2 / 14 (14.29%)
occurrences (all)	0	1	3
Injection site rash			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Vulva cyst			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pleurisy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Sleep disorder			
subjects affected / exposed	1 / 20 (5.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hepatic enzyme increased			

subjects affected / exposed	2 / 20 (10.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Transaminases increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	3
Meniscus injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 20 (5.00%)	3 / 15 (20.00%)	1 / 14 (7.14%)
occurrences (all)	1	3	1
Intercostal neuralgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	2 / 20 (10.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0

Visual impairment			
subjects affected / exposed	1 / 20 (5.00%)	2 / 15 (13.33%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	2 / 15 (13.33%)	0 / 14 (0.00%)
occurrences (all)	2	2	0
Nausea			
subjects affected / exposed	2 / 20 (10.00%)	1 / 15 (6.67%)	1 / 14 (7.14%)
occurrences (all)	2	1	1
Hepatobiliary disorders			
Primary biliary cholangitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Dermatitis allergic			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nail dystrophy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pruritus			

subjects affected / exposed	1 / 20 (5.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 15 (6.67%)	2 / 14 (14.29%)
occurrences (all)	3	1	2
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Groin pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Pain in extremity			

subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pseudarthrosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Still's disease			
subjects affected / exposed	5 / 20 (25.00%)	1 / 15 (6.67%)	2 / 14 (14.29%)
occurrences (all)	7	1	3
Tenosynovitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Gastrointestinal infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Infected bite			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	3 / 20 (15.00%)	3 / 15 (20.00%)	3 / 14 (21.43%)
occurrences (all)	3	3	5
Oral herpes			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Otitis media			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Periodontitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pertussis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 15 (6.67%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 20 (0.00%)	0 / 15 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Core Study Part II: Placebo Responders	Core Study Part II: Placebo Non-responder	LTE Phase: Canakinumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	6 / 7 (85.71%)	7 / 7 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anogenital warts			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Haematoma			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	3 / 7 (42.86%)
occurrences (all)	0	0	3
Injection site rash			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vulva cyst			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Cough			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pleurisy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Meniscus injury			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Headache			

subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Intercostal neuralgia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eyelid oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			

Primary biliary cholangitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nail dystrophy			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Back pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Joint swelling			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Osteoporosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pseudarthrosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Still's disease			
subjects affected / exposed	1 / 2 (50.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	2
Tenosynovitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hand-foot-and-mouth disease			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infected bite			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	3 / 7 (42.86%)
occurrences (all)	0	1	6
Oral herpes			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Otitis media			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Periodontitis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pertussis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Urinary tract infection			

subjects affected / exposed occurrences (all)	0 / 2 (0.00%) 0	0 / 7 (0.00%) 0	0 / 7 (0.00%) 0
Metabolism and nutrition disorders Appetite disorder subjects affected / exposed occurrences (all)	 0 / 2 (0.00%) 0	 1 / 7 (14.29%) 1	 0 / 7 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 May 2018	The study terminated prior to the planned completion date due to recruitment issues because of the marketing authorization of the study drug.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination due to recruitment issues as adult-onset Still’s disease is a rare disease.

Notes: