Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Canakinumab

Trial Indication(s)

Familial Mediterranean Fever (FMF)

Tumor Necrosis Factor receptor Associated Periodic Syndrome (TRAPS)

Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)

Protocol Number

CACZ885N2301

Protocol Title

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

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 4

Study Start/End Dates

Study Start Date: June 2014 (Actual)
Study Completion Date: July 2017 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a randomized, multicenter, double-blind, placebo-controlled study of canakinumab in patients with crFMF, hyper-immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), or TRAPS. This study evaluated the efficacy and safety of canakinumab at a starting dose of 150 mg sc for patients weighing > 40 kg or 2 mg/kg for patients weighing ≤ 40 kg administered q4w compared to placebo in patients with crFMF, HIDS/MKD, or TRAPS. The study consisted of 3 randomized cohorts (crFMF, HIDS/MKD, TRAPS) and 4 study epochs, as described below.

Randomized crFMF, HIDS/MKD, and TRAPS patients

Each randomized cohort (crFMF, HIDS/MKD, and TRAPS) followed the same study design across the 4 epochs:

1. A screening epoch (Epoch 1) of up to 12 weeks duration to assess patient eligibility
2. A randomized treatment epoch (Epoch 2) of 16 weeks (patients randomized to canakinumab 150 mg q4w or to placebo) to provide efficacy and safety data in a double-blind placebo-controlled parallel-arm setting

This randomized treatment epoch included 2 possible escape options:

- Blinded escape from Day 8 to Day 28 (where the randomized therapy was still blinded, and the patient could have been given an open-label rescue dose of 150 mg canakinumab)
- Open-label treatment from Day 29 to Day 112

3. A randomized withdrawal epoch (Epoch 3) of 24 weeks in which canakinumab responder patients who were initially randomized to canakinumab 150 mg q4w and did not re-flare in Epoch 2 were re-randomized to canakinumab 150 mg q8w or placebo to assess the potential for canakinumab to maintain clinical efficacy at a reduced dosing frequency
4. An open-label treatment epoch (Epoch 4) of 72 weeks to collect long-term safety data for canakinumab

Non-randomized patients and open label roll-over TRAPS patients

The following non-randomized patients were allowed to enter the study and were analyzed separately from the randomized cohorts:

- Japanese crFMF patients with non-exon 10 mutations entered the study in the open-label treatment of Epoch 2.
- Patients > 28 days but < 2 years old entered the study in the open-label treatment of Epoch 2.

The non-randomized group of Japanese crFMF patients with non-exon 10 mutations and patients > 28 days but < 2 years old with crFMF, HIDS/MKD, or TRAPS followed the study design below across the 4 epochs:

1. A screening epoch of up to 12 weeks duration to assess patient eligibility (Epoch 1)
2. An open-label epoch of 16 weeks (Epoch 2)
3. An open-label epoch of 24 weeks (Epoch 3)
4. An open-label treatment epoch of 72 weeks to collect long-term safety data for canakinumab (Epoch 4)

In addition to the non-randomized patients described above, TRAPS patients rolling over from Study ACZ885D2203 or ACZ885D2207M entered this study in Epoch 3 after undergoing Day 1 assessments for screening purposes. These patients received canakinumab as open-label treatment and were analyzed separately from the randomized TRAPS cohort, following the study design below:

1. An open-label epoch of 24 weeks (Epoch 3)
2. An open-label treatment epoch of 72 weeks to collect long-term safety data for canakinumab (Epoch 4)

Centers

68 centers in 16 countries: Italy(10), Turkey(5), Spain(6), United Kingdom(3), Japan(4), Belgium(5), Switzerland(1), United States(4), Russia(5), Israel(5), Germany(9), Canada(2), Ireland(1), Hungary(2), France(4), Netherlands(2)

Objectives:

Primary objective(s)

The primary objective of the randomized treatment epoch (Epoch 2) and of the overall study is to demonstrate that canakinumab treatment at a dose of 150 mg (or 2 mg/kg in patient weighing ≤ 40 kg) sc every 4 weeks 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.

Secondary objectives

The secondary objectives of the study are:

- To evaluate the percentage of patients who achieve a Physician Global Assessment of Disease Activity (PGA) < 2 ("minimal" or "none") at the end of Week 16
- To evaluate the percentage of patients with the serologic remission at the end of Week 16 (defined as C-reactive protein [CRP] ≤ 10 mg/L)
- To evaluate the percentage of patients with normalized Serum Amyloid A (SAA) level at the end of Week 16 (defined as SAA ≤ 10 mg/L)
- To evaluate the percentage of canakinumab responders in Epoch 2 who maintain a clinically meaningful response (absence of new flares) when switched to canakinumab every 8 weeks compared to placebo (Epoch 3)

Test Product (s), Dose(s), and Mode(s) of Administration

Canakinumab solution for subcutaneous injection was provided in vials that contained 150 mg/mL canakinumab in a 1 mL solution (batch numbers Y068 0613, Y011 0114 and Y183 1214).

Placebo solution for injection was provided in vials and matched the canakinumab solution (placebo batch numbers Y087 0713 and Y166 1114).

Statistical Methods

The primary efficacy variable of the randomized treatment epoch (Epoch 2) and for the overall study was the proportion of responders within each cohort. A responder was defined as a patient who had resolution of his/her index disease flare at Day 15 (PGA < 2, and CRP within normal range (≤ 10 mg/L) or reduction ≥ 70% from baseline) and did not experience a new flare (PGA ≥ 2 and CRP ≥ 30 mg/L) from the time of the resolution of the index flare until the end of Epoch 2.

The primary hypothesis tested was the superiority of canakinumab (150 mg or 2mg/kg q4w) relative to placebo with respect to the proportion of responders in the randomized treatment epoch (Epoch 2).

The hypothesis within each cohort was tested at a one-sided 2.5% level. The statistical null hypothesis was that there is no difference in the proportion of patients with responder rate at Week 16 in canakinumab dose 150 mg (or 2 mg/kg) q4w versus placebo.

The canakinumab treatment group was compared to placebo with respect to the proportion of responders at Week 16 using Fisher's exact test. The proportion of responders as well as the odds ratio and risk difference with corresponding 95% confidence interval were presented. The 95% confidence interval for the proportions was calculated using the exact (Clopper –Pearson) method.

If the primary objective was achieved, all secondary endpoints in Epoch 2 (PGA < 2, CRP ≤ 10 mg/L,SAA ≤ 10 mg/L at Week 16) were assessed in a hierarchical testing procedure to evaluate the superiority of canakinumab 150 mg q4w vs. placebo separately for each cohort. This was performed in order to control the overall Type I error rate ($\alpha = 0.025$, one sided tests) in the evaluation of these secondary efficacy variables. Testing was continued as long as each test showed statistical significance at the 2.5% level.

All efficacy evaluations up to the end of Week 40 were performed using the Full Analysis Set. The secondary efficacy objective of Epoch 3 was to evaluate the percentage of canakinumab responders in Epoch 2 who maintained a clinically meaningful response (absence of new flares) when switched to a canakinumab q8w regimen compared to placebo (Epoch 3). This objective was evaluated by assessing the efficacy of canakinumab 150 mg q8w as compared to placebo and was analyzed by cohort. The objective was included in the closed testing procedure.

A responder in the randomized withdrawal epoch (Epoch 3) was defined as no flare between Week 16 and Week 40. A flare was defined as PGA ≥ 2 and CRP ≥ 30 mg/L. Patients who discontinued the study in Epoch 3, or had an up-titration or escaped from the placebo group to a canakinumab group were also counted as having had a flare in Epoch 3. The canakinumab 150 mg q8w treatment group was compared to placebo with respect to the proportion of responders at Week 40 using the Fisher's exact test. Only canakinumab responders in Epoch 2 who were re-randomized at Week 16 were considered in the analysis. The proportion of responders, as well as the odds ratio (if estimable) and risk difference with corresponding 97.5% confidence interval are presented.

All safety evaluations up to the end of Week 40 were performed using the Safety set for Epoch 3. Safety data are presented by cohort and treatment (for patients who were re-randomized and remained in their initial treatment arm until the end of Epoch 3) or cumulative dose over 24 weeks (all other patients in Epoch 3).

For Epoch 4, safety data were presented by cohort and cumulative dose over the 72-week Epoch 4 (using cut-offs of < 2700 mg ≥ 2700 to < 5400 mg and ≥ 5400 mg). Safety data were also evaluated for the entire treatment period.

All safety evaluations up to the end of the study were performed using the Safety set. Treatment-emergent adverse events (AEs) were coded using MedDRA version 20.0. The crude incidence of treatment-emergent AEs was summarized by primary system organ class (SOC) and preferred term (PT). Descriptive summary statistics for laboratory parameters, vital signs and ECG parameters, and a listing of immunogenicity results by patient are provided.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria: - Patient's written informed consent (or parent's written informed consent in case of pediatric patient) at screening - Male and female patients at least 2 years of age at the time of the screening visit. Male and female patients >28 days but <2 years eligible for open label treatment only. - Confirmed diagnosis and active flare at randomization - CRP >10mg/L at randomization

Exclusion Criteria: - Use of the following therapies (within varying protocol defined timeframes): Corticosteroids, anakinra, canakinumab, rilonacept, tocilizumab, TNF inhibitors, abatacept, tofacitinib, rituximab, leflunomide, thalidomide, cyclosporine, intravenous immunoglobulin, 6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil, any other investigational biologics - History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in - situ cervical cancer), treated or untreated - Significant medical diseases, including but not limited to the following: a. History of organ transplantation b. Elevated liver enzymes ≥3x ULN d. Increase in total bilirubin e. Serious hepatic disorder (Child-Pugh scores B or C) f. Chronic Kidney Disease g. Thyroid disease h. Diagnosis of active peptic ulcer disease i. Coagulopathy j. Significant CNS effects including vertigo and dizziness - Any conditions or significant medical problems which immunecompromise the patient and/or places the patient at

unacceptable risk for immunomodulatory therapy - Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last dose

Participant Flow Table

Epoch 2

	Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo	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	Epoch 3: crFMF re-randomized from Epoch 2 - 150 mg	Epoch 3: crFMF re-randomized from Epoch 2 - Placebo	Epoch 3: HIDs/MKD re-randomized from Epoch 2 - 150 mg	Epoch 3: HIDS/MKD re-randomized from Epoch 2 - Placebo	Epoch 3: TRAPS re-randomized from Epoch 2 - 150 mg	Epoch 3: TRAPS re-randomized from Epoch 2 - Placebo	Epoch 3: crFMF, HIDS/MKD, TRAPS - not re-randomized	Epoch 4: crFMF - open label cumulative dose <2700 mg	Epoch 4: crFMF - open label cumulative dose 2700 - <5400 mg	Epoch 4: crFMF - open label cumulative dose >=5400 mg	Epoch 4: HIDS/MKD - open label cumulative dose <2700 mg	Epoch 4: HIDS/MKD - OL cumulative dose 2700 - <=5400 mg	Epoch 4: HIDS/MKD - open label cumulative dose >=5400 mg	Epoch 4: TRAPS - open label cumulative dose < 2700 mg	Epoch 4: TRAPS - open label cumulative dose 2700 - <5400 mg	Epoch 4: TRAPS - open label cumulative dose >=5400 mg
Started	31	32	37	35	22	24	2	2	18[1]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Completed	31	31	36	33	22	22	2	1	16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Not Completed	0	1	1	2	0	2	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lack of Efficacy	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Adverse Event	0	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Withdrawal by Subje	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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[1] This Epoch 3 group is shown in Epoch 2 to account for the 203 patients enrolled in the study.

Epoch 3

	Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo	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	Epoch 3: crFMF re-randomized from Epoch 2 - 150 mg	Epoch 3: crFMF re-randomized from Epoch 2 - Placebo	Epoch 3: HIDs/MKD re-randomized from Epoch 2 - 150 mg	Epoch 3: HIDS/MKD re-randomized from Epoch 2 - Placebo	Epoch 3: TRAPS re-randomized from Epoch 2 - 150 mg	Epoch 3: TRAPS re-randomized from Epoch 2 - Placebo	Epoch 3: crFMF, HIDS/MKD, TRAPS - not re-randomized	Epoch 4: crFMF - open label cumulative dose <2700 mg	Epoch 4: crFMF - open label cumulative dose 2700 - <5400 mg	Epoch 4: crFMF - open label cumulative dose >= 5400 mg	Epoch 4: HIDS/MKD - open label cumulative dose <2700 mg	Epoch 4: HIDS/MKD - OL cumulative dose 2700 - <= 5400 mg	Epoch 4: HIDS/MKD - open label cumulative dose >= 5400 mg	Epoch 4: TRAPS - open label cumulative dose < 2700 mg	Epoch 4: TRAPS - open label cumulative dose 2700 - <5400 mg	Epoch 4: TRAPS - open label cumulative dose >= 5400 mg
Started	2	1	0[1]	9	10	6	7	4	5	126	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Completed	2	1	0	9	10	6	7	3	5	120	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not Compl	0	0	0	0	0	0	0	1	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

eted																									
Physician Decision	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Adverse Event	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Lack of Efficacy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0	0	0	0
Withd	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0

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[1] Presented in Epoch 2.

Epoch 4

	Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo	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	Epoch 3: crFMF re-randomized from Epoch 2 - 150 mg	Epoch 3: crFMF re-randomized from Epoch 2 - Placebo	Epoch 3: HIDs/MKD re-randomized from Epoch 2 - 150 mg	Epoch 3: HIDS/MKD re-randomized from Epoch 2 - Placebo	Epoch 3: TRAPS re-randomized from Epoch 2 - 150 mg	Epoch 3: TRAPS re-randomized from Epoch 2 - Placebo	Epoch 3: crFMF, HIDS/MKD, TRAPS - not re-randomized	Epoch 4: crFMF - open label cumulative dose <2700 mg	Epoch 4: crFMF - open label cumulative dose 2700 - <5400 mg	Epoch 4: crFMF - open label cumulative dose >= 5400 mg	Epoch 4: HIDS/MKD - open label cumulative dose <2700 mg	Epoch 4: HIDS/MKD - OL cumulative dose 2700 - <=5400 mg	Epoch 4: HIDS/MKD - open label cumulative dose >= 5400 mg	Epoch 4: TRAPS - open label cumulative dose < 2700 mg	Epoch 4: TRAPS - open label cumulative dose 2700 - <5400 mg	Epoch 4: TRAPS - open label cumulative dose >= 5400 mg
Sta	0	0	0	43	14	2	18	34	14	31	22	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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Completed	0	0	0	41	14	2	18	33	14	30	21	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Not Completed	0	0	0	2	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AdverseEvent	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
Pregnancy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Withdrawalby	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0

Subject																										
Lack of Efficacy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Baseline Characteristics

	Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo	Epoch 2: Non-randomized open label treatment -	Epoch 2: Non-randomized open label HIDS/MKD	Epoch 2 (Epoch 3) - non-randomized open label	Total

							crFMF		TRAPS	
Number of Participants [units: participants]	31	32	37	35	22	24	2	2	18	203
Age Continuous (units: Years) Median (Full Range)										
crFMF cohort - randomized	18.0 (2 to 60)	18.0 (4 to 69)	NA (NA to NA)[1]	NA (NA to NA)[1]	NA (NA to NA)[1]	NA (NA to NA)[1]	NA (NA to NA)[1]	NA (NA to NA)[1]	NA (NA to NA)[1]	18 (2 to 69)
HIDS/MKD cohort - randomized	NA (NA to NA)[2]	NA (NA to NA)[3]	12.0 (2 to 43)	9.0 (3 to 47)	NA (NA to NA)[3]	NA (NA to NA)[3]	NA (NA to NA)[3]	NA (NA to NA)[3]	NA (NA to NA)[3]	11.0 (2 to 47)
TRAPS cohort - randomized	NA (NA to NA)[4]	NA (NA to NA)[4]	NA (NA to NA)[4]	NA (NA to NA)[4]	13.5 (3 to 76)	16.5 (2 to 57)	NA (NA to NA)[4]	NA (NA to NA)[4]	NA (NA to NA)[4]	15.5 (2 to 76)
crFMF - non-randomized	NA (NA to NA)[5]	NA (NA to NA)[5]	NA (NA to NA)[5]	NA (NA to NA)[5]	NA (NA to NA)[5]	NA (NA to NA)[5]	24.5 (20 to 29)	NA (NA to NA)[5]	NA (NA to NA)[5]	24.5 (20 to 29)
HIDS/MKD - non-randomized	NA (NA to NA)[6]	NA (NA to NA)[6]	NA (NA to NA)[6]	NA (NA to NA)[6]	NA (NA to NA)[6]	NA (NA to NA)[6]	NA (NA to NA)[6]	1.0 (1 to 1)	NA (NA to NA)[6]	1.0 (1 to 1)
roll-over TRAPS - non-randomized	NA (NA to NA)[7]	NA (NA to NA)[7]	NA (NA to NA)[7]	NA (NA to NA)[7]	NA (NA to NA)[7]	NA (NA to NA)[7]	NA (NA to NA)[7]	NA (NA to NA)[7]	42.5 (15 to 81)	42.5 (15 to 81)
Gender, Male/Female (units: Participants)										
Female	14	15	24	19	10	13	2	0	7	104
Male	17	17	13	16	12	11	0	2	11	99
Race (NIH/OMB) (units: Participants)										
American Indian or Alaska Native	0	0	0	0	0	0	0	0	0	0

Asian	0	1	0	1	2	4	2	1	0	11
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	27	27	34	31	20	18	0	1	16	174
More than one race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	4	4	3	3	0	2	0	0	2	18

[1] This row reflects crFMF cohort - randomized data only.
[2] This row reflect HIDS/MKD cohort - randomized data only.
[3] This row reflect HIDS/MKD cohort - randomized data only.
[4] This row reflect TRAPS cohort - randomized data only.
[5] This row reflects crFMF non-randomized data only.
[6] This row reflects HIDS/MIK non-randomized data only.
[7] This row reflects roll-over TRAPS non-randomized data only.

Summary of Efficacy

Primary Outcome Result(s)

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

Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo

Number of Participants Analyzed [units: participants]	31	32	37	35	22	24
Percentage of participants with resolution of initial flare and absence of new flares up to the end of the randomized treatment epoch (16 weeks) (units: Percentage of participants)	61.29	6.25	35.14	5.71	45.45	8.33

Statistical Analysis

Groups	Epoch 2: crFMF: 150 mg, Epoch 2: crCMF: placebo
Non-Inferiority/Equivalence Test	No
P Value	<0.0001
Method	Other Fisher's exact test
% Confidence Interval	to

Statistical Analysis

Groups	Epoch 2: HIDS/MKD: 150 mg, Epoch 2: HIDS/MKD:

	placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0020
Method	Other Fisher's exact test
% Confidence Interval	to

Statistical Analysis

Groups	Epoch 2: TRAPS: 150 mg, Epoch 2: TRAPS: placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0050
Method	Other Fisher's exact test
% Confidence Interval	to

Secondary Outcome Result(s)

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

	Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo
Number of Participants Analyzed [units: participants]	31	32	37	35	22	24
Percentage of participants who achieve Physician's global assessment < 2 (units: Percentage of participants)	64.52	9.38	45.95	5.71	45.45	4.17

Statistical Analysis

Groups	Epoch 2: crFMF: 150 mg, Epoch 2: crCMF: placebo
Non-Inferiority/Equivalence Test	No
P Value	<0.0001
Method	Regression, Logistic
Odds Ratio (OR)	16.96
95 % Confidence Interval 2-Sided	4.15 to 69.21

Statistical Analysis

Groups	Epoch 2: HIDS/MKD: 150 mg, Epoch 2: HIDS/MKD: placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0006
Method	Regression, Logistic
Odds Ratio (OR)	13.63
95 % Confidence Interval 2-Sided	2.83 to 65.59

Statistical Analysis

Groups	Epoch 2: TRAPS: 150 mg, Epoch 2: TRAPS: placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0028
Method	Regression, Logistic
Odds Ratio (OR)	23.79
95 % Confidence Interval 2-Sided	2.52 to 224.86

Percentage of participants with the serologic remission (defined as C-reactive protein (CRP) ≤ 10 mg/L)

	Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo
Number of Participants Analyzed [units: participants]	31	32	37	35	22	24
Percentage of participants with the serologic remission (units: Percentage of participants)	67.74	6.25	40.54	5.71	36.36	8.33

Statistical Analysis

Groups	Epoch 2: crFMF: 150 mg,

	Epoch 2: crCMF: placebo
Non-Inferiority/Equivalence Test	No
P Value	<0.0001
Method	Regression, Logistic
Odds Ratio (OR)	29.78
95 % Confidence Interval 2-Sided	5.86 to 151.31

Statistical Analysis

Groups	Epoch 2: HIDS/MKD: 150 mg, Epoch 2: HIDS/MKD: placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0010
Method	Regression, Logistic
Odds Ratio (OR)	12.71
95 % Confidence Interval 2-Sided	2.53 to 63.89

Statistical Analysis

Groups	Epoch 2: TRAPS: 150 mg,

	Epoch 2: TRAPS: placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0149
Method	Regression, Logistic
Odds Ratio (OR)	6.64
95 % Confidence Interval 2-Sided	1.20 to 36.57

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

	Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo
Number of Participants Analyzed [units: participants]	31	32	37	35	22	24
Percentage of participants with normalized Serum Amyloid A (SAA) level (units: Percentage of participants)	25.81	0.00	13.51	2.86	27.27	0.00

Statistical Analysis

Groups	Epoch 2: crFMF: 150 mg, Epoch 2: crCMF: placebo
Non-Inferiority/Equivalence Test	No

P Value	0.0286
Method	Regression, Logistic
Odds Ratio (OR)	17.46
95 % Confidence Interval 2-Sided	0.92 to 332.92

Statistical Analysis

Groups	Epoch 2: HIDS/MKD: 150 mg, Epoch 2: HIDS/MKD: placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0778
Method	Regression, Logistic
Odds Ratio (OR)	5.26
95 % Confidence Interval 2-Sided	0.53 to 51.97

Statistical Analysis

Groups	Epoch 2: TRAPS: 150 mg, Epoch 2: TRAPS: placebo
Non-Inferiority/Equivalence Test	No

P Value	0.0235
Method	Regression, Logistic
Odds Ratio (OR)	16.69
95 % Confidence Interval 2-Sided	1.04 to 268.50

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

	Epoch 2: crFMF: 150 mg	Epoch 2: crCMF: placebo	Epoch 2: HIDS/MKD: 150 mg	Epoch 2: HIDS/MKD: placebo	Epoch 2: TRAPS: 150 mg	Epoch 2: TRAPS: placebo
Number of Participants Analyzed [units: participants]	9	10	6	7	4	5
Percentage of participants of canakinumab responders from epoch 2 who maintained a clinically meaningful response (absence of new flares) (40 weeks) (units: Percentage of participants)	77.8	30.0	50.0	14.3	75.0	40.0

Statistical Analysis

Groups	Epoch 2: crFMF: 150 mg, Epoch 2: crCMF: placebo
Non-Inferiority/Equivalence	No

Test	
P Value	0.0513
Method	Regression, Logistic
Odds Ratio (OR)	8.17
95 % Confidence Interval 2-Sided	0.75 to 113.44

Statistical Analysis

Groups	Epoch 2: HIDS/MKD: 150 mg, Epoch 2: HIDS/MKD: placebo
Non-Inferiority/Equivalence Test	No
P Value	0.2168
Method	Regression, Logistic
Odds Ratio (OR)	6.00
95 % Confidence Interval 2-Sided	0.27 to 366.24

Statistical Analysis

Groups	Epoch 2: TRAPS: 150 mg, Epoch 2: TRAPS: placebo
Non-Inferiority/Equivalence	No

Test	
P Value	0.3571
Method	Regression, Logistic
Odds Ratio (OR)	4.50
95 % Confidence Interval 2-Sided	0.15 to 313.49

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

Time Frame	up to 112 weeks
Source Vocabulary for Table Default	MedDRA (20.0)
Assessment Type for Table Default	Systematic Assessment

	Non-randomized open label participants N = 4	TRARS roll-over participants N = 18	Randomized participants N = 181	Any ACZ participants N = 193
Total participants affected	3 (75.00%)	1 (5.56%)	47 (25.97%)	47 (24.35%)
Blood and lymphatic system disorders				
Anaemia	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Lymphadenopathy	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Neutropenia	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
Pancytopenia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Cardiac disorders				
Cardiac failure congestive	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Pericarditis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Congenital, familial and genetic disorders				
Familial mediterranean fever	0 (0.00%)	0 (0.00%)	4 (2.21%)	4 (2.07%)
Hyper IgD syndrome	1 (25.00%)	0 (0.00%)	4 (2.21%)	5 (2.59%)
Tumour necrosis factor receptor-associated periodic syndrome	0 (0.00%)	0 (0.00%)	4 (2.21%)	3 (1.55%)
Endocrine disorders				
Thyroiditis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Gastrointestinal disorders				
Abdominal pain	0 (0.00%)	0 (0.00%)	2 (1.10%)	1 (0.52%)

Ascites	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Constipation	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Diarrhoea	0 (0.00%)	1 (5.56%)	1 (0.55%)	2 (1.04%)
Dysphagia	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Ileal ulcer	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Inguinal hernia	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Umbilical hernia	0 (0.00%)	0 (0.00%)	2 (1.10%)	2 (1.04%)
Vomiting	0 (0.00%)	0 (0.00%)	2 (1.10%)	2 (1.04%)
General disorders and administration site conditions				
Hyperpyrexia	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Polyserositis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Pyrexia	0 (0.00%)	1 (5.56%)	7 (3.87%)	8 (4.15%)
Hepatobiliary disorders				
Bile duct stone	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Granulomatous liver disease	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Hepatic cirrhosis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Hepatic failure	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Immune system disorders				
Drug hypersensitivity	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Infections and infestations				
Acute sinusitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Anal abscess	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)

Appendicitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Atypical pneumonia	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
Bronchitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Cellulitis	0 (0.00%)	0 (0.00%)	2 (1.10%)	2 (1.04%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Diarrhoea infectious	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Gastroenteritis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Gastroenteritis rotavirus	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Herpes virus infection	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Infectious colitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Influenza	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Laryngitis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Orchitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Pelvic abscess	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Peritonitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Pharyngitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Pharyngotonsillitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Pneumonia	0 (0.00%)	0 (0.00%)	5 (2.76%)	5 (2.59%)
Pyelonephritis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Septic shock	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Tonsillitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Vulval abscess	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Injury, poisoning and procedural complications				
Scar	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)

Metabolism and nutrition disorders				
Dehydration	0 (0.00%)	0 (0.00%)	2 (1.10%)	2 (1.04%)
Hypercalcaemia	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Obesity	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Musculoskeletal and connective tissue disorders				
Arthralgia	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Bursitis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Nervous system disorders				
Seizure	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Psychiatric disorders				
Depression	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Intentional self-injury	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Schizophrenia	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Suicidal ideation	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Suicide attempt	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Renal and urinary disorders				
Acute kidney injury	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0.00%)	0 (0.00%)	1 (0.55%)	0 (0.00%)
Laryngeal stenosis	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)

Oropharyngeal pain	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Pleurisy	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Vocal cord polyp	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Skin and subcutaneous tissue disorders				
Drug eruption	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Granulomatous rosacea	0 (0.00%)	0 (0.00%)	1 (0.55%)	1 (0.52%)
Pyoderma gangrenosum	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)

Other Adverse Events by System Organ Class

Time Frame	up to 112 weeks
Source Vocabulary for Table Default	MedDRA (20.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Non-randomized open label participants N = 4	**TRARS roll-over participants N = 18**	**Randomized participants N = 181**	**Any ACZ participants N = 193**
Total participants affected	4 (100.00%)	18 (100.00%)	176 (97.24%)	188 (97.41%)
Blood and lymphatic system disorders				

Anaemia	0 (0.00%)	1 (5.56%)	8 (4.42%)	8 (4.15%)
Lymphadenopathy	0 (0.00%)	0 (0.00%)	27 (14.92%)	27 (13.99%)
Neutropenia	0 (0.00%)	0 (0.00%)	11 (6.08%)	10 (5.18%)
Cardiac disorders				
Atrial fibrillation	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Tachycardia	0 (0.00%)	1 (5.56%)	2 (1.10%)	3 (1.55%)
Congenital, familial and genetic disorders				
Familial mediterranean fever	1 (25.00%)	0 (0.00%)	29 (16.02%)	25 (12.95%)
Hyper IgD syndrome	1 (25.00%)	0 (0.00%)	21 (11.60%)	21 (10.88%)
Ear and labyrinth disorders				
Ear pain	0 (0.00%)	0 (0.00%)	13 (7.18%)	13 (6.74%)
Endocrine disorders				
Hyperthyroidism	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Eye disorders				
Eye allergy	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Eye pain	1 (25.00%)	0 (0.00%)	4 (2.21%)	5 (2.59%)
Scleritis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Gastrointestinal disorders				
Abdominal discomfort	0 (0.00%)	3 (16.67%)	2 (1.10%)	4 (2.07%)
Abdominal pain	0 (0.00%)	4 (22.22%)	59 (32.60%)	61 (31.61%)
Abdominal pain upper	0 (0.00%)	1 (5.56%)	28 (15.47%)	27 (13.99%)
Aphthous ulcer	1 (25.00%)	0 (0.00%)	18 (9.94%)	19 (9.84%)

Constipation	1 (25.00%)	1 (5.56%)	12 (6.63%)	13 (6.74%)
Dental caries	1 (25.00%)	0 (0.00%)	3 (1.66%)	4 (2.07%)
Diarrhoea	2 (50.00%)	4 (22.22%)	45 (24.86%)	49 (25.39%)
Dyspepsia	0 (0.00%)	2 (11.11%)	5 (2.76%)	7 (3.63%)
Gastric dilatation	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Gastritis	1 (25.00%)	0 (0.00%)	5 (2.76%)	6 (3.11%)
Haemorrhoids	1 (25.00%)	0 (0.00%)	1 (0.55%)	2 (1.04%)
Nausea	1 (25.00%)	0 (0.00%)	17 (9.39%)	18 (9.33%)
Proctitis	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Stomatitis	1 (25.00%)	0 (0.00%)	3 (1.66%)	4 (2.07%)
Teething	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Toothache	0 (0.00%)	1 (5.56%)	7 (3.87%)	8 (4.15%)
Vomiting	1 (25.00%)	1 (5.56%)	27 (14.92%)	26 (13.47%)
General disorders and administration site conditions				
Asthenia	0 (0.00%)	1 (5.56%)	11 (6.08%)	12 (6.22%)
Fatigue	0 (0.00%)	0 (0.00%)	12 (6.63%)	11 (5.70%)
Influenza like illness	0 (0.00%)	0 (0.00%)	12 (6.63%)	10 (5.18%)
Injection site reaction	0 (0.00%)	1 (5.56%)	28 (15.47%)	28 (14.51%)
Malaise	1 (25.00%)	1 (5.56%)	5 (2.76%)	7 (3.63%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	14 (7.73%)	14 (7.25%)
Pyrexia	1 (25.00%)	5 (27.78%)	71 (39.23%)	74 (38.34%)
Infections and infestations				
Bronchitis	2 (50.00%)	1 (5.56%)	13 (7.18%)	16 (8.29%)
Conjunctivitis	2 (50.00%)	1 (5.56%)	8 (4.42%)	11 (5.70%)

Cystitis	0 (0.00%)	1 (5.56%)	3 (1.66%)	4 (2.07%)
Ear infection	1 (25.00%)	1 (5.56%)	10 (5.52%)	12 (6.22%)
Gastroenteritis	2 (50.00%)	1 (5.56%)	24 (13.26%)	27 (13.99%)
Influenza	1 (25.00%)	2 (11.11%)	31 (17.13%)	33 (17.10%)
Lower respiratory tract infection	0 (0.00%)	1 (5.56%)	5 (2.76%)	6 (3.11%)
Nasopharyngitis	1 (25.00%)	0 (0.00%)	8 (4.42%)	8 (4.15%)
Oral herpes	0 (0.00%)	1 (5.56%)	12 (6.63%)	11 (5.70%)
Otitis media	0 (0.00%)	0 (0.00%)	13 (7.18%)	13 (6.74%)
Pharyngitis	0 (0.00%)	0 (0.00%)	16 (8.84%)	16 (8.29%)
Pilonidal cyst	0 (0.00%)	1 (5.56%)	1 (0.55%)	2 (1.04%)
Respiratory tract infection	0 (0.00%)	1 (5.56%)	11 (6.08%)	12 (6.22%)
Rhinitis	1 (25.00%)	2 (11.11%)	25 (13.81%)	28 (14.51%)
Sialoadenitis	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Sinusitis	0 (0.00%)	1 (5.56%)	7 (3.87%)	8 (4.15%)
Tonsillitis	0 (0.00%)	1 (5.56%)	15 (8.29%)	16 (8.29%)
Tonsillitis bacterial	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Tracheitis	0 (0.00%)	2 (11.11%)	0 (0.00%)	2 (1.04%)
Upper respiratory tract infection	0 (0.00%)	3 (16.67%)	47 (25.97%)	49 (25.39%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	16 (8.84%)	15 (7.77%)
Viral infection	0 (0.00%)	1 (5.56%)	15 (8.29%)	16 (8.29%)
Viral tonsillitis	1 (25.00%)	0 (0.00%)	1 (0.55%)	2 (1.04%)
Viral upper respiratory tract infection	1 (25.00%)	5 (27.78%)	38 (20.99%)	44 (22.80%)
Injury, poisoning and procedural				

complications				
Contusion	0 (0.00%)	1 (5.56%)	2 (1.10%)	3 (1.55%)
Skin abrasion	0 (0.00%)	1 (5.56%)	1 (0.55%)	2 (1.04%)
Thermal burn	0 (0.00%)	1 (5.56%)	2 (1.10%)	2 (1.04%)
Wound	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Investigations				
Alanine aminotransferase increased	1 (25.00%)	1 (5.56%)	3 (1.66%)	5 (2.59%)
Aspartate aminotransferase increased	1 (25.00%)	0 (0.00%)	1 (0.55%)	2 (1.04%)
Blood creatine phosphokinase increased	0 (0.00%)	1 (5.56%)	5 (2.76%)	6 (3.11%)
C-reactive protein increased	1 (25.00%)	0 (0.00%)	2 (1.10%)	3 (1.55%)
Eosinophil count increased	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Glomerular filtration rate decreased	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Neutrophil count decreased	1 (25.00%)	0 (0.00%)	1 (0.55%)	2 (1.04%)
Neutrophil count increased	1 (25.00%)	1 (5.56%)	2 (1.10%)	3 (1.55%)
Serum amyloid A protein increased	1 (25.00%)	3 (16.67%)	6 (3.31%)	9 (4.66%)
White blood cell count increased	1 (25.00%)	1 (5.56%)	2 (1.10%)	3 (1.55%)
Metabolism and nutrition disorders				

Dehydration	1 (25.00%)	0 (0.00%)	1 (0.55%)	2 (1.04%)
Hypocalcaemia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Hypophosphataemia	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (25.00%)	5 (27.78%)	39 (21.55%)	42 (21.76%)
Arthritis	0 (0.00%)	1 (5.56%)	2 (1.10%)	3 (1.55%)
Back pain	1 (25.00%)	2 (11.11%)	29 (16.02%)	32 (16.58%)
Intervertebral disc disorder	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Musculoskeletal chest pain	0 (0.00%)	1 (5.56%)	1 (0.55%)	2 (1.04%)
Musculoskeletal pain	0 (0.00%)	2 (11.11%)	17 (9.39%)	16 (8.29%)
Myalgia	0 (0.00%)	3 (16.67%)	19 (10.50%)	21 (10.88%)
Pain in extremity	1 (25.00%)	3 (16.67%)	23 (12.71%)	25 (12.95%)
Spinal pain	0 (0.00%)	1 (5.56%)	2 (1.10%)	3 (1.55%)
Tendon pain	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Tenosynovitis stenosans	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Pyogenic granuloma	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Nervous system disorders				
Headache	1 (25.00%)	2 (11.11%)	64 (35.36%)	62 (32.12%)
Somnolence	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Reproductive system and breast disorders				

Breast mass	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Polycystic ovaries	0 (0.00%)	1 (5.56%)	1 (0.55%)	2 (1.04%)
Vaginal haemorrhage	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0.00%)	3 (16.67%)	38 (20.99%)	40 (20.73%)
Epistaxis	0 (0.00%)	0 (0.00%)	11 (6.08%)	11 (5.70%)
Oropharyngeal pain	0 (0.00%)	1 (5.56%)	40 (22.10%)	39 (20.21%)
Pleuritic pain	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Pneumonitis	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)
Rhinitis allergic	0 (0.00%)	1 (5.56%)	3 (1.66%)	4 (2.07%)
Skin and subcutaneous tissue disorders				
Dermatitis allergic	1 (25.00%)	0 (0.00%)	1 (0.55%)	2 (1.04%)
Drug eruption	2 (50.00%)	0 (0.00%)	0 (0.00%)	2 (1.04%)
Eczema	1 (25.00%)	0 (0.00%)	10 (5.52%)	11 (5.70%)
Keloid scar	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Pain of skin	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Pyoderma gangrenosum	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Rash	0 (0.00%)	0 (0.00%)	19 (10.50%)	16 (8.29%)
Rash pruritic	1 (25.00%)	0 (0.00%)	1 (0.55%)	2 (1.04%)
Skin ulcer	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (0.52%)
Urticaria	1 (25.00%)	0 (0.00%)	9 (4.97%)	9 (4.66%)
Vascular disorders				
Hypertension	0 (0.00%)	2 (11.11%)	1 (0.55%)	3 (1.55%)
Hypotension	0 (0.00%)	1 (5.56%)	0 (0.00%)	1 (0.52%)

Other Relevant Findings

None

Conclusion:

The final results for Study N2301 indicate that optimal control of disease activity in the crFMF, TRAPS and HIDS patients can be achieved with canakinumab 150 mg or 300 mg at a 4-weekly dose interval (q4w) and maintained following long-term treatment on the same interval (all 3 cohorts) or even at an extended 8-weekly interval (q8w) for a subset of crFMF and TRAPS patients. HIDS/MKD patients demonstrated a need for higher doses administered at a 4-weekly interval to achieve and maintain a clinically meaningful response over time. Fast and sustained decreases in circulating SAA levels in conjunction with preservation of renal function indicated that canakinumab is an effective treatment for mitigating the most powerful risk factor for the development of amyloidosis and delaying progression to renal failure. The long-term safety profile in the 3 disease cohorts as indicated in Epoch 4 (72 weeks) and the entire study (112 weeks) revealed no new or unexpected signals compared with Week 16 and Week 40 interim analyses and with the known safety profile of other indications for which canakinumab is approved.

Date of Clinical Trial Report

November 29, 2017