CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319Orig1s085, 086, 087

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

BLA/Serial Number:	125319/s-85, s-86, s87
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Novartis Pharmaceuticals Corporation has submitted a supplemental biologics license application (sBLA) 125319, for Ilaris® (canakinumab) subcutaneous injection, seeking indication to treat patients aged 2 years and older with periodic fever syndromes including familial mediterranean fever (FMF), hyper immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS). The proposed dosage and administration is 150 mg for patients with body weight > 40 kg (or 2 mg/kg for patients with body weight ≤ 40 kg) once every 4 weeks. Efficacy and safety of canakinumab were evaluated in a single Phase 3 randomized, double-blind, placebo-controlled study CACZ885N2301 (referred to as N2301).

Data from the randomized treatment period (Epoch 2) of Study N2301 demonstrated efficacy of canakinumab in all 3 disease cohorts: FMF, HIDS/MKD, and TRAPS. Canakinumab provided statistically significant benefit over placebo with respect to the primary endpoint, the proportion of complete responders as defined by patients who resolved their index disease flare at Day 15 and had no new disease flare over 16 weeks of treatment from the time of resolution of index flare. The proportion of responders in patients treated with canakinumab compared to those treated with placebo were 61.3% versus 6.3% in FMF patients (Odds ratio=23.75; p-value<0.0001), 35.1% versus 5.7% in HIDS/MKD patients (Odds ratio=8.94; p-valule=0.0020), and 45.5% versus 8.3% in TRAPS patients (Odds ratio=9.17; p-value=0.0050), respectively. Secondary and sensitivity analyses showed consistent trends supporting the efficacy of canakinumab. Canakinumab improved multiple measures of clinical response, serological markers of inflammation, and health-related quality of life relative to placebo.

However, interpretation of many of these results is clouded by the protocol provision of allowing patients to receive add-on canakinumab or be up-titrated in case of persistent disease activity or re-flare. The majority of placebo patients (84% to 88%) switched to receive canankinumab or further dose escalation and approximately 32% to 51% of patients on initial canakinumab 150mg q4w dose were up-titrated to 300mg q4w by Week 16. By the end of Epoch 2 there were a limited number of patients remaining on initial randomized treatment, especially for the placebo group (4 in FMF, 3 in HIDS/MKD, and 2 in TRAPS) which makes many treatment comparisons, especially comparisons at Week 16, difficult to interpret. The protocol specified primary and secondary analyses considered patients who crossed over or up-titrated to be non-responders, so they essentially compared the efficacy of canakinumab against placebo with respect to the probability of achieving a complete response or threshold and *remaining on initially assigned treatment until the end of randomized treatment period (Week 16).* Analysis at the earlier time point Day 15 showed that more patients in the canakinumab group resolved their index flare compared with placebo across all 3 cohorts (80.7% versus 31.3% for FMF; 64.9% versus 37.1% for HIDS/MKD; 63.6% versus 20.8% for TRAPS). While some patients had already received add-on injection of canakinumab before Day 15, the short-term results at Day 15 are considered more reliable compared to evaluation of treatment effect at Week 16.

Subgroup analyses found no meaningful difference in the effect of canakinumab by gender, race, age group, prior use of biologics, and concomitant use of colchicine (for FMF cohort only). Interpretation of the results is limited due to small numbers of patients.

2 INTRODUCTION

2.1 OVERVIEW

2.1.1 Drug Class and Indication

This supplemental biologics licensing application (sBLA) 125319 is submitted for Ilaris® (canakinumab), a high-affinity fully human monoclonal anti-human interleukin-1β (IL-1β) antibody, for the treatment of three periodic fever syndromes. Canakinumab is currently approved for the treatment of cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory syndrome (FCAS) and muckle-wells syndrome (MWS) in patients 4 years of age and older and for system juvenile idiopathic arthritis (SJIA) in patients 2 years of age and older.

The current filing for canakinumab is to add the periodic fever syndrome indications as follows:

- Familial mediterranean fever (FMF) in adults and children aged 2 years and older in whom colchicine is contraindicated, is not tolerated, or does not provide an adequate response.
- Hyperimmunoglobulin D (Hyper-IgD) syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adults and children 2 years of age and older.
- Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) in adults and children aged 2 years and older.

The recommended start dose is 150 mg for patients with body weight > 40 kg (or 2 mg/kg for patients with body weight ≤ 40 kg). This is administered every 4 weeks as a single dose via subcutaneous injection.

2.1.2 History of Drug Development

The development plan for canakinumab in hereditary periodic fever conditions was submitted to the Division of Pulmonary, Allergy, and Rheumatology Products under IND 100040 in 2013. The program included a single confirmatory, randomized, placebo-controlled, Phase 3 trial (Study CACZ885N2301; referred to as N2301) to fulfill health authority requirements for the clinical evaluation of drugs that treat pediatric and adult patients with inherited orphan auto-inflammatory conditions. Four uncontrolled open-label proof of concept (PoC) studies with varying canakinumab doses were also conducted to support the primary indication of periodic fever syndromes.

The applicant had several interactions with the Division, including a pre-Phase 3 meeting held on May 13, 2013, a Type C meeting via written response on October 11, 2013, a Pre-BLA meeting held on June 2, 2015, and a Type C meeting via written response on February 12, 2016. Pertinent statistical parts of these meetings are summarized herein:

- A single Phase 3 study to support registration in these orphan conditions was appropriate given the limited numbers of patients available for inclusion in the clinical program.

- The three rare diseases (FMF, MKD/HIDS and TRAPS) each was considered to be distinct disease entity, therefore, three separate patient populations would be used for the assessment of efficacy and safety.
- Assessment of efficacy would be based on the results from each individual cohort and not on the pooling of data across patient populations.
- A randomized withdrawal period following the initial 16-week randomized treatment period would be incorporated to account for the waxing and waning nature of the disease and the difficulty in patient recruitment.
- The primary efficacy endpoint was the proportion of responders defined as patients who had resolution of their index disease flare and did not experience a new flare during the 16 weeks following resolution.
- The primary analysis of responders would use Fisher's exact test and would be conducted separately for each disease cohort.
- All FMF patients, as opposed to a subset 'colchicine resistant' population, should be studied.

Regarding the design of Study N2301, the Division raised concerns about its integrity as the protocol allowed patients to escape and receive open-label active therapy during the randomized placebo-controlled period. The Division recommended the applicant to address the limitation of this protocol provision and analyze the efficacy and safety data taking into account the different pre-defined dose escalation scenarios. An information request was issued to the applicant on May 11, 2016; in order to clarify the proportion of patients who remained on initial randomized treatment, as well as the time point when add-on injection or up-titration occurred. The applicant's response indicated that the majority of placebo patients crossed over to receive canakinumab or further dose escalation as early as Day 15 while at least half of canakinumab patients remained on initially randomized dose.

Furthermore, the Division initially advised that data from both the randomized placebo-controlled period and the randomized withdrawal period would likely be needed to demonstrate substantial evidence of efficacy within the context of a single study. The sponsor presented data from the randomized treatment period at the pre-BLA meeting showing significant efficacy of canakinumab which led to submission of this current sBLA without the additional data from the randomized withdrawal period.

2.1.3 Current Submission

The current submission contains results from the 16-week randomized treatment period (Epoch 2) within the placebo-controlled Phase 3 study N2301. It also includes results from four PoC open-label studies each targeting a single indication: two studies in FMF (Study CACZ885DTR01 with 9 patients and Study CACZ885D2204 with 7 patients), one study in HIDS/MKD (Study CACZ885D2402 with 9 patients), and one study in TRAPS (Study CACZ885D2203 with 20 patients).

This statistical review focuses on the Study N2301 Epoch 2 in the canakinumab development program. The four PoC open-label studies are not discussed here.

2.2 DATA SOURCES

The applicant submitted the clinical study report, protocol, statistical analysis plan, and referenced literature to the Agency. The data and documents for the electronic submission were archived under the network path location:

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\\Cdsesub1\evsprod\BLA125319\0212
\\Cdsesub1\evsprod\BLA125319\0213

3 STATISICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

In general, the electronic data submitted by the applicant are of sufficient quality to allow a thorough review of the data. I am able to reproduce the analyses of the primary and secondary efficacy endpoints for each cohort evaluated. My results are presented in this review and match those from the applicant unless otherwise noted.

3.2 EVALUATION OF EFFICACY

The safety and efficacy of canakinumab to treat periodic fever syndromes was evaluated in a single pivotal Phase 3 Study N2301 entitled as "A randomized, double-blind, placebo controlled study of canakinumab in patients with Hereditary Periodic Fevers (TRAPS, HIDS, or FMF), with subsequent randomized withdrawal/dosing frequency reduction and open-label long term treatment epochs".

3.2.1 Study Design and Endpoints

The primary objective of Study N2301was to demonstrate that canakinumab treatment at a dose of 150 mg (or 2 mg/kg in patient weighing ≤ 40 kg) subcutaneous 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. The study consisted of 3 randomized cohorts (one cohort per condition: FMF, HIDS/MKD and TRAPS), and all followed the same study design which included 4 study epochs. Epoch 1 was a 12-week screening period to assess eligibility and to allow patients to achieve significant biologic washout and to taper off non-allowed medications. Epoch 2 was a 16-week randomized treatment period to evaluate efficacy and safety of canakinumab given every 4 weeks in a double-blind placebo-controlled parallel-arm setting. Epoch 3 was a 24-week randomized withdrawal period to assess the efficacy and safety of canakinumab at reduced dosing frequency (given every 8 weeks) compared to placebo in patients who responded to canakinumab treatment in Epoch 2. Epoch 4 was a 72-week open-label treatment extension period in order to collect long-term safety data. The study was initiated in June, 2014 and is currently ongoing with the last patient completing the last visit (Week 16) in Epoch 2 on August 25, 2015. This review covers all efficacy data collected up to the Week 16, the end of the randomized treatment period (Epoch 2).

The design of Study N2301 Epoch 1 and Epoch 2 is illustrated in Figure 1. The study was mainly conducted outside the United States (FMF: 10 countries; HIDS/MKD: 13 countries; TRAPS: 14 countries). Only two patients were randomized in the United States. Following screening (Epoch 1) eligible patients were randomized in a ratio of 1:1 within each cohort to receive either canakinumab 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) once every 4 weeks (q4w) or placebo for a total of 16 weeks in Epoch 2. During Epoch 2, visits to assess efficacy and safety were scheduled at Day 15, Day 29, and subsequently at 4-week intervals. Patients were able to be up-titrated if they had persistent disease activity or re-flared before Day 29 (blinded escape) or after Day 29 (open-label treatment) according to Table 1. Patients who were on the highest allowed canakinumab dose of 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q4w and re-flared as indicated by physician's global assessment of disease activity (PGA) ≥ 2 and C-reactive protein (CRP) ≥ 30 mg/L were not eligible for further up-titration. Consequently, the actual treatment sequence for a patient could be one of the following:

- Randomized to 150 mg and stayed on this treatment (150mg q4w)
- Randomized to 150 mg and up-titrated to 300 mg (150mg q4w to 300 mg q4w)
- Randomized to placebo and stayed on placebo (placebo)
- Randomized to placebo and up-titrated to 150 mg (placebo to 150mg q4w)
- Randomized to placebo and up-titrated twice to 150 mg and 300 mg (placebo to 150mg q4w to 300mg q4w)

The protocol provision of allowing patients to cross over or be up-titrated had an important impact on the degree of adherence to initial randomized treatment, and subsequently, the interpretability of the results (see Section 3.2.4 for further discussion).

Additionally, a group of non-randomized patients were allowed to enter the study per applicant to fulfill requests by health authorities and to provide access to canakinumab treatment. These non-randomized patients are not evaluated in this review.

Figure 1 Screening (Epoch 1) and randomized treatment period (Epoch 2)

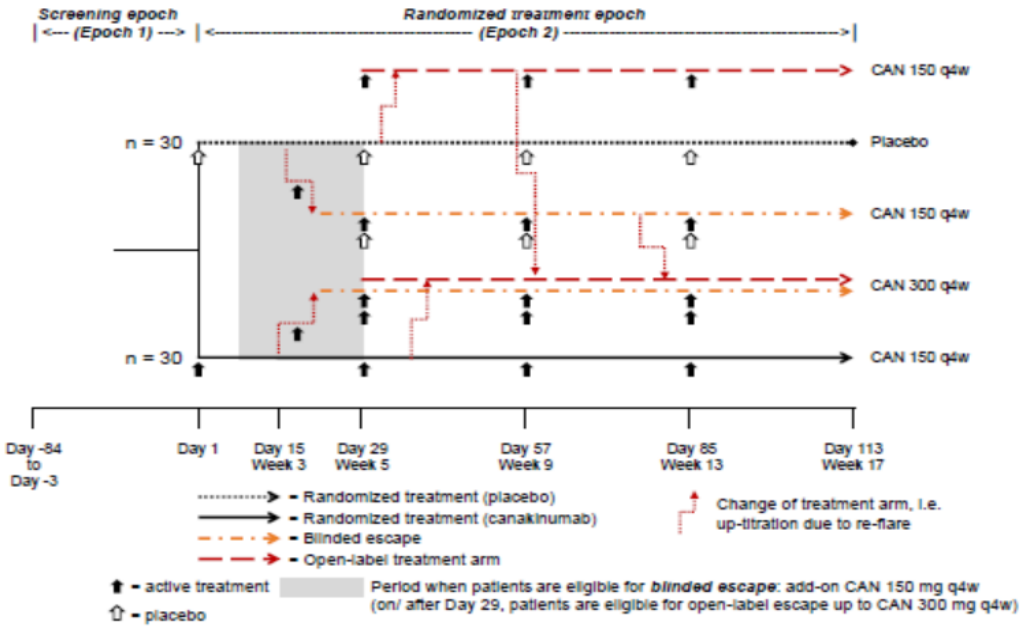


Table 1 Criteria for add-on injection and subsequent up-titration in Epoch 2

	PGA and CRP criteria	Treatment option	Up-titration
Day 8 to 14	Persistent PGA ≥ 2 **OR** CRP persistent > 10 mg/L with less than 40% reduction from baseline	Add-on injection allowed	Blinded up-titration effective at next scheduled visit (Day 29)
Day 15	PGA ≥ 2 **OR** CRP >10 mg/L and no reduction by at least 70% from baseline i.e., No index flare resolution*	Add-on injection allowed (only if add-on injection was not received earlier)	Blinded up-titration effective at next scheduled visit
Day 16 to 28	PGA ≥ 2 **OR** CRP >10 mg/L and no reduction by at least 70% from baseline	Add-on injection allowed (only if add-on injection was not received earlier)	Blinded up-titration effective at next scheduled visit
Day 29 to 112	PGA ≥ 2 **AND** CRP ≥30mg/L	Up-titration allowed	Open-label up-titration effective at next scheduled visit including Day 29 visit

* For patients with index flare resolution at Day 15, criteria defined for Day 29 was applied
A single add-on injection was allowed only once in Epoch 2

The primary efficacy endpoint was the proportion of complete responders within each cohort as defined by patients who had resolution of their index disease flare at Day 15 and did not experience a new disease flare during the remainder of the 16-week treatment period. Resolution of the index disease flare (initial flare at the time of the randomization) was defined at the Day 15 visit as a physician's global assessment (PGA) disease activity score less than 2 ("minimal or no disease", PGA < 2) and C-reactive protein (CRP) within normal range (CRP≤ 10 mg/L) or reduction ≥ 70% from baseline. A new flare was defined as a PGA ≥ 2 ("mild, moderate, or severe disease", clinical flare) and CRP ≥ 30 mg/L (serological flare). The index flare of the responder patients must have resolved at Day 15 without requiring add-on canakinumab injection. Non-responders were those patients who needed dose escalation in the canakinumab arms or escape from placebo to canakinumab, or patients who discontinued from the study due to any reason prior to the Week 16 primary endpoint. Of note the definition of complete responders involves a composite measure of PGA and CRP (See more discussion in Section 3.2.4).

The secondary variables were:

1) PGA: percentage of patients who achieved a PGA < 2 at Week 16
2) CRP: percentage of patients with serologic remission at Week 16 (CRP ≤ 10 mg/L)
3) Serum amyloid A (SAA): percentage of patients with a normalized serum amyloid level at Week 16 (SAA ≤ 10 mg/L)

Similar to the responder criteria for the primary endpoint, patients needing dose escalation in the canakinumab arms, or who escaped from placebo to canakinumab in the randomized treatment epoch, or discontinued from the study due to any reason prior to evaluation of the endpoint at week 16, were considered as not achieving the secondary endpoint.

The following exploratory variables were also measured:

- Physician's severity assessment of key disease-specific signs and symptoms
- Auto-inflammatory disease activity index (AIDAI)
- Patient/parent's global assessment of disease activity (PPGA)
- Health-related quality of life
    - SF-12 health survey-acyte version 2 (SF-12v2) for patients aged 18 years and older at baseline
    - Child health questionnaire–parent form 50 (CHQ-PF50) for patients between 5 and 18 years of age at baseline
    - Sheehan disability scale version 3 (SDS v3)

The study protocol was amended twice which among other updates further clarified the definition of the resolution of index flare and the blinded escape criteria. This occurred prior to study unblinding for the Week 16 primary endpoint analysis and did not affect the interpretation of study results.

Epoch 2 of Study N2301 was designed to have 90% power to detect a 45% treatment difference in the proportion of responders after 16 weeks, a 65% responder rate in the canakinumab arm relative to a 20% responder rate on placebo. A total of 60 patients per disease cohort were needed. The overall study recruitment was stopped when enrollment for the FMF and HIDS/MKD cohorts were completed and two-thirds of patients were enrolled in the TRAPS

cohort. Due to the extreme rarity of the disease, only 46 TRAPS patients were randomized, providing for 83% power to detect a between-treatment difference of 45%.

3.2.2 Statistical Methodologies

The following analysis datasets for Study N2301 Epoch 2 were defined in the protocol:

- **Randomized Set:** consisted of all patients who were randomized in the randomized treatment epoch (Epoch 2).
- **Full Analysis Set** (FAS): consisted of all randomized patients in the randomized treatment epoch who received at least one dose of study drug in Epoch 2. Patients were analyzed according to the treatment they were assigned to at randomization.
- **Per-protocol Set** (PPS): consisted of all patients in the FAS Epoch 2 who did not fulfill any criteria that could potentially confound the interpretation of analyses conducted on the FAS.
- **Safety Set:** consisted of all patients that received at least one dose of study drug in Epoch 2. Patients were analyzed according to the actual treatment sequence received during Epoch 2.

The primary efficacy endpoint was analyzed using the Fisher's exact test comparing canakinumab treatment to placebo with respect to proportion of responders at Week 16 within each cohort. The proportion of responders and the odds ratio with corresponding 95% confidence interval were presented. Patients who received dose escalation in the canakinumab arms or escaped from placebo to canakinumab, or patients who discontinued from the study due to any reason prior to the Week 16 primary endpoint were all considered as non-responders. Therefore, the primary analysis actually evaluates whether treatment of canakinumab, relative to placebo, increases the probability of patients achieving a composite endpoint defined by resolution of the index flare by Day 15, no new flare through Week 16, and remaining on initially assigned treatment and in the study through Week 16. The primary analysis was based on FAS including all randomized patients who were treated with at least one dose of study drug.

The secondary endpoints, including the proportion of patients achieving PGA<2, CRP ≤ 10mg/L, SAA ≤ 10mg/L, respectively, at Week 16 were analyzed using a logistic regression model with treatment group, and baseline PGA, CRP or SAA values, respectively, as explanatory variables for each cohort. Those patients who received canakinumab other than the initially randomized dose or discontinued from the study due to any reason before Week 16, were considered as not achieving the secondary endpoints. Therefore, the secondary analyses in fact evaluate whether treatment of canakinumab, relative to placebo, increases the probability of patients achieving PGA<2, CRP ≤ 10mg/L, or SAA ≤ 10mg/L, respectively, at Week 16, and remaining on the initially assigned treatment and in the study through Week 16.

A pre-specified hierarchical testing procedure was used to control the overall Type I error rate ($\alpha = 0.025$, one sided test) within each cohort. The primary endpoint was evaluated first. If canakinumab was superior to placebo in terms of responders in the randomized treatment epoch, then all secondary endpoints were assessed in the order shown in Section 3.2.1 separately for each cohort. Testing was continued as long as each test showed statistical significance at the 2.5%

level. For exploratory endpoints, data were analyzed descriptively without adjustment for multiplicity.

In order to evaluate robustness of the study result, the applicant performed five sensitivity analyses as listed below. The primary analysis in Epoch 2 was repeated for the FAS,

1) where patients receiving a single add-on injection before Day 15 were excluded;
2) where patients receiving a single add-on injection from Day 8 to Day 14 despite not fulfilling the criteria for add-on injection were excluded;
3) where patients receiving a single add-on injection before Day 15 were considered a responder unless a new flare occurred from Day 15 onward in Epoch 2;
4) where only local CRP values were used and if local CRP values were missing at Day 15 then the index flare was considered as not resolved;
5) where only central CRP values were used and if central CRP values were missing at Day 15 then the index flare was considered as not resolved.

Additional analyses conducted by the sponsor were as follows:

1) The primary analysis in Epoch 2 was repeated using the PPS;
2) The primary analysis in Epoch 2 was repeated, where the definitions of the resolution of the index flare and new flare were derived from the centralized SAA values within the normal range (≤ 10 mg/L) or reduction of ≥ 70% from baseline;
3) The primary and secondary efficacy variables were analyzed using the FAS, where patients initially randomized to canakinumab were considered as responders if the patient had resolution of their index flare at Day 15 and no flare after Day 15, or for those patients who were up-titrated to canakinumab 300 mg q4w before Day 29 if they had resolution of their index flare at Day 29 (PGA < 2 and CRP within normal range (≤ 10 mg/L) or reduction of ≥ 70% from baseline) and no flare after Day 29.

3.2.3 Patient Disposition, Demographics and Baseline Characteristics

A total of 181 subjects were randomized in study N2301 including 63 in FMF, 72 in HIDS/MKD, and 46 in TRAPS cohorts. All except 6 patients (FMF: 1; HIDS/MKD: 3; and TRAPS: 2) completed the 16-week Epoch 2. Patient disposition is shown in Table 2. The vast majority of patients initially randomized to the placebo group switched to the canakinumab 150 mg q4w group and/or had up-titration to canakinumab 300 mg q4w by Week 16. The proportion of patients remaining on placebo through Week 16 was 16% in FMF, 12% in HIDS/MKD, and 13% in TRAPS, respectively. For patients who were initially randomized to the canakinumab 150mg q4w group, about 32% to 51% required up-titration to canakinumab 300 mg q4w. The percentage of patients remaining on canakinumab 150mg q4w through Week 16 was 68% in FMF, 49% in HIDS/MKD, and 50% in TRAPS, respectively. All patients received at least one dose of study drug thus the randomized set is the same as the full analysis dataset (FAS) for each cohort. More detailed discussion about patients changing treatment and/or up-titration is in Section 3.2.4.

Table 2 FMF cohort: patient disposition, Epoch 2

Initial Randomized Treatment	**150mg q4w (N=31)**		**Placebo (N=32)**			**Total (N=63)**
Actual Treatment Sequence (%)	150mg	150mg to 300mg	Placebo	Placebo to 150mg	Placebo to 150mg to 300mg	
	21 (68%)	10 (32%)	5 (16%)	22 (69%)	5 (15%)	
Completed	21	10	4	22	5	62
Discontinued	-	-	1	-	-	1
Discontinuation reason						
Adverse event	-	-	-	-	-	-
Lack of efficacy	-	-	-	-	-	-
Subject/Guardian decision	-	-	1	-	-	1
Analysis Datasets						
Randomized Set	31			32		63
Full Analysis Set	31			32		63
Safety Set	31			32		63
Per Protocol Set	30			26		56

Source: Reviewer

Table 3 HIDS/MKD cohort: patient disposition, Epoch 2

Initial Randomized Treatment	150mg q4w (N=37)		Placebo (N=35)			Total (N=72)
Actual Treatment Sequence (%)	150mg 18 (49%)	150mg to 300mg 19 (51%)	Placebo 4 (12%)	Placebo to 150mg 19 (54%)	Placebo to 150mg to 300mg 12 (34%)	
Completed	18	18	3	19	11	69
Discontinued	-	1	1	-	1	3
Discontinuation reason						
Adverse event	-	1	1	-	-	2
Lack of efficacy	-	-	-	-	1	1
Subject/Guardian decision	-	-	-	-	-	-
Analysis Datasets						
Randomized Set	37			35		72
Full Analysis Set	37			35		72
Safety Set	37			35		72
Per Protocol Set	33			31		64

Source: Reviewer

Table 4 TRAPS cohort: patient disposition, Epoch 2

Initial Randomized Treatment	150mg q4w (N=22)		Placebo (N=24)			Total (N=46)
Actual Treatment Sequence (%)	150mg 11 (50%)	150mg to 300mg 11 (50%)	Placebo 3 (13%)	Placebo to 150mg 19 (79%)	Placebo to 150mg to 300mg 2 (8%)	
Completed	11	11	2	19	1	44
Discontinued	-	-	1	-	1	2
Discontinuation reason						
Adverse event	-	-	-	-	-	
Lack of efficacy	-	-	-	-	1	1
Subject/Guardian decision	-	-	1	-	-	1
Analysis Datasets						
Randomized Set	22			24		46
Full Analysis Set	22			24		46
Safety Set	22			24		46
Per Protocol Set	20			21		41

Source: Reviewer

Demographic and baseline disease characteristics of patients were generally comparable between the randomized canakinumab and placebo groups, with the exception of baseline CRP and SAA values (Tables 5, 6, 7). In the FMF and TRAPS cohorts, the randomized canakinumab 150mg q4w group had higher median CRP and SAS values while in the HIDS/MKD cohort the median CRP and SAA values were lower in the canakinumab 150mg q4w group than in the randomized placebo group. The average age was 22 years for FMF patients, 13.5 years for HIDS/MKD patients, and 22 years for TRAPS patients. Approximately 46% of FMF patients, 75% of HIDS/MKD patients, and 59% of TRAPS patients were younger than 18 years old. There were balanced numbers of males and females in the FMF and TRAPS cohorts while slightly more females (59.7%) than males (40.3%) were enrolled in the HIDS/MKD cohort. Most patients were Caucasian and all had a confirmed mutation, the MEFV gene for FMF, the MVK gene for HIDS/MKD, and the TNFRSF1A gene for TRAPS, respectively. The median duration of disease and median number of flares per year at randomization reflected chronic severe disease (FMF: 14.7 years, 18 flares per year; HIDS/MKD: 9.8 years, 12 flares per year; TRAPS: 8.2 years, 9 flares per year).

Table 5 FMF cohort: demographic and baseline disease characteristics (FAS)

Variable	150mg q4w N=31	Placebo N=32	Total N=63
Age (years)			
N	31	32	63
Mean	22.5	21.8	22.1
SD	15.0	13.4	14.1
Median	18.0	18.0	18.0
Min - Max	2 - 60	4 - 69	2 - 69
Sex - n (%)			
Male	17 (54.8)	17 (53.1)	34 (54.0)
Female	14 (45.2)	15 (46.9)	29 (46.0)
Race - n (%)			
Caucasian	27 (87.1)	27 (84.4)	54 (85.7)
Asian	0 (0.0)	1 (3.1)	1 (1.6)
Other	4 (12.9)	4 (12.5)	8 (12.7)
Confirmed gene mutation – n (%)			
No	0 (0.0)	0 (0.0)	0 (0.0)
Yes	31 (100.0)	32 (100.0)	63 (100.0)
Time since first symptoms (years)			
N	29	31	60
Mean	17.1	15.1	16.1
SD	11.2	8.7	9.9
Median	15.4	13.3	14.7
Min – Max	1-46	3-32	1-46
Number of flares per year			
N	31	32	63
Mean	27.9	20.5	24.2
SD	30.3	13.2	23.3
Median	20.0	17.5	18.0
Min – Max	5-156	3-60	3-156
CRP (mg/L)			
N	31	32	63
Mean	163.9	118.2	140.7
SD	134.8	112.7	125.2
Median	120.0	79.7	94.0
Min-Max	20-503	10-480	10-503
SAA (mg/L)			
N	31	32	63
Mean	1684.8	865.4	1268.6
SD	2570.4	1018.3	1971.3
Median	746.0	600.0	600.0
Min - Max	77-10856	6-3791	6-10856
PGA of disease activity – n (%)			
None	0 (0.0)	0 (0.0)	0 (0.0)
Minimal	0 (0.0)	0 (0.0)	0 (0.0)
Mild	3 (9.7)	6 (18.8)	9 (14.3)
Moderate	17 (54.8)	19 (59.4)	36 (57.1)
Severe	11 (35.5)	7 (21.9)	18 (28.6)

Source: Clinical study report Table 11-4

Table 6 HIDS/MKD cohort: demographic and baseline disease characteristics (FAS)

Variable	150mg q4w N=37	Placebo N=35	Total N=72
Age (years)			
N	37	35	72
Mean	13.0	13.9	13.5
SD	8.5	11.6	10.1
Median	12.0	9.0	11.0
Min – Max	2-43	3-47	2-47
Sex - n (%)			
Male	13 (35.1)	16 (45.7)	29 (40.3)
Female	24 (64.9)	19 (54.3)	43 (59.7)
Race - n (%)			
Caucasian	34 (91.9)	31 (88.6)	65 (90.3)
Asian	0 (0.0)	1 (2.9)	1 (1.4)
Other	3 (8.1)	3 (8.6)	6 (8.3)
Confirmed gene mutation – n (%)			
No	0 (0.0)	0 (0.0)	0 (0.0)
Yes	37 (100.0)	35 (100.0)	72 (100.0)
Time since first symptoms (in years)			
N	36	35	71
Mean	11.6	12.8	12.2
SD	6.1	11.5	9.1
Median	10.8	7.9	9.8
Min - Max	3-24	2-45	2-45
Number of flares per year			
N	37	35	72
Mean	15.0	14.0	14.5
SD	6.2	7.2	6.7
Median	12.0	12.0	12.0
Min - Max	4-24	4-26	4-26
CRP (mg/L)			
N	37	35	72
Mean	162.6	181.5	171.8
SD	141.8	153.8	147.0
Median	98.0	121.6	113.5
Min – Max	16-562	10-614	10-614
SAA (mg/L)			
N	36	35	71
Mean	3191.0	2959.6	3077.0
SD	3172.8	2676.6	2920.0
Median	2393.0	2731.0	2725.0
Min – Max	6-12000	24-9929	6-12000
PGA of disease activity – n (%)			
None	0 (0.0)	0 (0.0)	0 (0.0)
Minimal	0 (0.0)	0 (0.0)	0 (0.0)
Mild	10 (27.0)	7 (20.0)	17 (23.6)
Moderate	22 (59.5)	21 (60.0)	43 (59.7)
Severe	5 (13.5)	7 (20.0)	12 (16.7)

Source: Clinical study report Table 11-5

Table 7 TRAPS cohort: demographic and baseline disease characteristics (FAS)

Variable	150mg q4w N=22	Placebo N=24	Total N=46
Age (years)			
N	22	24	46
Mean	21.0	23.6	22.4
SD	19.2	18.3	18.6
Median	13.5	16.5	15.5
Min – Max	3-76	2-57	2-76
Sex - n (%)			
Male	12 (54.5)	11 (45.8)	23 (50.0)
Female	10 (45.5)	13 (54.2)	23 (50.0)
Race - n (%)			
Caucasian	20 (90.9)	18 (75.0)	38 (82.6)
Asian	2 (9.1)	4 (16.7)	6 (13.0)
Other	0 (0.0)	2 (8.3)	2 (4.3)
Confirmed gene mutation – n (%)			
No	0 (0.0)	0 (0.0)	0 (0.0)
Yes	22 (100.0)	24 (100.0)	46(100.0)
Time since first symptoms (in years)			
N	21	24	45
Mean	14.9	12.4	13.6
SD	16.3	14.1	15.1
Median	9.8	7.0	8.2
Min - Max	2-70	1-49	1-70
Number of flares per year			
N	22	22	44
Mean	9.2	10.9	10.0
SD	4.7	7.5	6.2
Median	9.5	8.5	9.0
Min - Max	3-24	3-30	3-30
CRP (mg/L)			
N	22	24	46
Mean	183.4	133.1	157.2
SD	195.4	127.9	163.8
Median	135.1	84.6	112.5
Min – Max	13-855	1-532	1-855
SAA (mg/L)			
N	22	24	46
Mean	2073.6	2558.4	2326.5
SD	2733.8	3880.0	3352.9
Median	1155.5	773.5	1078.5
Min – Max	4-8977	4-12000	4-12000
PGA of disease activity – n (%)			
None	0 (0.0)	0 (0.0)	0 (0.0)
Minimal	0 (0.0)	0 (0.0)	0 (0.0)
Mild	9 (40.9)	11 (45.8)	20 (43.5)
Moderate	11 (50.0)	11 (45.8)	22 (47.8)
Severe	2 (9.1)	2 (8.3)	4 (8.7)

Source: Clinical study report Table 11-6

3.2.4 Results and Conclusions

3.2.4.1 Primary and secondary analyses

The primary efficacy endpoint was the proportion of patients who resolved their index disease flare at Day 15 and had no new flare over the 16 weeks of treatment since the time of the resolution of the index flare. The primary analysis attained statistical significance in all three disease cohorts (Table 8). The proportion of responders in patients treated with canakinumab compared to those treated with placebo were 61.3% versus 6.3% in the FMF cohort, 35.1% versus 5.7% in the HIDS/MKD cohort, and 45.5% versus 8.3% in the TRAPS cohort, respectively. Canakinumab was superior to placebo as shown by the statistically significantly higher proportion of patients receiving canakinumab who achieved a complete response compared with patients receiving placebo.

Table 8 Primary analysis: Proportion of responders after 16 weeks by cohort (FAS)

Cohort	150mg q4w n/M (%)	Placebo n/M (%)	Treatment Comparison Odds Ratio (95% CI)	P-value
FMF	19/31 (61.29)	2/32 (6.25)	23.75 (4.38, 227.53)	<0.0001*
HIDS/MKD	13/37 (35.14)	2/35 (5.71)	8.94 (1.72, 86.41)	0.0020*
TRAPS	10/22 (45.45)	2/24 (8.33)	9.17 (1.51, 94.61)	0.0050*

n=number of responders; M=number of evaluable patients; CI=confidence Interval.
* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.
Source: Reviewer

Analyses of the secondary efficacy variables are summarized in Table 9. Canakinumab therapy led to overall improvement measured by physician's global assessment (PGA) and inflammatory markers (CRP and SAA). Since the primary objective of the study was achieved, the secondary endpoints were assessed in the pre-specified closed testing procedure. The results show that canakinumab was superior to placebo for secondary endpoints of PGA < 2 and CRP ≤ 10 mg/L at Week 16 in all 3 disease cohorts. For SAA ≤ 10 mg/L at Week 16, canakinumab was superior to placebo in the TRAPS cohort. In the FMF and HIDS/MKD cohorts, there were trends toward greater improvements on canakinumab compared with placebo, but differences were not statistically significant.

Table 9 Secondary analyses: Proportion of patients achieving PGA < 2, or CRP ≤ 10 mg/L, or SAA ≤ 10 mg/L after 16 weeks by cohort (FAS)

Cohort	Parameter	150mg q4w n/M (%)	Placebo n/M (%)	Treatment Comparison Odds Ratio (95% CI)	P-value
FMF	PGA < 2	20/31 (64.52)	3/32 (9.38)	16.96 (4.15, 69.21)	<0.0001*
	CRP ≤ 10 mg/L	21/31 (67.74)	2/32 (6.25)	29.78 (5.86, 151.31)	<0.0001*
	SAA ≤ 10 mg/L	8/31 (25.81)	0/32 (0.00)	17.46 (0.92, 332.92)	0.0286
HIDS/MKD	PGA < 2	17/37 (45.95)	2/35 (5.71)	13.63 (2.83, 65.59)	0.0006*
	CRP ≤ 10 mg/L	15/37 (40.54)	2/35 (5.71)	12.71 (2.53, 63.89)	0.0010*
	SAA ≤ 10 mg/L	5/37 (13.51)	1/35 (2.86)	5.26 (0.53, 51.97)	0.0778
TRAPS	PGA < 2	10/22 (45.45)	1/24 (4.17)	23.79 (2.52, 224.86)	0.0028*
	CRP ≤ 10 mg/L	8/22 (36.36)	2/24 (8.33)	6.64 (1.20, 36.57)	0.0149*
	SAA ≤ 10 mg/L	6/22 (27.27)	0/24 (0.00)	16.69 (1.04, 268.50)	0.0235*

n=number of responders; M=number of evaluable patients; CI=confidence Interval.
* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.
Source: Reviewer

While the above analyses showed superiority of canakinumab over placebo in all 3 disease cohorts, interpretation of these results is clouded by the nature of the design. The protocol provision allowed patients to receive add-on canakinumab or be up-titrated if they had persistent disease activity or re-flared. Patients randomized to the placebo group could switch over to receive canakinumab 150mg q4w and/or 300mg q4w thereafter if needed. Patients randomized to the canakinumab 150mg q4w group were also able to be up-titrated to 300mg q4w. By Week 16 there were only a limited number of patients remaining on initial randomized treatment, especially for the placebo group (More details in Section 3.2.4.2). This makes many treatment comparisons difficult to interpret and the issue is more problematic for the secondary endpoints since comparisons were made *at a specific time point Week 16*. The primary endpoint involved resolution of index flare at Day 15 and no new flare over the 16 weeks of treatment. As such the primary analysis essentially compared the efficacy of canakinumab against placebo with respect to the probability of achieving a complete response *and remaining on initially assigned treatment until the end of 16-week randomized treatment period.* The secondary endpoints, including components of the primary endpoint (CRP and PGA) and SAA, were evaluated as binary outcomes at Week 16 in which patients who crossed over or up-titrated or discontinued early were all considered as non-responders. Given the fact that vast majority of patients assigned to placebo crossed over to canakinumab prior to Week 16, it is difficult to determine whether observed differences are due to a treatment effect on the outcome of interest (e.g., PGA<2) or due to differences in the proportions of patients remaining on initially assigned treatment.

Various sensitivity analyses conducted by the applicant showed a significantly higher percentage of responders for the canakinumab group compared with placebo, consistent with the primary results. Most of these analyses were alternative methods of patient inclusion or responder definition but did not evaluate the sensitivity of results to violations in assumptions. One such analysis (Additional analysis 3 in Section 3.2.2) intended to assess potential benefit of up-titration and saw some improvement in signs and symptoms after up-titration. Since there was no control group of patients who had persistent disease activity/flare but remained on the 150 mg

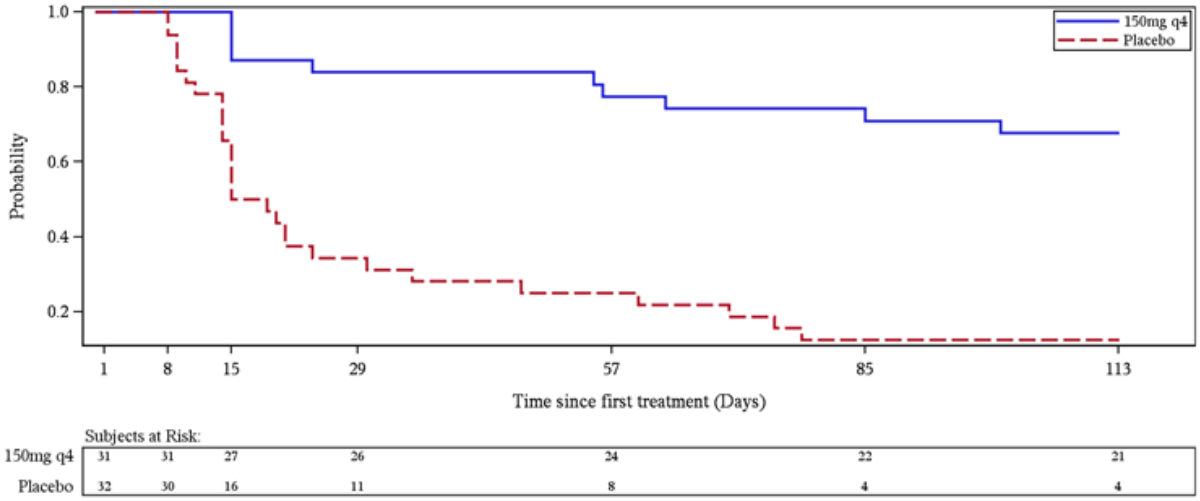
q4w, it is difficult to determine if differences over time in patients who up-titrated were due to true differences in treatment effects between the doses.

3.2.4.2 Analysis at Day 15

Because of placebo patient's crossover and/or up-titration, it is difficult to interpret the efficacy data obtained at Week 16. Therefore, this section evaluates the time course of patients deviating from initial randomized treatment as well as resolution of index flare at Day 15 which was the earliest time point for efficacy assessment in Epoch 2.

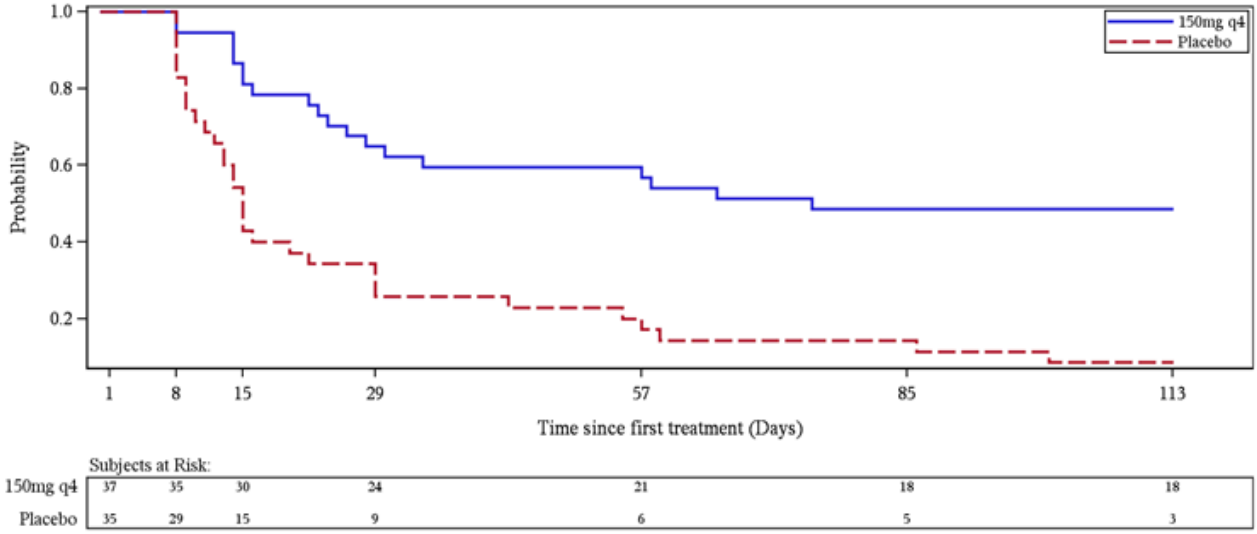
Figures 2, 3, and 4 illustrate the percentage of patients who remained on initial randomized dose over time for FMF, HIDS/MKD, and TRAPS cohort, respectively. Patients received add-on canakinumab injection or started dose escalation as early as 1 to 2 weeks following randomization and first medication. While at least half of the patients randomized to canakinumab 150mg q4w (49% to 68%) stayed on the initial dose through the entire treatment period, the vast majority of patients randomized to placebo (84% to 88%) switched over to canakinumab 150mg q4w and/or were further up-titrated to 300mg q4w. There were only 4 FMF patients, 3 HIDS/MKD patients, and 2 TARPS patients left on placebo by Week 16. The proportion of patients who were initially randomized to canakinumab 150 mg q4w and required dose escalation to 300 mg q4w before Day 29 were 16.1% in FMF, 32.4% in HIDS/MKD and 36.4% in TRAPS, respectively. In contrast, the proportion of patients who were initially randomized to placebo and needed blinded escape before Day 29 was 62.5% in FMF, 62.9% in HIDS/MKD, and 75.0% in TRAPS, respectively.

Figure 2 FMF cohort: Number (proportion) of patients who remained on initial randomized dose over time (FAS)



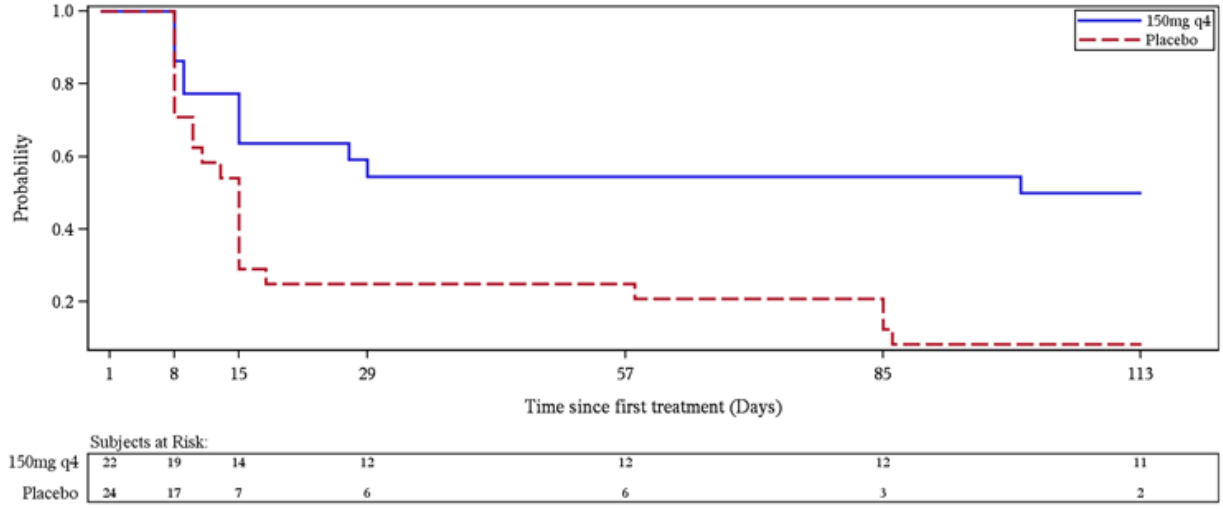
Source: Applicant's response to FDA information request submitted on 5/25/2016 (SN0221)

Figure 3 HIDS/MKD cohort: Number (proportion) of patients who remained on initial randomized dose over time (FAS)



Source: Applicant's response to FDA information request submitted on 5/25/2016 (SN0221)

Figure 4 TRAPS cohort: Number (proportion) of patients who remained on initial randomized dose over time (FAS)



Source: Applicant's response to FDA information request submitted on 5/25/2016 (SN0221)

The analysis of add-on injection and resolution of index flare at Day 15 is presented in Table 10. Before Day 15, more patients randomized to placebo received an add-on injection of canakinumab than patients randomized to canakinumab 150 mg q4w. At Day 15, a higher proportion of canakinumab-treated patients compared to placebo-treated patients experienced resolution of their index flare as measured by PGA < 2, and CRP within normal range (≤ 10 mg/L) or reduction by at least 70% from baseline. The efficacy of canakinumab at Day 15 was observed in all 3 disease cohorts. Of note some patients had already received add-on injection of canakinumab before Day 15. Nevertheless, compared to evaluation of treatment effect at Week 16, the short-term results at Day 15 are more reliable since less cross-over and/or up-titration had occurred at Day 15 than at later time points.

Table 10 Analysis of add-on injection and resolution of index flare at Day 15

Cohort	Add-on injection before Day 15		Resolution of index flare at Day 15			
	150mg q4w n/M (%)	Placebo n/M (%)	150mg q4w n/M (%)	Placebo n/M (%)	Treatment Comparison Odds Ratio (95% CI)	P-value
FMF	0/31 (0.0)	6/32 (18.8)	25/31 (80.7)	10/32 (31.3)	9.2 (2.5, 35.2)	0.0001*
HIDS/MKD	2/37 (5.4)	11/35 (31.4)	24/37 (64.9)	13/35 (37.1)	3.1 (1.1, 9.2)	0.0168*
TRAPS	4/22 (18.2)	9/24 (37.5)	14/22 (63.6)	5/24 (20.8)	6.7 (1.5, 31.0)	0.0037*

n=number of responders; M=number of evaluable patients; CI=confidence Interval.
* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.
Source: Reviewer

3.2.4.3 Analysis of efficacy measures over time

This section further evaluates the effect of canakinumab during 16 weeks of treatment using various efficacy outcomes. These analyses were considered exploratory and were not controlled for multiplicity.

The measurements of physician's global assessment (PGA), C-creative protein (CRP), and serum amyloid A (SAA) are summarized at each visit by initial randomized group in Tables 11, 12, and 13, respectively. Note that these analyses include all follow-up data, including measurements taken after cross-over or up-titration. Within-group improvements from baseline in PGA scores as well as CRP and SAA levels were seen in patients treated with canakinumab at all time points. At Day 15, greater improvements were observed in patients treated with canakinumab as compared to placebo in all cohorts for all 3 endpoints. The differences between groups steadily declined toward zero over time. This trend would not be surprising for an efficacious treatment, given that the randomized 150mg q4w group included patients who had add-on injection or were up-titrated to 300mg q4w while the randomized placebo group included patients who switched to canakinumab 150 mg q4w and/or were up-titrated 300mg q4w. Comparisons to placebo from Day 15 onward are limited by the high proportion of patients switching from placebo to canakinumab starting at Day 8. By including all data regardless of cross-over or up-titration, analyses at later time points in fact compared effects of canakinumab to delayed administration of canakinumab.

Table 11 Average PGA by initial randomized group over time (FAS)

Cohort	Visit	150mg q4		Placebo		150mg q4 - Placebo	
		N	Mean	N	Mean	Mean	95% CI
FMF	Baseline	31	3.3	32	3.0	0.2	-0.1 0.5
	Day 15	31	0.6	31	1.2	-0.6	-1.2, -0.0
	Day 29	30	0.5	31	0.5	0.0	-0.4, 0.4
	Week 16	31	0.4	31	0.4	-0.1	-0.5, 0.3
HIDS	Baseline	37	2.9	35	3.0	-0.1	-0.4, 0.2
	Day 15	36	0.6	33	1.0	-0.4	-0.9, 0.2
	Day 29	37	0.5	34	0.7	-0.2	-0.6, 0.3
	Week 16	37	0.4	33	0.4	0.0	-0.3 0.4
TRAPS	Baseline	22	2.7	24	2.6	0.1	-0.3, 0.4
	Day 15	22	0.7	23	0.9	-0.2	-0.8, 0.4
	Day 29	22	0.5	24	0.8	-0.3	-0.9, 0.2
	Week 16	22	0.6	22	0.5	0.1	-0.4, 0.6

Source: Reviewer

Table 12 Average CRP by initial randomized group over time (FAS)

Cohort	Visit	150mg q4		Placebo		150mg q4 - Placebo	
		N	Mean	N	Mean	Mean	95% CI
FMF	Baseline	31	163.9	32	118.2	45.6	-17.1, 108.4
	Day 15	30	10.6	30	61.6	-51.0	-88.2, -13.8
	Day 29	30	9.0	31	12.5	-3.6	-12.1, 5.0
	Week 16	31	5.0	31	12.5	-7.5	-16.9, 1.9
HIDS	Baseline	37	162.6	35	181.5	-18.9	-88.5, 50.8
	Day 15	36	25.7	33	51.4	-25.7	-58.6, 7.3
	Day 29	37	18.1	34	25.3	-7.2	-24.0, 9.5
	Week 16	37	18.5	33	20.9	-2.3	-28.2, 23.6
TRAPS	Baseline	22	183.4	24	133.1	50.3	-49.4, 150.1
	Day 15	19	25.4	22	61.8	-36.4	-94.5, 21.7
	Day 29	22	8.6	23	24.9	-16.3	-32.9, 0.29
	Week 16	22	9.7	22	12.2	-2.6	-18.0, 12.9

Source: Reviewer

Table 13 Average SAA by initial randomized group over time (FAS)

Cohort	Visit	150mg q4		Placebo		150mg q4 - Placebo	
		N	Mean	N	Mean	Mean	95% CI
FMF	Baseline	30	1734.3	26	995.9	738.3	-308.3, 1785.0
	Day 15	30	87.2	27	341.6	-254.4	-494.2, -14.5
	Day 29	28	121.6	29	113.4	8.2	-143.4, 159.8
	Week 16	29	39.6	31	151.5	-111.9	-241.5, 17.7
HIDS	Baseline	32	3565.8	34	3035.2	530.6	-918.7, 1980.0
	Day 15	34	326.7	29	1136.4	-809.7	-1741.1, 121.7
	Day 29	33	426.0	32	327.4	98.6	-331.0, 528.2
	Week 16	34	1003.4	30	119.9	883.4	-46.0, 1812.9
TRAPS	Baseline	20	2274.9	22	2790.5	-515.5	-2647.2, 1616.1
	Day 15	20	175.4	22	1084.7	-909.3	-2171.1, 352.5
	Day 29	21	73.7	23	737.9	-664.2	-1536.7, 208.3
	Week 16	21	150.6	21	242.6	-92.0	-577.4, 393.4

Source: Reviewer

Tables 14, 15, and 16 show the average PGA, CRP, and SAA scores respectively at each visit by actual treatment received. It is important to note that these comparisons condition on post-randomization outcomes and therefore patients in the different groups may differ with respect to important prognostic factors. Furthermore, patients may move between columns in these tables over time, with the canakinumab 150mg q4w group including some patients who switched from placebo and the canakinumab 300 mg q4w group including patients initially randomized to canakinumab 150 mg q4w or placebo. Nevertheless, exploratory results are presented to provide additional supportive evidence of efficacy. Improvements in PGA, CRP, and SAA were observed in patients treated with canakinumab in all 3 disease cohorts. Of note, although the small number of patients who remained on placebo until Week 16 probably represented those with less severe disease, there still tended to be greater improvement in these measures in patients receiving canakinumab than in those receiving placebo.

Table 14 Average PGA by actual treatment over time (FAS)

Cohort	Visit	150mg q4		300mg q4		Placebo	
		N	Mean	N	Mean	N	Mean
FMF	**Baseline**	31	3.3	0	-	32	3.0
	Day 15	37	0.5	0	-	25	1.4
	Day 29	45	0.3	5	1.0	11	0.9
	Week 16	43	0.3	15	0.6	4	1.0
HIDS	**Baseline**	37	2.9	0	-	35	3.0
	Day 15	44	0.6	2	1.0	23	1.3
	Day 29	47	0.6	12	0.5	12	0.8
	Week 16	37	0.3	30	0.5	3	1.0
TRAPS	**Baseline**	22	2.7	0	-	24	2.6
	Day 15	27	0.7	4	0.0	14	1.2
	Day 29	32	0.7	8	0.5	6	0.8
	Week 16	30	0.4	12	0.8	2	1.5

Source: Reviewer

Table 15 Average CRP by actual treatment over time (FAS)

Cohort	Visit	150mg q4		300mg q4		Placebo	
		N	Mean	N	Mean	N	Mean
FMF	**Baseline**	31	163.9	0	-	32	118.2
	Day 15	42	36.6	4	47.4	14	31.5
	Day 29	44	8.5	8	12.0	9	20.9
	Week 16	43	6.6	15	5.7	4	43.2
HIDS	**Baseline**	37	162.6	0	-	35	181.5
	Day 15	45	36.8	8	82.8	16	19.0
	Day 29	40	17.5	22	29.8	9	19.1
	Week 16	37	11.6	30	17.8	3	136.9
TRAPS	**Baseline**	22	183.4	0	-	24	133.1
	Day 15	29	46.5	7	58.3	5	17.2
	Day 29	27	9.2	12	31.0	6	23.6
	Week 16	30	6.6	12	22.7	2	5.9

Source: Reviewer

Table 16 Average SAA by actual treatment over time (FAS)

Cohort	Visit	150mg q4		300mg q4		Placebo	
		N	Mean	N	Mean	N	Mean
FMF	**Baseline**	30	1734.3	0	-	26	995.9
	Day 15	39	125.4	4	475.2	14	360.6
	Day 29	41	118.2	8	35.1	8	195.7
	Week 16	41	95.1	15	37.5	4	346.0
HIDS	**Baseline**	32	3565.8	0	-	34	3035.2
	Day 15	42	785.3	7	1030.6	14	276.1
	Day 29	35	139.9	21	821.4	9	265.4
	Week 16	34	509.5	27	735.1	3	180.3
TRAPS	**Baseline**	20	2274.9	0	-	22	2790.5
	Day 15	30	786.8	6	488.8	6	139.2
	Day 29	27	33.8	11	689.2	6	1671.0
	Week 16	29	115.0	11	441.9	2	31.5

Source: Reviewer

Tables 17 to 21 present analyses for exploratory efficacy endpoints including patient/parent's global assessment of disease activity (PPGA), auto-inflammatory disease activity index (AIDAI), physical component summary of SF-12 health survey (SF-12 PCS), mental component summary of child health questionnaire–parent form 50 (CHQ-PF50 MCS), and sheehan disability scale (SDS). Results are presented by initial randomized group, including measurements taken after cross-over and up-titration. These additional patient- or parent-reported outcomes are important because they might be considered to more directly measure patient benefit than the biomarkers and clinician-reported measures assessed as primary and secondary endpoints. For PPGA and AIDAI, there were relatively consistent trends toward greater improvements (reductions) at Day 15 across all cohorts and the differences gradually went away over time. There were less consistent trends for SF-12 PCS, CHQ-PF50 MCS scores, and SDS which were only evaluated at Day 29 and/or Week 16. Again, comparisons to placebo from Day 15 onward are limited by the considerable proportion of patients switching from placebo to canakinumab and patients on canakinumab treatment receiving up-titration to 300mg q4w.

Table 17 Average PPGA by initial randomized group over time (FAS)

Cohort	Visit	150mg q4		Placebo		150mg q4 - Placebo	
		N	Mean	N	Mean	Mean	95% CI
FMF	**Baseline**	31	1.8	31	1.4	0.3	-0.2, 0.9
	Day 15	30	0.7	30	0.9	-0.2	-0.6, 0.3
	Day 29	31	0.8	30	0.6	0.3	-0.2, 0.7
	Week 16	30	0.7	28	0.5	0.2	-0.3, 0.7
HIDS	**Baseline**	37	1.5	35	1.2	0.3	-0.1, 0.6
	Day 15	37	0.6	34	1.1	-0.5	-1.0, 0.0
	Day 29	37	0.5	34	0.5	0	-0.3, 0.4
	Week 16	34	0.6	32	0.3	0.3	0.0, 0.6
TRAPS	**Baseline**	21	1.9	24	1.8	0.1	-0.5, 0.7
	Day 15	21	0.9	24	1.5	-0.6	-1.2, 0.0
	Day 29	21	0.7	24	0.9	-0.2	-0.8, 0.5
	Week 16	20	0.8	21	0.8	0	-0.7, 0.7

Source: Reviewer

Table 18 Average AIDAI by initial randomized group over time (FAS)

Cohort	Visit	150mg q4		Placebo		150mg q4 - Placebo	
		N	Mean	N	Mean	Mean	95% CI
FMF	**Baseline**	31	2.9	31	2.2	0.7	-0.2, 1.7
	Day 15	30	1.5	30	1.4	0.1	-0.7, 0.9
	Day 29	31	1.3	30	0.9	0.4	-0.3, 1.0
	Week 16	30	0.9	28	0.6	0.3	-0.3, 0.9
HIDS	**Baseline**	37	2.7	35	2.3	0.4	-0.5, 1.2
	Day 15	37	1.0	34	1.9	-1.0	-1.7, -0.2
	Day 29	37	1.0	34	0.9	0.1	-0. 6, 0.8
	Week 16	34	1.0	32	0.7	0.3	-0.3, 1.0
TRAPS	**Baseline**	21	3.7	24	3.4	0.3	-1.1, 1.6
	Day 15	21	2.1	24	3.3	-1.2	-2.7, 0.2
	Day 29	21	1.5	24	1.9	-0.4	-1.7, 0.9
	Week 16	20	1.8	21	1.8	-0.1	-1.6, 1.4

Source: Reviewer

Table 19 Average SF-12 PCS by initial randomized group over time (FAS)

Cohort	Visit	150mg q4		Placebo		150mg q4 - Placebo	
		N	Mean	N	Mean	Mean	95% CI
FMF	**Baseline**	17	38.6	16	36.3	2.4	-3.0 , 7.8
	Day 29	16	47.5	15	43.7	3.9	-2.8, 10.5
	Week 16	17	48.2	15	48.2	-0.1	-7.8, 7.7
HIDS	**Baseline**	9	33.6	8	39.5	-6.0	-16.2, 4.3
	Day 29	9	45.6	7	55.1	-9.5	-18.3, -0.7
	Week 16	7	49.2	8	55.9	-6.7	-14.5 , 1.2
TRAPS	**Baseline**	8	37.6	11	32.9	4.7	-6.8 , 16.2
	Day 29	8	48.0	11	44.5	3.5	-9.3, 16.4
	Week 16	6	50.0	10	46.5	3.5	-9.0 , 15.9

Source: Reviewer

Table 20 Average CHQ-PF50 MCS by initial randomized group over time (FAS)

Cohort	Visit	150mg q4		Placebo		150mg q4 - Placebo	
		N	Mean	N	Mean	Mean	95% CI
FMF	**Baseline**	11	20.7	14	27.3	-6.6	-15.9, 2.8
	Day 29	12	44.7	14	33.3	11.4	-1.3, 24.1
	Week 16	9	43.2	13	44.9	-1. 8	-11. 6, 8.0
HIDS	**Baseline**	21	25.5	18	29.1	-3.7	-12.7, 5.4
	Day 29	22	35.2	16	30.1	5.1	-5.2, 15.4
	Week 16	19	36.1	15	38.6	-2.4	-13.6, 8.7
TRAPS	**Baseline**	11	24.1	9	28.5	-4.4	-17.6, 8.8
	Day 29	11	31.8	8	34.6	-2.7	-21.3, 15.8
	Week 16	9	38.1	6	45.9	-7.8	-24.2 , 8.7

Source: Reviewer

Table 21 Average SDS by initial randomized group over time (FAS)

Cohort	Visit	150mg q4		Placebo		150mg q4 - Placebo	
		N	Mean	N	Mean	Mean	95% CI
FMF	**Baseline**	27	17.9	30	18.4	-0.5	-4.6, 3.6
	Week 16	28	9.8	25	8.3	1.5	-3.8, 6.9
HIDS	**Baseline**	33	15.8	32	15.4	0.5	-3.5, 4.5
	Week 16	26	8.3	28	6.5	1.8	-2.2, 5.8
TRAPS	**Baseline**	18	19.2	23	15.8	3.3	-2.3, 9.0
	Week 16	13	8.5	18	6.6	1.9	-4.2, 8.0

Source: Reviewer

3.3 EVALUATION OF SAFETY

According to the clinical study report, there were no new or unexpected safety findings in Study N2301. No deaths were reported in any cohort (FMF, HIDS/MKD, or TRAPS). No anti-canakinumab anti-drug antibodies were detected in any patient in any cohort.

In the FMF cohort, the incidence of adverse events (AEs) was 81.0% in patients receiving any dose of canakinumab and was comparable across all treatment groups. The most commonly reported AEs were FMF (22.4%), injection site reaction (13.8%), and diarrhea (12.1%). AEs considered by the investigator to be related to study treatment were reported by 32.8% of patients who received any canakinumab. In this group the incidence of SAEs was low (8.6%) and no SAE was reported in more than 1 patient.

In the HIDS/MKD cohort, the incidence of AEs was 86.8% in patients receiving any dose of canakinumab and was comparable across all treatment groups. The most commonly reported AEs were pyrexia (23.5%), headache (17.6%), and diarrhea and oropharyngeal pain (each 11.8%). AEs considered by the investigator to be related to study treatment were reported by 30.9% of patients who received any canakinumab. In this group the incidence of SAEs was 11.8%. With the exception of pneumonia, reported in 2 patients in the Placebo to 150 mg q4w group, no SAE was reported in more than 1 patient.

In the TRAPS cohort, the incidence of AEs was 76.7% in patients receiving any dose of canakinumab and was comparable across all treatment groups. The most commonly reported were pyrexia (14.0%), and abdominal pain, injection site reaction, and nasopharyngitis (each 11.6%). AEs related to study treatment were reported by 32.6% of patients who received any canakinumab. In this group the incidence of SAEs was low (4.7%) and no SAE was reported in more than 1 patient.

The reader is referred to the review by Medical Officer, Dr. Borigini, Mark, M.D., for a more detailed discussion of the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses for the primary efficacy endpoint were conducted to assess the consistency of treatment effects across demographic and clinical subgroups including gender, race, age, prior use of any biologics, and colchicine status (for the FMF cohort only). The treatment effects were evaluated in each subgroup for each cohort using the same Fisher's exact test as used for the primary analysis. Since these were descriptive analyses, overall Type I error was not controlled. The subgroup analysis results were generally consistent with those from the overall study population.

4.1 Gender, Race, Age, and Geographic Region

Number of patients in selected demographic subgroups is listed in Table 22.

Table 22 Sample sizes for particular demographics

Category	Cohort		
	FMF	**HIDS/MKD**	**TRAPS**
Randomized	63	72	46
Male	34 (53.9%)	29 (40.3%)	23 (50.0%)
Caucasian	54 (85.7%)	65 (90.3%)	38 (82.6%)
12 to 17 years old	29 (46.0%)	54 (75.0%)	27(58.7%)

Source: Reviewer

Comparison between treatment groups for the proportion of responders after 16 weeks is presented by gender (Table 23), race (Table 24), and age group (Table 25), respectively. Treatment effect estimates were relatively large and reasonably consistent across these subgroups. Subgroup analysis by geographic region was not performed due to the small number of patients (only 2 patients in the entire study) in the United States.

Table 23 Proportion of responders after 16 weeks by gender (FAS)

	Male			Female		
Cohort	**150 mg q4w n/M (%)**	**Placebo n/M (%)**	**Treatment comparison OR (95%**	**150 mg q4w n/M (%)**	**Placebo n/M (%)**	**Treatment comparison OR (95% CI)**
FMF	12/17(70.6)	0/17(0.0)	Inf (8.0, inf)	7/14(50.0)	2/15(13.3)	6.5 (0.9, 75.4)
HIDS/MKD	3/13(23.1)	0/16(0.0)	Inf (0.8, inf)	10/24(41.7)	2/19(10.5)	6.1 (1.0, 63.4)
TRAPS	5/12(41.7)	0/11(0.0)	Inf (1.4, inf)	5/10(50.0)	2/13(15.4)	5.5 (0.6, 71.1)

n=number of responders; M=number of evaluable patients; CI=confidence Interval; Inf=infinity; OR=odds ratio
Source: Reviewer

Table 24 Proportion of responders after 16 weeks by race (FAS)

	Caucasian			Other		
Cohort	150 mg q4w n/M (%)	Placebo n/M (%)	Treatment comparison OR (95% CI)	150 mg q4w n/M (%)	Placebo n/M (%)	Treatment comparison OR (95%
FMF	17/27(63.0)	2/27(7.4)	21.2 (3.7, 208.5)	2/4 (50.0)	0/5 (0.0)	Inf (0.4, inf)
HIDS/MKD	13/34(38.2)	2/31(6.5)	8.9 (1.7, 87.5)	0/3 (0.0)	0/4 (0.0)	NA
TRAPS	9/20(45.0)	2/18(11.1)	6.6 (1.0, 70.2)	1 /2 (50.0)	0/6 (0.0)	Inf (0.2, inf)

n=number of responders; M=number of evaluable patients; CI=confidence Interval; Inf=infinity; OR=odds ratio
Source: Reviewer

Table 25 Proportion of responders after 16 weeks by age group (FAS)

	< 18 years			≥ 18 years		
Cohort	150 mg q4w n/M (%)	Placebo n/M (%)	Treatment comparison OR (95% CI)	150 mg q4w n/M (%)	Placebo n/M (%)	Treatment comparison OR (95% CI)
FMF	10/14 (71.4)	1/15 (6.7)	35.0 (2.9, 1622.67)	9/17 (52.9)	1/17 (5.9)	18.0 (1.8, 836.7)
HIDS	9/28 (32.1)	2/26 (7.7)	5.7 (1.0, 58.4)	4/9 (44.4)	0/9 (0.0)	Inf (1.1, Inf)
TRAPS	5/14 (35.7)	1/13 (7.7)	6.7 (0.6, 341.0)	5/8 (62.5)	1/11 (9.1)	16.7 (1.0, 864.2)

n=number of responders; M=number of evaluable patients; CI=confidence Interval; Inf=infinity; OR=odds ratio
Source: Reviewer

4.2 Other Special/Subgroup Population

The responder profile among patients with prior exposure to biologics was similar to those without prior exposure (Table 26). For both subgroups in all 3 disease cohorts, a higher proportion of patients on canakinumab compared to placebo achieved a complete response at Week 16. Table 27 presents proportion of responders after 16 weeks by colchicine status in the FMF cohort. Canakinumab showed greater efficacy in patients with concomitant colchicine use and exhibited a trend toward efficacy in patients without colchicine use although there were only 8 patients in this latter group.

Table 26 Proportion of responders after 16 weeks by prior use of biologics (FAS)

	Prior use of biologics			No prior use of biologics		
Cohort	150 mg q4w n/M (%)	Placebo n/M (%)	Treatment comparison OR (95% CI)	150 mg q4w n/M (%)	Placebo n/M (%)	Treatment comparison OR (95% CI)
FMF	4/7 (57.1)	0/8 (0.0)	Inf (1.4, Inf)	15/24 (62.5)	2/24 (8.3)	18.3 (3.1, 183.9)
HIDS	1/9 (11.1)	0/4 (0.0)	Inf (0.0, Inf)	12/28 (42.9)	2/31 (6.5)	10.9 (2.0, 107.5)
TRAPS	4/8 (50.0)	1/8 (12.5)	7.00 (0.4, 392.8)	6/14 (42.9)	1/16 (6.3)	11.3 (1.0, 551.0)

n=number of responders; M=number of evaluable patients; CI=confidence Interval; Inf=infinity; OR=odds ratio
Source: Reviewer

Table 27 Proportion of responders after 16 weeks by colchicine status (FAS)

	Concomitant colchicine use			No use of concomitant colchicine		
Cohort	150 mg q4w n/M (%)	Placebo n/M (%)	Treatment comparison OR (95% CI)	150 mg q4w n/M (%)	Placebo n/M (%)	Treatment comparison OR (95% CI)
FMF	18/29 (62.1)	0/26 (0.0)	Inf (10.4, inf)	1/2 (50.0)	2/6 (33.3)	2.0 (0.0, 195.7)

n=number of responders; M=number of evaluable patients; CI=confidence Interval; Inf=infinity; OR=odds ratio
Source: Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

This submission contains a pivotal phase 3, randomized, multicenter, double-blind, placebo-controlled study (N2301) which evaluated 150 mg canakinumab administered subcutaneously every 4 weeks for the treatment of patients ages 2 years and older with periodic fever syndrome including FMF, HIDS/MKD, and TRAPS. Efficacy and safety conclusions are derived from the 16 weeks of randomized treatment epoch (Epoch 2).

Results in FMF, HIDS/MKD, and TRAPS each demonstrated statistical superiority of canakinumab relative to placebo on the primary endpoint: the proportion of complete responders as defined by patients who had resolution of their index disease flare at Day 15 and did not experience a new disease flare during the remainder of the 16-week treatment period. The proportion of complete responders were 61.3% for canakinumab versus 6.3% for placebo in FMF patients (Odds ratio=23.75; p-value<0.0001), 35.1% versus 5.7% in HIDS/MKD patients (Odds ratio=8.94; p-value=0.0020), and 45.5% versus 8.3% in TRAPS patients (Odds ratio=9.17; p-value=0.0050). Analyses of secondary endpoints of PGA < 2 (no or minimal disease activity), CRP ≤ 10mg/L (serological remission) and SAA ≤ 10 mg/L (serum normalization) at Week 16 showed consistent trends supporting the efficacy of canakinumab in all 3 cohorts. Evidence from other endpoints such as health-related quality of life as well as sensitivity and subgroup analyses were generally consistent with the primary and secondary results.

There were three statistical issues noted in this review. First of all, the protocol provision allowed patients to receive add-on canakinumab or be up-titrated in case of persistent disease activity or re-flare. The majority of placebo patients (84% to 88%) switched to receive canankinumab or further dose escalation and approximately 32% to 51% of patients on initial canakinumab 150mg q4w dose were up-titrated to 300mg q4w. By the end of Epoch 2 there were a small number of patients remaining on the initially assigned treatment, especially for the placebo group (4 in FMF, 3 in HIDS/MKD, and 2 in TRAPS). The greater amount of escape due to persistent disease and re-flare on placebo than on canakinumab is on its own a marker of efficacy; however, the considerable amount of cross-over and up-titration also makes many treatment comparisons, particularly comparisons at Week 16, difficult to interpret. The protocol specified primary and secondary analyses considered patients who crossed over or up-titrated to be non-responders. The primary efficacy analysis essentially compared the efficacy of canakinumab against placebo with respect to the probability of achieving a complete response *and remaining on initially assigned treatment until the end of 16-week randomized treatment period.* For the secondary endpoints which comparisons were made *at Week 16 only*, it is hard to determine whether observed differences are due to treatment effect on the outcome of interest (e.g., PGA<2) or due to differences in the proportions of patients remaining on initially assigned treatment. Analysis at the earlier time point Day 15 showed that more patients in the canakinumab group resolved their index flare compared with placebo across all 3 cohorts (80.7% vs. 31.3% for FMF; 64.9% vs. 37.1% for HIDS/MKD; 63.6% vs. 20.8% for TRAPS). While some patients had already received add-on injection of canakinumab before Day 15, the short-

term results at Day 15 are considered more reliable since less cross-over and/or up-titration had occurred at Day 15 than at later time points.

Second, the study was not adequately designed to evaluate any potential benefit of up-titration. There was no control group of patients who had persistent disease activity or flare but remained on the canakinumab 150mg q4w group. Patient needing up-titration from Day 29 onward received canakinumab in an open-label manner. Therefore, while some improvements in signs and symptoms were observed after up-titration, it is challenging to conclude whether such results were due to true differences between the doses.

Finally, efficacy and safety data are available from only a single study instead of at least two adequate and well-controlled studies usually required to establish drug effectiveness. However, it is noted that the three cohorts are clinically related conditions; each independently demonstrated statistically significant evidence of canakinumab efficacy over placebo, and the results from various efficacy measures were consistent across all cohorts. This, together with data leading to previous approval of use in cryopyrin-associated periodic syndromes (CAPS), provides important independent substation to support a conclusion of substantial evidence of effectiveness in each proposed new indication.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The collective evidence from the pivotal phase 3, randomized, double-blind, placebo-controlled study N2301 supports the efficacy of canakinumab for the treatment of periodic fever syndromes including FMF, HIDS/MKD, and TRAPS in patients ages 2 years and older. Data from the randomized treatment period of Study N2301 showed that canakinumab was statistically significantly superior to placebo in all three disease cohorts with respect to the proportion of patients who had index flare resolved by Day 15 and did not experience a new flare during the 16 weeks of treatment period. Efficacy of canakinumab over placebo was also observed for secondary and exploratory endpoints which included multiple domains of clinical response, serological markers of inflammation, and health-related quality of life. The large estimated magnitude of effects on primary and secondary endpoints, combined with supportive results for exploratory patient- or parent-reported outcomes, suggests clinically important treatment effects for canakinumab in these three populations. Results from subgroup analyses were generally in line with the overall population.

However, because a large percentage of placebo patients crossed over to canakinumab shortly after the first administration of study drug, and some patients on canakinumab were further up-titrated, there were a limited number of patients remaining on initial randomized treatment at Week 16. Therefore, secondary endpoint results at Week 16 are difficult to interpret and likely inappropriate for labeling.

5.3 LABELING RECOMMENDATIONS

The focus of the labeling review will be on Section 14 Clinical Studies. Edits to the labeling are pending. While the results at Week 16 may not be appropriate for labeling, it remains to be determined which data or time point should be included to support the indication of FMF,

HIDS/MKD, and TRAPS. Our preliminary review led to the following recommendations on the applicant's proposed labeling:

- Remove [redacted]
- Provide clarification that patients who crossed over from placebo to canakinumab, or who up-titrated the dose of canakinumab, or who discontinued the study early were considered as non-responders in the primary analysis
- Describe in text or table the proportions of patients who crossed over from placebo to canakinumab and/or received up-titration
- Delete the paragraph on [redacted]
- Remove [redacted] pending additional discussion.

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/s/

LAN ZENG
08/12/2016

GREGORY P LEVIN
08/17/2016

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

sBLA Number: 125319 **Applicant: Novatis** **Stamp Date: 3/28/2016**

supplements-85, 86, 87

Drug Name: Canakinumab **NDA/BLA Type: sBLA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Study to be reviewed: CACZ885N2301

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician	Date
Supervisor/Team Leader	Date

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/s/

LAN ZENG
06/06/2016

GREGORY P LEVIN
06/06/2016