CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319Orig1s085, 086, 087

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 8, 2016
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	125319 Supplements 85, 86, and 87
Applicant	Novartis
Date of Submission	March 23, 2016 (85), March 28, 2016 (86), and March 29, 2016 (87)
PDUFA Goal Date	September 23, 2016
Proprietary Name / Established (USAN) names	Ilaris®/canakinumab
Dosage forms / Strength	Glass vial containing Ilaris as a lyophilized powder for reconstitution
Proposed Indication(s)	1. Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adults and children 2 years of age and older (sup 85) 2. Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adults and children 2 years of age and older (sup 86) 3. Familial Mediterranean Fever (FMF) in adults and children 2 years of age and older (sup 87)
Recommended:	*Approval*

1. Introduction

This supplemental biologic license application (sBLA) 125316, supplements 85, 86, and 87, is for Ilaris® (canakinumab) for three Periodic Fever Syndromes: Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF). For each indication, the proposed age range is adults and children 2 years of age and older.

Cankinumab is a recombinant, human anti-human IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass which was approved in the United States (U.S.) on June 17, 2009, for the indication of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults and children 4 years of age and older including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). It was subsequently approved on May 9, 2013, for systemic juvenile idiopathic arthritis (SJIA) for patients with a body weight greater than or equal to 7.5 kg.

On March 23, 28, and 29, 2016, the sponsor submitted supplements 85, 86, and 87 for Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF), respectively.

In support of the new indications, the sponsor submitted data from Epoch 2 of the ongoing study CACZ885N2301 (N2301).

The PDUFA due date for supplement 85 is September 23, 2016, and it is anticipated that action will be taken on all three supplements on the same date. The review classification for this application is priority.

2. Background

The periodic fever syndromes are rare disorders of innate immunity characterized by recurring episodes of fever and systemic inflammatory symptoms, affecting the serosal surfaces, joints, skin, and eyes. The attacks of fever and localized inflammation occur periodically or irregularly and are not explained by usual infections. Generally, the periodic fever syndromes are considered autoinflammatory diseases. They differ from autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis in that they lack high-titer autoantibodies or antigen-specific T-cells.

Periodic fever syndromes include familial Mediterranean fever (FMF), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MDK)/hyperimmunoglobulin D and periodic fever syndrome (HIDS), the cryopyrin-associated periodic syndromes (CAPS), and periodic fevers with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome. There are currently no approved treatments for HIDS/MKD and TRAPS. Colchicine is approved for the treatment of FMF.

Despite similarities, the periodic fever syndromes have differing etiologies, inheritance, duration and frequency of attacks, and clinical characteristics. Persistent inflammation is a risk factor for the development of amyloidosis, but the risk of amyloidosis can be different in the different periodic fever syndromes.

A comparison of FMF, HIDS/MKD, and TRAPS is provided in Table 1. FMF is the most common of the monogenic periodic fever syndromes. FMF is an autosomal recessive disorder in which there is a mutation in the FMF gene (*MEFV*) encoding the protein pyrin that helps regulate production of interleukin-1β (IL-1β). FMF predominantly affects populations living in the Mediterranean region.

FMF is characterized by episodic attacks of fever lasting one to three days. Symptoms include abdominal pain, pleurisy, and arthralgias or arthritis. Colchicine (Colcrys) is approved for the treatment of FMF in adults and children 4 years and older.

TRAPS is an autosomal dominant periodic fever with incomplete penetrance. It is caused by mutation in the soluble TNF receptor superfamily 1A gene (the *TNFR1* gene). More than 40 different mutations have been reported. Most mutations mediate their effect via decreased shedding of Type 1A TNF receptor protein, leading to prolonged inflammation.

TRAPS patients are frequently of northern European descent. More than half of patients develop symptoms in the first decade of life, but the age ranges from 2 weeks to 53 years. Generally, flares occur every 6 weeks and last more than 1 week. Flares are characterized by conjunctivitis, periorbital edema, localized myalgias, rash, abdominal pain, and, arthralgias. The rash typically is single or multiple erythematous patches that overlie areas of myalgias. Distinct features are the prolonged attacks, conjunctivitis, and localized myalgias.

HIDS is a rare autosomal recessive genetic disease associated with defects in the mevalonate kinase (MVK) gene. Mevalonate kinase is a key enzyme in the cholesterol and isoprenoid synthesis pathway. The mechanism by which defects in the mevalonate kinase leads to pro-inflammatory gene expression is not fully understood, but may involve activation of caspase I and elevation of IL-1β.

HIDS/MKD occurs primarily among families of European descent, especially Dutch and French. HIDS/MKD typically presents during the first year of life with a median age of onset of 6 months (range one week to 10 years of age).[1] The clinical manifestations of attacks in HIDS/MKD include fever and the presence of lymphadenopathy, splenomegaly, arthralgia/arthritis, abdominal pain, and rash. The acute episodes last 3-6 days long and recur every 4-8 weeks. The acute episodes can be triggered by childhood immunizations and physical and emotional stress. The disease is usually characterized by elevated serum polyclonal IgD levels.

Table 1: Characteristics of FMF, TRAPS, and HIDS/MKD

Periodic Fever Syndrome	Gene	Mode of inheritance	Predominant ethic groups	Usual age at onset	Potential precipitants of attacks	Distinctive clinical features	Typical duration of attacks	Typical frequency of attacks
FMF	*MEVF* Chromosome 16	Autosomal recessive (dominant in rare families)	Eastern Mediterranean	Childhood/early adult	Usually none Occasionally menstruation, fasting, stress, trauma	Short severe attacks Colchicine-responsive Erysipelas-like erythema	1-3 days	Variable
TRAPS	*TNFRSF1A* Chromosome 12	Autosomal dominant, can be *de novo*	Northern Europa but reported in many ethnic groups	Childhood/early adult	Usually none. Sometimes travel, stress, fasting, menstrual cycle	Prolonged symptoms	More than a week, may be very prolonged	Variable, may be continuous or q6w
HIDS/MKD	*MVK* Chromosome 12	Autosomal recessive	Northern European	Infancy	Immunizations	Diarrhea and lymphadenopathy	3-7 days	1-2 monthly

Modified from: Lachmann HJ. Clinical Immunology Review Series: An approach to the patient with a periodic fever syndrome. Clin Exp Immunol. 2011 Sep: 165(3):301-9.

[1] Van der Hilst JC, et al. Medicine (Baltimore). 2008;87(6):301.

CAPS represent a family of syndromes associated with mutations in cryopyrin, now termed NLRP3 (nucleotide-binding domain and leucine-rich repeat containing family, pyrin domain-containing 3). Mutations in NLRP3 impair control of inflammasome assembly, leading to aberrant production of IL-1β. Patients with CAPS typically fall into one of three clinical syndromes with overlapping clinical features: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disorder (NOMID, also called CINCA for chronic infantile neurologic cutaneous and articular syndrome). FCAS is manifested by brief episodes of fever and maculopapular or urticarial rashes that are triggered by exposure to cold. MWS is associated with fevers and urticarial rashes. NOMID is a rare, severe disease characterized by persistent fevers and rashes, from birth. Canakinumab is approved for the treatment of CAPS (FCAS and MWS).

PFAPA is of unknown etiology. While it is characterized by recurrent, unexplained fevers, it is unknown whether it is an autoinflammatory condition. Interestingly, most patients have resolution of the febrile episodes with time and long-term consequences have not been identified.

There are other autoinflammatory disorders that do not typically present with fever, such as Blau syndrome, deficiency of the interleukin (IL)-1-receptor antagonist (DIRA), pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA syndrome), chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature (CANDLE), and deficiency of the interleukin-36 receptor antagonist (DITRA). There continues to be development in terms of our understanding of autoinflammatory disorders.

Relevant regulatory History

Canakinumab was approved in the United States (U.S.) on June 17, 2009, for the indication of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults and children 4 years of age and older including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). It was subsequently approved on May 9, 2013, for the systemic juvenile idiopathic arthritis (SJIA) for patients with a body weight greater than or equal to 7.5 kg. The current supplements seek to add the indications of TRAPS, HIDS/MKD, and FMF.

At a pre-phase 3 meeting (May 13, 2013), the sponsor proposed to (b) (4) [redacted] from a regulatory standpoint, CAPS, TRAPS, HIDS, and FMF will be treated as individual disorders (b) (4) [redacted]

In addition, the Division did not agree with the sponsor's proposal to (b) (4) [redacted] Rather, the division recommended performing a randomized controlled study that also incorporated a randomized withdrawal period after the initial 16-week randomized period.

In an advice letter (February 10, 2014), concerns were raised regarding the proposed phase 3 study design. Specifically, (b) (4) The Division noted concerns regarding the proposed intra-subject dose escalation, which would make it difficult to identify the dose and dosing interval that is associated with the apparent efficacy and risk-benefit profile. In addition, concerns were raised regarding the short length of the open-label lead-in period. It was recommended that distinct endpoints be used for the three diseases studied.

At a pre-sBLA meeting on June 2, 2015 (meeting minutes dated July 1, 2015), it was noted that data from both the randomized placebo-controlled period (Epoch 2) and the randomized withdrawal period (Epoch 3) would be needed to support the submission of an application. In addition, there were concerns with the integrity of the randomized placebo-controlled period due to the provisions in the protocol allowing patients to escape and receive open-label active therapy after Day 29 in Epoch 2. Also, the Division recommended that the applicant study a broader population of FMF patients and not just those who are colchicine resistant since canakinumab would be expected to work for the broader FMF population. The Division noted that Novartis should clearly present the efficacy and safety data taking into account the different pre-defined dose escalation scenarios within study CACZ885N2301 (N2301).

In Type C written responses (February 12, 2016), the applicant proposed submitting 16-week data from the double-blind, placebo-controlled part of Study N2301 (Epoch 2) to support applications for three indications: crFMF, HIDS/MKD, and TRAPS. The Division noted that the decision to only submit Epoch 2 data to support the proposed sBLAs was at the sponsor's discretion and the adequacy of the data would be a review issue. The sponsor was asked to address the clinically-meaningful benefit in the intended population, the impact of the cross-over of placebo-treated patients at early time-points on the interpretation of efficacy, and to provide a rationale that the observed short-term benefit could support chronic administration of canakinumab.

Orphan drug status

Novartis has been granted orphan-drug designation for development of canakinumab for the treatment of TRAPS (September 4, 2012), hyperimmunoglobulin D and periodic fever syndrome (HIDS) (December 5, 2013), and FMF (December 5, 2013).

Breakthrough Therapy Designation

On April 21, 2016, Ilaris was granted breakthrough designation for the treatment of patients with FMF in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response, HIDS/MKD, and TRAPS under IND 100040.

Priority Review

The Applicant requested and was granted priority review based on the rationale that FMF, HIDS/MKD, and TRAPS are serious diseases with unmet medical need and canakinumab may

provide a significant improvement in safety or effectiveness of the treatment of these serious diseases.

3. CMC/Device

- **General product quality considerations**

No new CMC or device data were submitted as part of this supplement. See Section 5 regarding presentation considerations.

- **Facilities review/inspection**

Not applicable for this sBLA.

- **Other notable issues (resolved or outstanding)**

There are no other notable issues.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were required for or submitted in this supplement. There are no outstanding nonclinical issues.

5. Clinical Pharmacology/Biopharmaceutics

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.**

The pharmacokinetics characteristics of canakinumab in healthy volunteers, CAPS, and SJIA patients were previously reviewed in the original BLA submission and supplement 062.

In the current submission, PK data were collected in the pivotal study (N2301) and early phase 2 studies. The PK parameters of canakinumab in TRAPS, HIDS/MKD, and FMF patients were consistent with the approved indications, such as CAPS. The exposure of canakinumab was not influenced by disease.

- The PK of canakinumab was linear with no evidence of time dependency in clearance in patients with TRAPS, HIDS/MKD, and crFMF.
- Serum clearance of canakinumab and its volume of distribution were dependent on bodyweight at baseline. The estimated serum clearance of canakinumab was 0.16L/day in patients with TRAPS, HIDS/MKD, and crFMF (with typical bodyweight of 70 kg). The corresponding volume of distribution at steady state was 5.82 L. The half-life (T1/2) of canakinumab in patients with TRAPS, HIDS/MKD, and crFMF was approximately 25.7 ± 6.5 days.

- The key pharmacokinetic parameters of canakinumab such as clearance and volume of distribution were not impacted by age above 2 years old and albumin level at baseline in patients with TRAPS, HIDS/MKD, and crFMF after correction for the subject's bodyweight.

Based on population PK analysis, canakinumab exposure (AUC and Cmin) were comparable across age groups (≥2 yrs) following subcutaneous administration of the same weight based dose in patients less than 40kg. In pediatric patients, of ages less than 2 years (n=5, age range = 0.2 to 1.2 years), the steady state trough concentrations of canakinumab were within the concentration range of older age groups with the same weight based dosing regimen.

Immunogenicity
Overall the incidence of ADA is low in PFS patients. The incidence of treatment related anti-canakinumab antibodies was < 1% in crFMF, HIDS/MKD and TRAPS patients across all Phase 2 and 3 studies. No patient had neutralizing antibodies. No anti-drug antibodies (ADA) were detected in any patient in Study N2301. Two patients (1 crFMF and 1 TRAPS) in the Phase 2 studies had treatment-emergent ADA, with no link to adverse events (AEs), loss of efficacy or change in PK.

Presentation
Currently, canakinumab is available as a lyophilized powder that needs to be reconstituted with water for injection prior to administration. Study N2301 utilized a solution for injection in vial. The sponsor proposed introduction of the 150 mg/ml solution for injection in vial in supplement 125319/88. This supplement received a complete response on July 29, 2016, due to microbiology deficiencies. See the CDTL memo dated July 29, 2016, for additional details. In supplement 125319/88, the sponsor assessed the comparability of canakinumab 150 mg/1mL solution for injection in vial, (b) (4) Thus, it is reasonable to assume that the findings would also apply to the solution in vial. Given that the sponsor has bridged the lyophilized powder and the solution for injection in vial with CMC and bioequivalence data, it is reasonable for the lyophilized powder presentation to be utilized for the proposed indications.

- **Other notable issues (resolved or outstanding)**

There are no outstanding issues. The Office of Clinical Pharmacology has determined the information in the application is acceptable.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Mark Borigini, MD
Primary statistical reviewer: Lan Zeng, MS; Statistical Team Leader: Gregory Levin, PhD

Overview of the clinical program
The primary evidence of efficacy is derived from the 16-week, randomized treatment period (Epoch 2) of Study CACZ885N2301 (N2301) (Table 2).

Table 2: Overview of Study CACZ885N2301 (N2301)

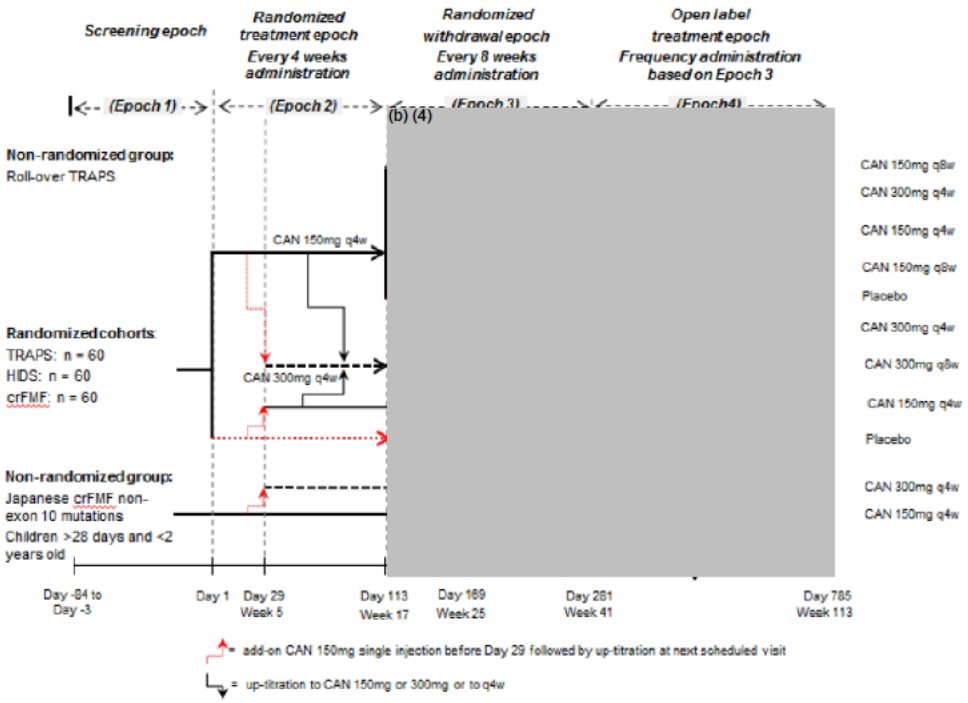
Dates	Sites	Design	Study arms	Primary objective	Total n
June 2014-ongoing (cutoff date August 25, 2015)	Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, Russia, Spain, Switzerland, Turkey, United Kingdom, US	R, DB, PC study in TRAPS, HIDS and crFMF with subsequent RW/dose reduction and OLE treatment epochs	Canakinumab 150 mg (or 2 mg/kg in patients ≤ 40 kg) sc q4 weeks PBO	Resolution of index flare at Day 15 and no new disease flares over 16 weeks of treatment	181

Abbreviations: R=randomized; DB=double blind; PC=placebo controlled; TRAPS=Tumor Necrosis Factor Receptor Associated Periodic Syndrome; HIDS/MKD=Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency; crFMF=colchicine resistant Familial Mediterranean Fever; RW=randomized withdrawal; OLE=open label extension; PBO=placebo; sc=subcutaneous; q4=every 4
Source: Reviewer generated

Study N2301
Study N2301 was a randomized, double-blind, placebo-controlled study of canakinumab in patients with crFMF, HIDS/MKD, or TRAPS. It consisted of three randomized cohorts (crFMF, HIDS/MKD, and TRAPS), and 4 study epochs (Figure 1). This study is ongoing and the primary efficacy data available are from Epoch 2, the 16-week randomized treatment epoch.

The study population consisted of male and female patients with confirmed crFMF, HIDS/MKD, or TRAPS who were at least 2 years of age at the time of the screening visit. At randomization, patients had active disease, as defined by a physician's global assessment of disease activity (PGA) ≥2 and CRP >10 mg/L. Patients >28 days but <2 years old with bodyweight ≥3.75 kg at the time of the screening visit could be followed as non-randomized patients.

Figure 1: Overall study design of study N2301

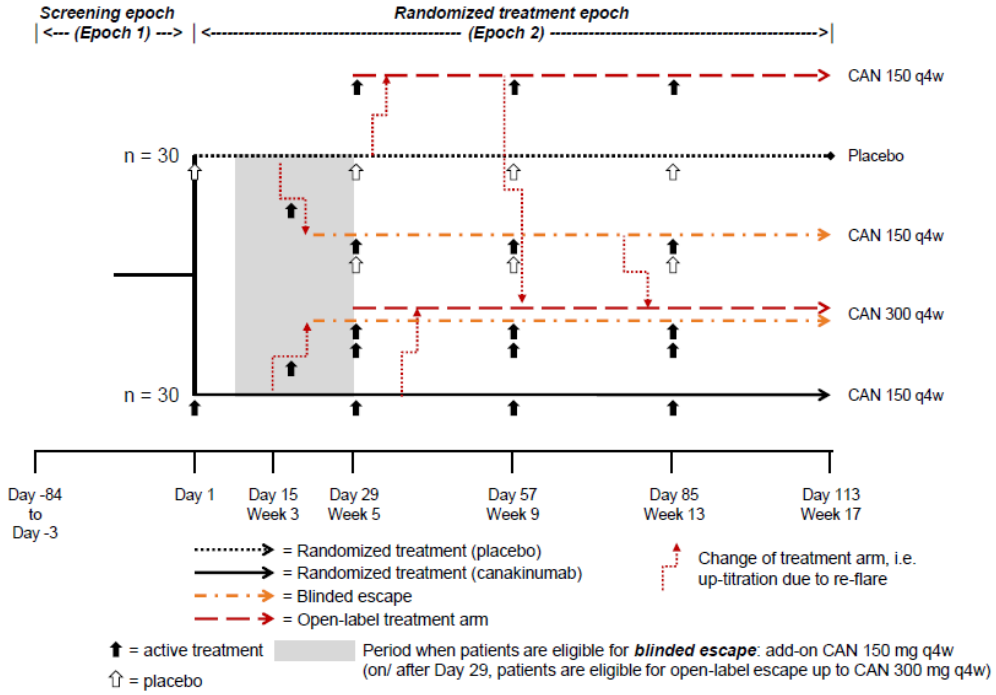


Source: Clinical Study Report, Figure 9-1, page 51, submitted 3/23/16

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

1. A screening epoch to assess patients' eligibility of up to 12 weeks duration (**Epoch 1**)
2. A randomized, double-blind, placebo controlled treatment epoch (**Epoch 2**) of 16 weeks
3. A randomized withdrawal epoch (**Epoch 3**) of 24 weeks where canakinumab responder patients who were initially randomized to canakinumab 150 mg q4w and did not re-flare in Epoch 2 are 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

Figure 2: Design of Epochs 1 and Epochs 2 in Study N2301



Source: Clinical Study Report, Figure 9-2, page 51, submitted 3/23/16

The study design of Epochs 1 and 2 is shown in Figure 2. At the baseline of Epoch 2, eligible patients were randomized in a ratio of 1:1 within each cohort (crFMF, HIDS/MKD, or TRAPS) to one of 2 treatment arms: canakinumab 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) every 4 weeks (q4w) or placebo.

Epoch 2 included two possible escape options:

a. Blinded escape from Day 8 to Day 28 (where the randomized therapy is still blinded and the patient can be given an open-label rescue dose of 150 mg canakinumab)
b. Open-label treatment from Day 29 to Day 112

See Table 3 for an overview of the criteria for add-on injections and subsequent up-titration in Epoch 2. From Day 8 to 28, if patients experienced PGA ≥2 or CRP persistent >10 mg/L with less than 40% reduction from baseline, they received a single add-on sc injection of canakinumab (150 mg sc [or 2 mg/kg for patients ≤ 40 kg]) as a blinded escape option. From Day 15 up to Day 28, patients whose index flare did not resolve, or who had persistent disease activity (PGA ≥ 2 or CRP >10 mg/L and no reduction by at least 70% from baseline), could also receive an additional dose of 150 mg (or 2 mg/kg for patients ≤ 40 kg), provided the add-on injection was not given earlier. If the patient's condition did not improve after administration of the single add-on canakinumab injection, rescue medication (corticosteroids) was used until Day 29. Of note, patients who received blinded add-on canakinumab were considered non-responders for the primary analysis.

For patients who received the single add-on canakinumab injection, up-titration to canakinumab 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q4w was initiated from Day 29 onward. These patients were not eligible for further up-titration.

Given the study design, the actual treatment sequence for patients could be one of the following:

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

Table 3: 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

Source: Clinical Study Report, Table 9-1, page 55, submitted 3/23/16

Randomized withdrawal epoch (Epoch 3)

All patients randomized to canakinumab 150 mg (or 2 mg/kg for patients weighing ≤40 kg) q4w at baseline who completed Epoch 2 without re-flare are re-randomized in (b) (4)

- Canakinumab 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) q8w
- Placebo

(b) (4)

(b) (4)

Open-label treatment epoch (Epoch 4)

(b) (4)

Non-randomized patients

The following non-randomized patients were allowed to enter the study and are 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 into the open-label treatment of Epoch 2.
- Roll-over TRAPS patients previously participating in clinical study ACZ885D2203 and/or the subsequent Multiple Patient Program (MPP) treatment plan ACZ885D2207M are allowed to enter the study (b) (4) Epoch 3.

Patients in the non-randomized group were assigned to open-label treatment with canakinumab 150 mg (or 2 mg/kg for patients weighing ≤ 40 kg) q4w. This non-randomized group was eligible for add-on injection and up-titration, but always received open-label medication.

Brief Description of Efficacy Endpoints

Physician's global assessment of disease activity (PGA)
The PGA was evaluated by the investigator based on a 5-point scale:

- 0 = None (no) disease associated clinical signs and symptoms
- 1 = Minimal disease associated signs and symptoms
- 2 = Mild disease associated signs and symptoms
- 3 = Moderate disease associated signs and symptoms
- 4 = Severe disease associated signs and symptoms

Physician's severity assessment of key disease-specific signs and symptoms
Key signs and symptoms differed for each individual condition. The following signs and symptoms were assessed:

1. TRAPS: skin rash, musculoskeletal pain, abdominal pain, eye manifestations
2. HIDS/MKD: lymphadenopathy, aphthous ulcers, abdominal pain
3. crFMF: chest pain, abdominal pain, arthralgia/arthritis, skin rash

Physician's severity assessment of key disease-specific signs and symptoms were evaluated by the investigator based on a 5-point scale:

- 0 = Absent
- 1 = Minimal
- 2 = Mild
- 3 = Moderate
- 4 = Severe

Fever (body temperature ≥ 38°C [100.4°F]), was assessed via vital sign measurements

Resolution of the index flare
Resolution of the index flare was defined as PGA < 2, and CRP within normal range (≤ 10 mg/L) or reduction by at least 70% from baseline.

New disease flare
From Day 29 onwards, a new disease flare was defined as simultaneous occurrence of a clinical flare and a serological flare defined as follows:

- PGA ≥ 2 (clinical flare)
- CRP ≥ 30 mg/L (serological flare)

For patients who achieved resolution of index flare at Day 15, this definition was applied from Day 16 until the end of Epoch 2.

Auto-inflammatory Disease Activity Index (AIDAI)
The AIDAI was collected daily on an electronic diary by the patient (for children, a parent could assist when needed) in the evening. Scores were calculated per week.

The AIDAI diary contains 13 items as follows: (a) fever, ≥ 38°C (100.4°F); (b) overall symptoms; (c) abdominal pain; (d) nausea/vomiting; (e) diarrhea; (f) headaches; (g) chest

pain; (h) painful nodes; (i) arthralgia or myalgia; (j) swelling of the joints; (k) eye manifestations; (l) skin rash; (m) pain relief drugs taken.

All items have to be scored as either yes or no. It has been validated[2] for use in hereditary recurrent fever syndromes.

Patient/Parent's global assessment of disease activity (PPGA)
Patient's assessment of disease activity (PPGA) was collected on an electronic diary daily in the evening.

The PPGA is based on a 5-point scale:

- 0 = None/absent (no) disease associated clinical signs and symptoms
- 1 = Minimal disease associated signs and symptoms
- 2 = Mild disease associated signs and symptoms
- 3 = Moderate disease associated signs and symptoms
- 4 = Severe disease associated signs and symptoms

Medical Outcome Short Form (12) Health Survey – Acute version 2 (SF-12v2)
The SF-12® measures the impact of disease on overall quality of life and consists of eight subscales (physical function, pain, general and mental health, vitality, social function, physical and emotional health) which can be aggregated to derive a physical-component summary score (PCS) and a mental-component summary score (MCS). Scores are determined with the use of norm-based methods which standardize scores based on an assessment of the general U.S. population free of chronic conditions.

Child Health Questionnaire – Parent Form (CHQ-PF50)
The CHQ-PF50 is an instrument used to measure HRQoL in children 5 to 17 years of age from a parent's perspective. This questionnaire was to be completed by the parent with no input from the patient.

The CHQ-PF50 provides summary (physical and psychosocial health) scores for a 14-concept health status and for well-being concepts: physical functioning, role/social emotional, role/social behavior, role/social physical, bodily pain, general behavior, mental health, self-esteem, general health perception, change in health, parental impact – emotional, parental impact – time, family activities, and family cohesion.

Sheehan Disability Scale (SDS)
The Sheehan Disability Scale (SDS) was developed to assess functional impairment in three inter-related domains: work/ school, social, and family life. The patient rates the extent to which work/school, social life or family responsibilities are impaired by his or her symptoms on a 10-point visual analog scale (VAS).

Rationale for dose and dosing regimen

[2] Piram M, et al (2014) Validation of the Auto-Inflammatory Diseases Activity Index (AIDAI) for hereditary recurrent fever syndromes. Ann Rheum Dis; 73(12):2168-73.

No formal dose finding studies were conducted. The dosing regimen evaluated was based on the dose for the approved indications, such as CAPS, and phase 2 studies in crFMF, HIDS/MKD, and TRAPS (Table 4).

For CAPS, the recommended dose for patients with body weight greater than 40 kg is 150 mg sc every 8 weeks. For CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg, the recommended dose is 2 mg/kg sc every 8 weeks. Study N2301 used the same initial dosing schedule as recommended for CAPS, but with a shorter interval between administration (every 4 weeks rather than every 8 weeks). For SJIA, the approved dose is 4 mg/kg (with a maximum of 300 mg) every 4 weeks for patients with body weight greater than or equal to 7.5 kg. Thus, the proposed dosing interval for crFMF, HIDS/MKD, and TRAPS is the same as for SJIA.

The efficacy and safety of canakinumab for the treatment of crFMF, HIDS/MKD, and TRAPS was initially evaluated in four proof of concept, open-label uncontrolled studies. These studies included patients with crFMF (Study CACZ885DTR01 in adults and Study CACZ885D2204 in pediatric patients), HIDS/MKD (Study CACZ885D2402) and TRAPS (Study CACZ885D2203). The studies in crFMF (DTR01 and D2204) and TRAPS (D2203) utilized a dosing scheduled of 150mg (2 mg/kg if ≤40 kg) sc q4w with the option to increase to 300 mg q4w for ongoing disease activity. The study in HIDS/MKD (D2402), utilized a dosing schedule of 300 mg q6w (4 mg/kg if ≤40kg) with the option to increase to 450 mg (6mg/kg if ≤40 kg). Each study suggested canakinumab reduced signs and symptoms of the evaluated periodic fever syndrome (Table 4).

In the pivotal phase 3 study, N2301, the initial dosing regimen of 150 mg sc (or 2 mg/kg sc for patients weighing ≤ 40 kg) q4w was utilized to harmonize dosing between the 3 diseases. The study incorporated an option for up-titration to a maximal dose of canakinumab 300 mg (or 4 mg/kg for patients weighing ≤ 40 kg) q4w for ongoing disease activity. In order to evaluate if clinical efficacy could be maintained at a lower dosing frequency, canakinumab 150 mg sc (or 2 mg/kg sc for patients weighing ≤ 40 kg) at a reduced frequency of every 8 weeks is being evaluated during the ongoing, randomized withdrawal epoch (Epoch 3). The sponsor has not included efficacy data from Epoch 3 in this submission. While it was reasonable to evaluate q4w dosing in the pivotal study, a PMC is recommended for the sponsor to submit efficacy data from Epoch 3 to see if efficacy can be maintained with q8w dosing.

Table 4: Summary of uncontrolled phase 2 studies in crFMF, HIDS/MKD, and TRAPS

Study *Dates*	Patients	Dose/Study design	N	Duration	Results
DTR01 *Dec 2010-Oct 2011*	crFMF (ages 12 to 75 years)	**canakinumab 150 mg** (2mg/kg if <40 kg) sc q4 wks or 300 mg (4 mg/kg if <40 kg) sc if ≥1 new flare during treatment period *(3 mo)* Follow up *(2 mo)*	9	6 mo	100% of patients had at least a 50% reduction in the attack frequency during the 3 month treatment period. 5/9 patients experienced an attack within the 2-month follow-up period (median time to flare was 71 days)
D2204 *Dec 2010-Feb 2012*	crFMF (4 to 20 years)	**canakinumab 150 mg** (2mg/kg if <40 kg) sc q4 wks or 300 mg (4 mg/kg if <40 kg) sc at the second dosing if any new attacks occurred *(3 mo)* Follow up *(2 mo)*	7	6 mo	6/7 (86%) of patients had at least 50% reduction in attack frequency during the 3 month treatment period 5/7 patients experienced a relapse after the last dose of canakinumab (median time to flare was 25 days)
D2402 *March 2011-Jul 2014*	HIDS/MKD (≥2 years)	**canakinumab 300 mg** (4mg/kg if ≤40 kg) sc q6 wks* *(6 mo)* Withdrawal *(6 mo)* **canakinumab 300 mg** (4mg/kg if ≤40 kg) sc q6 wks *(24 mo)*	9	3 yrs	Median number of flares decreased from 5 (3-12) during the 6-month historical period to 0 (0-2) during the 6-month treatment period 7/9 patients flared during the withdrawal period (median time to flare 110 days)
D2203 *Oct 2010-June 2014*	TRAPS (≥4 years)	**canakinumab 150 mg** (2mg/kg if ≤40 kg) sc q4 wks in addition to a single dose escalation up to 300 mg (4 mg/kg if ≤40 kg) in nonresponders at Day 8 *(4 mo)* Withdrawal *(5 mo)* **canakinumab 150 or 300 mg** sc q4 wks *(24 mo)*	20	33 mo	19/20 (95%) of patients achieved complete or almost complete response at Day 15 20/20 (100%) of patients relapsed during the 5-month follow-up period (median time to flare 91.5 days)

HIDS/MKD = Hyper IgD syndrome/Mevalonate Kinase Deficiency, TRAPS = TNF receptor-associated periodic syndrome, crFMF = colchicine-resistant familial Mediterranean fever, N = total number of subjects studied, yrs = years, mo = months, wks = weeks, qX wks = every X weeks, sc = sub-cutaneous

* Patients who experienced a new HIDS/MKD flare between baseline and Week 4 should have received an additional 150 mg (2 mg/kg for patients ≤40 kg) dose at the moment of flare, and would have received 450 mg (6 mg/kg for patients ≤40 kg) every 6 weeks thereafter starting at Week 6

Statistical Considerations

The primary analysis population was the Full Analysis Set (FAS) defined as all randomized patients. All data were analyzed separately for each independent randomized cohort (crFMF, HIDS/MKD, and TRAPS). For the primary endpoint, Fisher's exact test was utilized with a 2.5% one-sided significance level. Patients who needed dose escalation in the cankinumab arms, who crossed-over from placebo to canakinumab or who discontinued from the study due to any reason prior to evaluating the primary endpoint were considered non-responders.

If the primary objective of the study was met in all three cohorts then the treatment effect of canakinumab on the secondary efficacy endpoints was to be assessed using a hierarchical testing procedure, which evaluated the superiority of canakinumab 150 mg q4w over placebo using a logistic regression model.

Patient population

A total of 181 patients (63 crFMF, 72 HIDS/MKD, and 46 TRAPS) were randomized and treated with canakinumab of whom 175 patients completed Epoch 2. The baseline demographic and disease characteristics were generally reflective of patients with active

crFMF, HIDS/MKD, and TRAPS. All patients in Study N2301 had a confirmed genetic mutation (or genetic/enzymatic for HIDS/MKD) representative of the 3 disease cohorts.

FMF
In the overall FMF cohort, the mean age was 22 years and 46% of the cohort was < 18 years old, with 3 patients < 6 years old. Most crFMF patients were Caucasian and all had confirmed mutation in the MEFV gene. Approximately half (46%) of the patients were female. The median duration of disease was 14.7 years, with a median 18 flares per year, and most patients had PGA moderate (57%) or severe (29%) disease. The mean baseline CRP was 140 mg/L. In the crFMF cohort, 97% of patients had previously taken colchicine. While the sponsor has limited the indication for treatment of FMF for patients in whom colchicine is contraindicated, is not tolerated, or does not provide an adequate response, there is not a specific rationale for why canakinumab would not be anticipated to have a similar response in FMF patients regardless of previous response to colchicine. However, this issue was not directly evaluated as few patients did not use colchicine.

HIDS/MKD
In the overall HIDS/MKD cohort, the mean age was 13.5 years and 75% of the cohort was < 18 years old, with 17 patients < 6 years old. There were slightly more females (60%) than males. Most HIDS/MKD patients were Caucasian and all had confirmed mutation in the MVK (mevalonate kinase) gene. The median duration of disease was 9.8 years, with a median 12 flares per year, and the majority of patients had PGA moderate (60%) or severe (17%) disease. The mean baseline CRP was 172 mg/L.

TRAPS
In the overall cohort, the mean age was 22 years and 59% of the cohort was < 18 years old, with 7 patients < 6 years old. Approximately half of the patients were females. Most TRAPS patients were Caucasian and all had confirmed mutation in the TNFRSF1A gene. The median duration of disease was 8.2 years, with a median 9 flares per year, and over half of patients had PGA moderate (48%) or severe (9%) disease. The mean baseline CRP was 157 mg/L.

- **Efficacy review**

Data from 16 weeks of study N2301 were submitted in this sBLA. The study is ongoing and includes a randomized withdrawal (Epoch 3) and open label (Epoch 4) portion that have not been completed. The focus of this review is the efficacy results related to change in the signs and symptoms of crFMF, HIDS/MKD, and TRAPS from baseline to week 16.

Epoch 2 of study N2301 was well-controlled and utilized endpoints that are clinically reasonable in crFMF, HIDS/MKD, and TRAPS. Of note, while there are differences between FMF, HIDS/MKD, and TRAPS, the sponsor's choice of endpoint assessment and the timing of assessment are reasonable to evaluate the efficacy of canakinumab for the reduction of signs and symptoms of these diseases given that there are overlapping manifestations.

Patient disposition (Epoch 2)

See Table 5 for patient disposition in study N2301. An important aspect of the study design is that the majority of patients initially randomized to placebo were switched to canakinumab (FMF: 27/32, 84%; HIDS/MKD: 31/35, 89%; TRAPS: 21/24, 88%). The proportion of patients remaining on placebo through Week 16 was 16%, 12%, and 13% in the FMF, HIDS/MKD, and TRAPS cohorts, respectively. For patients initially randomized to canakinumab 150 mg q4w, approximately 32-51% required up-titration to canakinumab 300 mg q4w. The proportion of patients remaining on canakinumab 150 mg q4w through Week 16 was 68%, 49%, and 50% in the FMF, HIDS/MKD, and TRAPS cohorts, respectively.

Table 5: Patient disposition in study N2301 by disease cohort

FMF						
Initial randomized treatment	**Canakinumab 150mg (N=31)**		**Placebo (N=32)**			**Total (N=63)**
Actual treatment	150mg	150mg to 300mg	Placebo	Placebo to 150mg	Placebo to 300mg	
	21 (68%)	10 (32%)	5 (16%)	22 (69%)	5 (15%)	
Completed	21	10	4	22	5	62
Discontinued	-	-	1	-	-	1
Responders after 16 weeks	19 (61.3%)		2 (6.3%)			21
Full analysis Set	31		32			63
HIDS/MKD						
Initial randomized treatment	**Canakinumab 150mg (N=37)**		**Placebo (N=35)**			**Total (N=72)**
Actual treatment	150mg	150mg to 300mg	Placebo	Placebo to 150mg	Placebo to 300mg	
	18 (49%)	19 (51%)	4 (12%)	19 (54%)	12 (34%)	
Completed	18	18	3	19	11	69
Discontinued	-	1	1	-	1	3
Responders after 16 weeks	13 (35.1%)		2 (5.7%)			15
Full analysis Set	37		35			72
TRAPS						
Initial randomized treatment	**Canakinumab 150mg (N=22)**		**Placebo (N=24)**			**Total (N=46)**
Actual treatment	150mg	150mg to 300mg	Placebo	Placebo to 150mg	Placebo to 300mg	
	11 (50%)	11 (50%)	3 (13%)	19 (79%)	2 (8%)	
Completed	11	11	2	19	1	44
Discontinued	-	-	1	-	1	2
Responders after 16 weeks	10 (45.5%)		2 (8.3%)			12
Full analysis Set	22		24			46

Source: Data from Dr. Lan, statistical reviewer

Primary endpoint

In study N2301, the primary efficacy analysis compared of the proportion of responders (i.e., patients who had resolution of the index disease flare at Day 15 and did not experience a new flare from the time of resolution of the index flare until the end of Epoch 2 at day 112)

between the randomized treatment groups. Patients who needed dose escalation or crossed-over from placebo to canakinumab, or who discontinued from the study prior to evaluating the primary endpoint were considered non-responders. Blinded escape was allowed starting at day 8.

Resolution of the index flare (initial flare at the time of the randomization) was defined at the Day 15 visit as patients who had levels of PGA < 2 and CRP either within normal range (defined as ≤ 10 mg/L) or a reduction of CRP ≥ 70% from baseline. For absence of new flares over the first 16 weeks, a new flare was defined from the time of the resolution of the index flare as levels of PGA ≥ 2 and CRP ≥ 30 mg/L.

The primary objective was achieved in all 3 disease cohorts, supporting the efficacy of canakinumab compared to placebo (Table 6).

Table 6: Comparison between treatment groups of patients who responded at Week 16 by cohort (full analysis set)

	Canakinumab 150mg q4w		Placebo		Treatment comparison		
Cohort	**n/M (%)**	**95% CI**	**n/M (%)**	**95% CI**	**Risk difference (95% CI)**	**Odds Ratio (95% CI)**	**One-sided p-value**
crFMF	19/31 (61.3)	(42.19, 78.15)	2/32 (6.3)	(0.77, 20.81)	0.55 (0.31, 0.73)	23.75 (4.38, 227.53)	<0.0001*
HIDS/MKD	13/37 (35.1)	(20.21, 52.54)	2/35 (5.7)	(0.70, 19.16)	0.29 (0.06, 0.50)	8.94 (1.72, 86.41)	0.0020*
TRAPS	10/22 (45.5)	(24.39, 67.79)	2/24 (8.3)	(1.03, 27)	0.37 (0.08, 0.61)	9.17 (1.51, 94.61)	0.0050*

Source: Summary of clinical efficacy, Table 3-4, page 49, submitted 3/23/16
* Indicates statistical significance (one-sided) at p-value of 0.025 level based on Fisher exact test

Three of the 4 non-randomized patients (2 crFMF patients with non-exon 10 mutations and 1 HIDS/MKD patient >28 days but <2 years old), achieved resolution of their index flare on Day 15 and did not experience a new flare through the end of Epoch 2. The remaining patient with HIDS/MKD >28 but <2 years old, also achieved resolution of the index flare at Day 15, but discontinued the study during Epoch 2 due to an AE and was considered a non-responder.

Secondary endpoints

There were three predefined secondary efficacy endpoints in Study N2301 at Week 16 (end of Epoch 2): the percentage of patients who achieved a PGA < 2 ("minimal" or "none"), the percentage of patients with serologic remission (defined as CRP ≤ 10 mg/L), and the percentage of patients with normalized Serum Amyloid A (SAA) level (defined as SAA ≤ 10 mg/L). Patients who needed dose escalation in the canakinumab treatment groups, or who escaped from the placebo arms to canakinumab in Epoch 2, or discontinued from the study due to any reason prior to evaluating the endpoint at Week 16, were considered as having PGA ≥ 2, CRP > 10 mg/L, and SAA > 10 mg/L, respectively.

Canakinumab was superior to placebo for the secondary endpoints of PGA < 2 and CRP ≤ 10mg/L at Week 16 in all crFMF, HIDS/MKD, and TRAPS cohorts. For SAA ≤ 10mg/L at Week 16, canakinumab was statistically significantly superior to placebo in the TRAPS cohort and trended towards improvements compared to placebo in the crFMF and HIDS/MKD cohorts, but differences in those two cohorts were not statistically significant (Table 7).

Table 7: Results of the secondary endpoints at Week 16 in study N2301 by cohort (full analysis set)

	Canakinumab 150mg q4w		Placebo		Treatment comparison		
Cohort	**n/M (%)**	**95% CI**	**n/M (%)**	**95% CI**	**Odds Ratio**	**(95% CI)**	**One-sided p-value**
crFMF							
PGA <2	20/31 (65)	(45, 81)	3/32 (9)	(2, 25)	16.96	(4, 69)	<0.0001*
CRP ≤10mg/L	21/31 (68)	(49, 83)	2/32 (6)	(0.8, 21)	29.78	(6, 151)	<0.0001*
SAA ≤10mg/L	8/31 (26)	(12, 45)	0/32 (0)	(0, 11)	17.46	(0.9, 333)	0.0286
HIDS/MKD							
PGA <2	17/37 (46)	(29, 63)	2/35 (6)	(0.7, 19)	13.63	(3, 66)	0.0006*
CRP ≤10mg/L	15/37 (41)	(25, 58)	2/35 (6)	(0.7, 19)	12.71	(3, 64)	0.0010*
SAA ≤10mg/L	5/37 (14)	(5, 29)	1/35 (3)	(0.07, 15)	5.26	(1, 52)	0.0778
TRAPS							
PGA <2	10/22 (45)	(24, 68)	1/24 (4)	(0.1, 21)	23.79	(3, 225)	0.0028*
CRP ≤10mg/L	8/22 (36)	(17, 59)	2/24 (8)	(1, 27)	6.64	(1, 37)	0.0149*
SAA ≤10mg/L	6/22 (27)	(11, 50)	0/24 (0)	(0, 14)	16.69	(1, 269)	0.0235*

Source: Summary of clinical efficacy, Tables 11-14 (129), 11-16 (131), 11-18 (133)
n=number of patients in each cohort who had PGA<2, CRP≤10 mg/L or SAA ≤ 10mg/L; M=total number of patients in the cohort
*Indicates statistical significance (one-sided) at the p-value of 0.025 level based on the logistic regression model with treatment group and baseline PGA, CRP, or SAA as explanatory variables for each cohort

The results of the primary and secondary endpoints support the efficacy of canakinumab for FMF, HIDS/MKD, and TRAPS. However, there are important limitations in the data and study design. Specifically, the vast majority of patients on placebo crossed over to canakinumab prior to Week 16, which makes treatment comparisons difficult to interpret, especially for the secondary endpoints that were assessed at a specific time point. In addition, approximately 44% of patients initially randomized to canakinumab 150 mg up-titrated to 300 mg q4w. Therefore, for evaluations of binary endpoints in which patients who cross over or up-titrate are considered to be non-responders, it is difficult to determine whether observed differences between canakinumab and placebo are due to difference in treatment effects on the outcome of interest or due to differences in the proportions of patients remaining on the initially assigned treatment. Furthermore, evaluations of continuous endpoints are essentially uncontrolled due to the small subset of placebo patients remaining on assigned therapy at later time points. Because of the design of the study and the considerable cross-over from the control arm to canakinumab, reliable results are largely limited to short-term endpoints (such as resolution of index flare). Thus, the statistical reviewers performed analyses at earlier time points to also support the efficacy of canakinumab for crFMF, HIDS/MKD, and TRAPS. At Day 15, more patients on placebo than canakinumab required an add on injection and fewer patients on placebo had resolution of the index flare (Table 8). In addition, data from other efficacy measures over time support the efficacy of canakinumab in FMF, HIDS/MKD, and TRAPS.

Table 8: 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: Statistical Review dated 8/17/16

The applicant provided analyses intended to assess potential benefit of up-titration. However, since there was no control group of patients who had persistent disease activity but remained on the 150 mg q4w dose, 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.

In summary, the data support the efficacy of canakinumab for the treatment of FMF, HIDS/MKD, and TRAPS. Of note, while efficacy and safety data are available only from a single study, the submitted data were found to be adequate to support approval for the three proposed indications for two reasons. First, the three cohorts are clinically related conditions and the study demonstrated statistically significant evidence of canakinumab efficacy over placebo for various efficacy measures that were consistent across the three cohorts. Second, the safety and efficacy of canakinumab for CAPS, which is a related condition, has already been established. Thus, the submitted data were adequate to support substantial evidence of efficacy in each proposed indication.

8. Safety

Canakinumab has been approved since 2009 for the treatment of cryopyrin-associated periodic syndromes (CAPS). It was subsequently approved for systemic juvenile idiopathic arthritis (SJIA) in 2013. The highest doses are approved in SJIA, where patients received 4 mg/kg (maximum of 300 mg) administered subcutaneous (sc) every 4 weeks (q4w). Serious infections, hypersensitivity reactions, and macrophage activation syndrome occurred in the canakinumab safety database and these safety issues are included in the Warnings and Precautions section of the label.

- **Discuss the adequacy of the database, major findings/signals, special studies, etc.**

In this submission, the sponsor provides safety data from the ongoing, pivotal confirmatory phase 3 study CACZ885N2301 (hereafter referred to as Study N2301). The focus of the safety analyses are the 16-week, randomized, double-blind, placebo-controlled treatment phase (Epoch 2). Additional analyses utilize the data cut-off date of August 25, 2015, which

includes some data from the randomized, withdrawal (Epoch 3) and open label (Epoch 4) periods.

Additionally, 4 completed Phase 2 studies in the 3 indications (D2203, D2402, DTR01, and D2204, Table 4) support this application, in conjunction with supportive safety data from 5 completed Phase 2 and 3 studies in the approved indication of CAPS (D2304, D2201, A2102, D2306, and D2308).

In this safety review, the "Any ACZ" group includes all patients randomized to canakinumab and patients who were randomized to placebo and subsequently switched to cankinumab during Epoch 2. The "Total ACZ" group includes Epoch 2 and available data from Epochs 3 and 4 up to the data cutoff. Importantly, very few patients who were randomized to placebo at baseline stayed on placebo until the end of Epoch 2 (5 crFMF patients, 4 HIDS/MKD patients, and 3 TRAPS patients total). The median duration of exposure was 113 days and the median number of doses was ~5 for each of the cohorts. The number of patients in the Any ACZ group was 58 for crFMF, 68 for HIDS/MKD, and 43 for TRAPS. Of these patients, 102 were pediatric patients ranging from 2 years to 17 years of age exposed to canakinumab. There were also 2 non-randomized patients under 2 years of age with HIDS/MKD and 2 non-randomized adult patients with crFMF with non-exon 10 mutations exposed to canakinumab.

Additional safety experience with canakinumab has been in the clinical development programs in CAPS and SJIA where over 300 patients were treated with cankinumab. In this CAPS pool, a total of 177 patients received ≥ 24 weeks of treatment, a total of 130 patients received ≥ 48 weeks of treatment, and a total of 75 patients received ≥ 96 weeks of treatment.

Overall, the safety profile of canakinumab during the crFMF, HIDS/MKD, and TRAPS clinical development program is consistent with the safety profile of canakinumab during the SJIA and CAPS development programs. No new safety signals were identified during Study N2301.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Deaths

There were no deaths in any studies of periodic fever syndrome patients (studies D2402, D2203, DTR01, D2204, and N2301) as of the cut-off date.

Serious Adverse Events

In Study N2301, the event rate per 100 patient-years exposure was lower in the Total ACZ (n=169) than the placebo group (n=91) (30.5 and 85.2/100 PYR, respectively). The SOC with the highest frequency of SAEs was infections and infestations (4.1% in the Total ACZ group and 2.2% in the Total Placebo group). This is consistent with canakinumab's known safety profile.

The exposure-adjusted SAE rate was higher in the Total ACZ group for crFMF, HIDS/MKD, and TRAPS (Total ACZ group: 30.5 and placebo group: 85.2) vs. the CAPS pooled group (ACZ885: 15.9). However, the overall profile of SAEs in Study N2301 was similar to that reported in the CAPS pooled population.

crFMF

In Epoch 2, the incidence of SAEs was low in the Any ACZ group (5 patients, 8.6%). There were two patients who had SAEs while on placebo. No SAE was reported in more than 1 patient. A total of 10 SAEs occurred in any treatment group, with 3 SAEs occurring while the patient was on placebo (atypical pneumonia, cough, and FMF). The other SAEs included ascites, bile duct stone, granulomatous liver disease, hepatic cirrhosis, obesity, pharyngotonsillitis, and umbilical hernia.

No SAEs were reported in the non-randomized crFMF patients.

HIDS/MKD

In Epoch 2, the incidence of SAEs was 11.8% (8 patients) in the Any ACZ group. A total of 14 SAEs occurred in any treatment group, with 4 SAEs occurring while the patient was on placebo (abdominal pain, diarrhea infectious, neutropenia, and seizure). With the exception of pneumonia, reported in 2 patients in the placebo to 150 mg group, no SAE was reported in more than 1 patient. The other SAEs were conjunctivitis, FMF, hyper IgD syndrome, MKD, pericarditis, pharyngitis, polyserositis, self-injurious behavior, and suicide attempt.

One non-randomized HIDS/MKD patient experienced SAEs of pancytopenia and hepatic failure. While both SAEs were considered to be related to study treatment due to their occurrence after the start of study treatment, the patient had a history of immune cytopenic purpura and abnormal hepatic function prior to enrollment in the study. Thus, there did not appear to be causality between the events of pancytopenia and hepatic failure and canakinumab exposure.

TRAPS

In Epoch 2, the incidence of SAEs was low, affecting 4.7% (2 patients) in the Any ACZ group. No SAE was reported in more than 1 patient. A total of 4 SAEs occurred in any treatment group, with no SAEs occurring while the patient was on placebo. The SAEs were dysphagia, laryngeal stenosis, oropharyngeal pain, and TRAPS.

Discontinuations Due to Adverse Events

In Epoch 2 for the crFMF and TRAPS cohorts, there were no adverse events leading to discontinuation. In the HIDS/MKD cohort, 2 patients (2.9%) in the any ACZ group discontinued due to an adverse event. One patient in the placebo to 150 mg q4w to 300 mg q4w group discontinued study treatment due to HIDS flare, and subsequently discontinued from the study due to the primary reason of lack of efficacy.

Common Adverse Events

crFMF

The exposure adjusted event rates per 100 patient-days of AEs were comparable across the treatment groups (2.07 in the 150 mg q4w group, 4.51 in the placebo group, and 2.48 in the Any ACZ group). The most commonly reported AEs by preferred term in the Any ACZ group were FMF (22.4%), injection site reaction (13.8%), and diarrhea (12.1%).

HIDS/MKD

The exposure adjusted event rates per 100 patient-days of AEs were comparable across the treatment groups (2.42 in the 150 mg q4w group, 2.82 in the placebo group, and 3.86 in the Any ACZ group). The most commonly reported AEs in the Any ACZ group were pyrexia (23.5%), headache (17.6%), and diarrhea and oropharyngeal pain (each 11.8%).

Both of the non-randomized HIDS/MKD patients who were >28 but <2 years of age experienced AEs during Epoch 2. One patient reported AEs of upper respiratory tract infection, hepatic failure, hypocalcemia, hypophosphatemia, and pancytopenia. The patient had a history of immune thrombocytopenic purpura and abnormal hepatic function prior to enrollment in the study. The other patient had multiple non-serious AEs, the most frequently reported being diarrhea, aphthous ulcer, nasopharyngitis, and pyrexia. This patient also experienced events of alanine aminotransferase increased and aspartate aminotransferase increased.

TRAPS

The exposure adjusted event rates per 100 patient-days of AEs were comparable across the treatment groups (1.42 in the 150mg q4w group, 2.08 in the placebo group, and 2.76 in the any ACZ group). The most commonly reported AEs in the Any ACZ group were pyrexia (14%), and abdominal pain, injection site reaction, and nasopharyngitis (each 11.6%).

- **Immunogenicity**

No crFMF, HIDS/MKD, or TRAPS patients tested positive for anti-drug antibodies at any time during Epoch 2.

- **Special safety concerns**

Infections

In Epochs 2-4, the exposure-adjusted event rate of infections and infestations was similar between the Total ACZ (204.6/100 PYR) and the Total placebo (202.3/100 PYR) groups. In Epochs 2-4 the majority of infections were non-serious, mild to moderate infections of the upper respiratory tract that did not lead to discontinuation. No patient was confirmed by the

Infection Adjudication Committee to have an opportunistic infection in Epoch 2 or in Epochs 2-4 up to the data cut-off date. Overall, the infection profile observed in the N2301 pooled dataset was consistent with that of the CAPS pooled dataset. The exposure adjusted event rate (per 100 patient-years) was similar between the Total ACZ group (204.6) in Epochs 2-4 and the CAPS group (193.9). The most common SAEs were similar in the CAPS and FMF, HIDS/MKD, and TRAPS studies.

crFMF

In Epoch 2, the exposure adjusted event rate per 100 patient-days of AEs in the infections and infestations SOC was lower in the ACZ group compared to placebo (0.48 per 100 patient-days in the Any ACZ group and 1.07 per 100 patient days in the placebo group). The most common infections in the Any ACZ group were nasopharyngitis (10.3%) and upper respiratory tract infection (8.6%). There were two SAEs related to infection: pharyngotonsillitis (any ACZ) and atypical pneumonia (placebo).

HIDS/MKD

In Epoch 2, the exposure adjusted event rate of AEs in the infections and infestations SOC was slightly higher in the ACZ group compared to the placebo group (1.00 per 100 patient-days in the Any ACZ group and 0.56 per 100 patient-days in the placebo group). The data did not suggest a higher frequency of infections in patients treated with 300 mg q4w canakinumab vs patients treated with 150 mg q4w canakinumab. The most common infections in the Any ACZ group were nasopharyngitis (10.3%) and upper respiratory tract infection (8.8%).

TRAPS

In Epoch 2, the exposure adjusted event rate of AEs in the infections and infestations SOC was similar between ACZ and placebo (0.56 per 100 patient-days in the Any ACZ group and 0.69 per 100 patient-days in the placebo group). The most common infections in the Any ACZ group were nasopharyngitis (11.6%), and rhinitis and upper respiratory tract infection (9.3% each). There were no SAEs related to infection.

Malignancies

No malignancy events were reported in any cohort (crFMF, HIDS/MKD, or TRAPS) during Epoch 2 or Epochs 2-4.

Neutropenia

Overall, few neutrophil count reductions > Grade 2 (Grade 2: 7.1% and Grade 3: 1.2%) occurred in the Study N2301 in Epoch 2 or across Epochs 2-4. The exposure-adjusted event rate of neutropenia-related AEs per 100 patient-years in Epoch 2 was low and comparable across the cohorts of canakinumab-treated patients.

Injection Site Reactions

The exposure adjusted event rate of injection site reactions was higher in the ACZ group compared to the placebo group. Injection site reactions are known adverse drug reactions with canakinumab and are described in the currently approved labeling.

Hypersensitivity

In Epochs 2-4, across the crFMF, HIDS/MKD, and TRAPS cohorts, few patients reported an AE related to potential hypersensitivity. Cases included gingival swelling, urticarial, and face edema. All of the cases were mild and resolved without study drug discontinuation.

Drug-induced liver injury

The sponsor performed a review of all possible cases of drug-induced liver injury based on elevated liver enzyme AEs and clinical chemistry lab-identified events. There were no confirmed drug-induced liver injuries in N2301 Epoch 2 or Epochs 2-4. The exposure-adjusted event rate of potential DILI-related AEs in Epoch 2 was lower in the Total ACZ group (16.8, 95% CI: 7.3, 33.1) than the Total placebo group (24.9, 95% CI: 3.0, 89.9). Overall, the proportion of patients with possible DILI-related AEs was slightly lower in the Total ACZ group of N2301 (1.8%) compared with the CAPS pooled population (4.1%).

In the non-randomized group, a patient with HIDS/MKD experienced a notable SAE of hepatic failure. The patient was 19 months old at the time when he entered the screening Epoch 1. During screening, he had elevated liver function tests and was diagnosed with immune thrombocytopenic purpura treated with pulse steroid therapy. At that time, the liver function test elevations were thought to be related to a viral infection. He was considered a screen failure and did not receive canakinumab. He underwent re-screening approximately three months later. His liver function tests were elevated at screening (ALT 172 IU/L, AST 32 IU/L, and alkaline phosphatase 345 IU/L). He was enrolled in the study and received one dose of open-label canakinumab 2mg/kg sc. He subsequently developed worsening hepatic failure and pancytopenia. A liver biopsy showed hepatocyte necrosis. He was treated with G-CSF and methylprednisolone. Given that the patient had liver function elevations and pre-existing immune thrombocytopenic purpura prior to receiving canakinumab, the relationship between the events and exposure to canakinumab is unclear. Further, the clinical picture is complicated by the fact that liver involvement has been reported in HIDS/MKD.[3]

- **Safety conclusions**

Dr. Borigini has concluded that the safety profile of canakinumab in the study in crFMF, HIDS/MKD, and TRAPs is consistent with the known safety profile of canakinumab from the previous CAPS and SJIA experience, and no new safety signals have been identified. I concur with Dr. Borigini's conclusions. The sponsor has provided support for the safety of canakinumab in adult and pediatric patients (including patients <2 years of age) with FMF, HIDS/MKD, and TRAPS.

[3] Hinson DD, et al. American Journal of Medical Genetics 1998;78:408-12.

- **Discussion of notable safety issues (resolved or outstanding)**

See above.

9. Advisory Committee Meeting

No issues were identified that would warrant another advisory committee meeting. Thus, an advisory committee meeting was not held for this supplemental application.

10. Pediatrics

- **Peds exclusivity board review - PPSR/WR –**Not applicable.
- **PeRC Review Outcome-PMCs, deferrals, waivers, pediatric plan, peds assessment**

Canakinumab received orphan drug designation for the treatment of TRAPS (September 4, 2012), hyperimmunoglobulin D and periodic fever syndrome (HIDS) (December 5, 2013), and FMF (December 5, 2013). Thus, these applications are exempt from the requirements of the Pediatric Research Act (PREA). However, these supplements include data in children and the sponsor is seeking approval for patients 2 years of age and older with crFMF, HIDS/MKD, and TRAPS.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not applicable
- **Exclusivity or patent issues of concern—**Not applicable
- **Financial disclosures**—No issues.
- **Other GCP issues**—No issues
- **DSI audits**—Not performed for this supplemental application. No issues were identified to warrant clinical study site inspections for this submission.
- **Any other outstanding regulatory issues**—Not applicable.

12. Labeling

Labeling negotiations are ongoing at the time of this review. A summary of the major labeling considerations is included below:

Indications and usage

- Given that there are safety data in patients younger than 2 years of age and there are pharmacology data to help inform dosing in children less than 2 years of age, it is recommended that the lower bound of the age range be removed so that the product could be used as indicated for children and adults with FMF, HIDS/MKD, and TRAPS.

- Recommend removing the restriction in the FMF population for patients in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response. It is anticipated that canakinuamb would be effective in FMF, regardless of previous exposure to colchicine. Of note, the CLINICAL STUDIES section will describe the patient population and note that the studied population included patients in whom colchicine was contraindicated, was not tolerated, or did not provide an adequate response.

Dosing and administration

- The proposed dosing will be revised (b) (4) The dosing will be modified to suggest the dose can be increased to 300 mg or 4mg/kg (based on weight) at the clinician's discretion if an inadequate response is not obtained.

Adverse reactions

- Recommend streamlining the text to eliminate redundancy. In addition, given that the majority of patients randomized to placebo crossed over to canakinumab, interpretation of proportions utilizing the number of patients initially randomized to canakinumab or placebo is very limited. Thus, comparisons based on proportions will be revised.

Clinical studies

- (b) (4)
- Information will be added describing the proportions of patients who crossed over or up-titrated on the placebo and canakinumab arms, since the patient disposition impacts the evaluations of primary and secondary efficacy endpoints.
- (b) (4)
- Potentially misleading language (e.g., (b) (4) will be removed.
- (b) (4) In the study design, the vast majority of patients assigned to placebo crossed over to canakinumab prior to Week 16. Therefore, for evaluations of binary endpoints in which patients who cross over or up-titrate are considered to be non-responders, it is difficult to determine whether observed differences between canakinumab and placebo are due to difference in treatment effects on the outcome of interest or due to differences in the proportions of patients remaining on the initially assigned treatment. Furthermore, evaluations of continuous endpoints are essentially uncontrolled due to the small subset of placebo patients remaining on assigned therapy at later time points. Because of the design of the study and the considerable cross-over from the control arm to canakinumab, reliable results are largely limited to short-term endpoints (such as resolution of index flare).

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action for these supplemental applications is approval. While there are limitations in the study design given that the majority of patients randomized to placebo crossed over to canakinumab by Week 16, the applicant has provided substantial evidence of efficacy for these rare, serious diseases.

- **Risk Benefit Assessment**

The overall risk-benefit of canakinumab for the treatment of FMF, HIDS/MKD, and TRAPS is positive. The applicant has provided substantial evidence of the benefit of canakinumab for these three rare periodic fever syndromes. The safety profile in FMF, HIDS/MKD, and TRAPS did not reveal new safety signals.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

There are no recommendations for other Postmarketing Risk Evaluation and Management Strategies.

- **Recommendation for other Postmarketing Requirements and Commitments**

The following postmarketing commitment is recommended:

Provide efficacy and safety data from Epoch 3 of study, ACZ885N2301 to evaluate whether canakinumab 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneous q8w is able to maintain efficacy in FMF, HIDS/MKD, and TRAPS.

- **Recommended Comments to Applicant**

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET W MAYNARD
09/08/2016