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*APPLICATION NUMBER:*

**125319Orig1s085, 086, 087**

**CLINICAL REVIEW(S)**

## CLINICAL REVIEW

|                        |                                                                                                                                                                                                                                                                                                                |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Application Type       | Supplemental BLA                                                                                                                                                                                                                                                                                               |
| Application Number(s)  | 125319 85/86/87                                                                                                                                                                                                                                                                                                |
| Priority or Standard   | Priority                                                                                                                                                                                                                                                                                                       |
| Submit Date(s)         | March 23, 2016                                                                                                                                                                                                                                                                                                 |
| Received Date(s)       | March 23, 2016                                                                                                                                                                                                                                                                                                 |
| PDUFA Goal Date        | September 22, 2016                                                                                                                                                                                                                                                                                             |
| Division / Office      | DPARP/ODE 2                                                                                                                                                                                                                                                                                                    |
| Reviewer Name(s)       | Mark Borigini, MD                                                                                                                                                                                                                                                                                              |
| Review Completion Date |                                                                                                                                                                                                                                                                                                                |
| Established Name       | Canakinumab                                                                                                                                                                                                                                                                                                    |
| (Proposed) Trade Name  | ILARIS                                                                                                                                                                                                                                                                                                         |
| Therapeutic Class      | Interleukin-1B blocker                                                                                                                                                                                                                                                                                         |
| Applicant              | Novartis                                                                                                                                                                                                                                                                                                       |
| Formulation(s)         | Lyophilized powder 180 mg (150 mg/mL)                                                                                                                                                                                                                                                                          |
| Dosing Regimen         | <ul style="list-style-type: none"><li>• &gt;40kg: 150 mg Q4wk (can administer second dose after 7 days for inadequate response and then increase to 300 mg q4wk)</li><li>• ≤40 kg: 2mg/kg (can increase to 4 mg/kg for inadequate response) Q4wk</li></ul>                                                     |
| Indication(s)          | Familial Mediterranean Fever (FMF) in adults and children in whom colchicine is contraindicated, is not tolerated, or does not provide an adequate response, Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) |
| Intended Population(s) | Ages 2 years and older                                                                                                                                                                                                                                                                                         |

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Clinical Review  
Mark Borigini, MD  
sBLA125319 85/86/87  
ILARIS (canakinumab)

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The subcutaneous formulation of canakinumab (ILARIS) was originally approved in 2009 for the treatment of adults and children older than 4 years of age with cypropyrin-associated periodic syndromes (CAPS), and approval of canakinumab for the treatment of children with systemic juvenile idiopathic arthritis (SJIA) occurred in 2013. The current application is seeking approval of canakinumab doses, depending on the weight and response of a given patient, of 2 mg/kg to 300 mg administered by subcutaneous injection every four weeks to treat adults and children with Familial Mediterranean Fever in whom colchicine is contraindicated, is not tolerated, or does not provide an adequate response (crFMF), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS).

The primary efficacy data derives from the phase 3 study CACZ885N2301 (N2301). Study N2301 was a four-part study, consisting of a screening period (Epoch 1), a 16-week, randomized, double-blind, placebo-controlled treatment phase (Epoch 2) comparing a single dose of canakinumab 150 mg (2 mg/kg if  $\leq 40$  kg) versus placebo in children with active crFMF (63 subjects), HIDS/MKD (72 subjects), or TRAPS (46 subjects), a 24-week randomized withdrawal phase (Epoch 3) with subjects re-randomized to placebo or canakinumab 150 mg q 8 weeks, and a 72-week open-label treatment phase (Epoch 4). The study was adequately designed and conducted to allow for an interpretation of the effect of canakinumab in patients with crFMF, HIDS/MKD, or TRAPS.

Review of the data from Study N2301 demonstrated that the study met the pre-specified primary endpoint, with a greater proportion of canakinumab-treated subjects achieving resolution of their index flare (Physician Global Assessment (PGA)  $< 2$ , and C-reactive protein (CRP)  $\leq 10$  mg/L or reduction  $\geq 70\%$  from baseline) at Day 15 and who did not experience a new flare (PGA  $\geq 2$  and CRP  $\geq 30$  mg/L) from the time of resolution of the index flare until the end of Epoch 2 compared to placebo-treated subjects (respectively, 61% versus 6% for crFMF, 35% versus 6% for HIDS/MKD, and 45% versus 8% for TRAPS). In addition, more subjects in the canakinumab group resolved their index flare at Day 15 compared with placebo (81% versus 31% for crFMF, 65% versus 37% for HIDS/MKD, and 64% versus 21% for TRAPS).

The data were further supported by subgroup and sensitivity analyses, as testing of major secondary endpoints, which all showed that for PGA  $< 2$  and CRP  $\leq 10$ , canakinumab was superior to placebo for all three conditions; for serum amyloid A (SAA)  $\leq 10$ , improvement was observed in all three conditions, but statistical significance only reached in TRAPS subjects.

While the data demonstrated the efficacy of canakinumab in subjects with active crFMF, HIDS/MKD, or TRAPS, as measured by responder rate, PGA, and inflammatory markers, given that most placebo subjects switched to canakinumab and some patients required up-titration as early as Day 8, the comparison between canakinumab and placebo is difficult to interpret. Nonetheless, the indications studied are orphan in nature, without treatments that are consistently beneficial to the patients affected, and canakinumab does offer, based on the efficacy data under review thus far (Epoch 2), an option that these individuals do not currently have.

Supportive data were contributed by four proof-of-concept (PoC) phase 2 studies in subjects with crFMF (Study CACZ885N2301 and Study CACZ885D2204), HIDS/MKD (Study CACZ885D2402), and TRAPS (Study CACZ885D2203). Available safety data from the ongoing Epoch 3 and Epoch 4 of Study N2301 are pooled with safety data from Epoch 2 to provide safety information for longer term treatment (Study N2301 Epochs 2 – 4 dataset). In addition, pooled safety data from five completed phase 2 and 3 studies in subjects with CAPS were included to further support the safety profile for canakinumab in the group of periodic fever syndromes.

The data were sufficient to provide an adequate amount of drug exposure for evaluation of the safety of canakinumab in the crFMF, HIDS/MKD, and TRAPS populations. Review of the data did not identify any new safety signals and the overall safety profile of canakinumab in children and adults with these three conditions appears to provide an acceptable degree of risk given the severity of the disease and the demonstrated efficacy of canakinumab.

Based on my review of the clinical data as a whole, I recommend approval of subcutaneously administered canakinumab at the doses proposed for the treatment of FMF, HIDS/MKD, and TRAPS in children and adults.

### Risk Benefit Assessment

The risk-benefit assessment of canakinumab at dosages of 2 mg/kg to 300 mg subcutaneously administered every four weeks for the treatment of crFMF, HIDS/MKD, and TRAPS is in favor of approval for the current application given the magnitude of the clinically meaningful responses observed in the randomized controlled trial and the overall safety profile of canakinumab in the crFMF, HIDS/MKD, and TRAPS populations. Approval of canakinumab will provide an additional efficacious therapy for patients who have active crFMF, HIDS/MKD, or TRAPS.

## 1.2 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no current clinical recommendations for postmarketing risk evaluation and mitigation strategies for canakinumab in patients with crFMF, HIDS/MKD, or TRAPS.

### 1.3 Recommendations for Postmarket Requirements and Commitments

Study N2301 is ongoing and Epoch 3 will provide data from the randomized withdrawal portion of the study. According to the sponsor's study report, the following subjects (randomized canakinumab responders in Epoch 2) are eligible for Epoch 3: <sup>(b) (4)</sup>

 we recommend data from Epoch 3 be provided as a postmarketing commitment. These data can be provided postmarketing, rather than premarketing given the established safety profile (which includes no new safety signals associated with its use in the crFMF, HIDS/MKD, and TRAPS populations studied in the sponsor's latest BLA supplements) and clear efficacy for which breakthrough therapy designation has been granted

## 2 Introduction and Regulatory Background

The current submission is for canakinumab in Familial Mediterranean Fever (FMF) for which colchicine is contraindicated, is not tolerated, or does not provide an adequate response (hereafter referred to as colchicine-resistant/intolerant FMF or crFMF), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) and Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS). These three rare diseases are a group of clinically distinct autoinflammatory conditions, which, together with CAPS, have been classified under a single term of periodic fever syndromes. There are currently no approved treatments for crFMF, HIDS/MKD and TRAPS.

These conditions can be grouped based on their common pathophysiology, driven by dysregulation of interleukin-1 $\beta$  (IL-1 $\beta$ ) production, and shared clinical features of recurrent episodes of inflammation and fever. Although the underlying genetic defects and molecular etiology differ across the periodic fever syndromes, the disease mechanism common across these autoinflammatory conditions involves abnormal activation of the innate immune system, leading to dysregulation of cytokines and excessive inflammation.

The overlapping clinical manifestations across the periodic fever syndromes are recurrent episodes of systemic inflammation accompanied by high and disabling fever and characteristic signs and symptoms in target organs and body systems (i.e., serositis, neutrophilic rash, mucocutaneous ulcers, arthralgia/arthritis, and aseptic meningitis/headaches). The recurrent episodes of fever and severe localized inflammation are not explained by usual childhood infections. The episodes are usually associated with elevated serum levels of acute-phase reactants (e.g., C-

reactive protein (CRP), serum amyloid A (SAA), fibrinogen), an elevated erythrocyte sedimentation rate (ESR), and leukocytosis. Febrile episodes and associated symptoms in patients with these diseases can have a notable effect on quality of life (QoL), affecting school, work and interpersonal relationships. Although the inflammatory attacks cause much morbidity and significantly decreases the QoL of patients, the major source of mortality and most serious complication in patients with FMF, HIDS/MKD or TRAPS is represented by progressive secondary amyloidosis that may develop over several years and can progress to chronic kidney disease with subsequent renal failure. Renal amyloidosis is observed in up to 60% of untreated FMF patients, up to 25% of TRAPS patients, and in <10% of HIDS/MKD patients.

FMF is an autosomal recessive disease that affects mainly people of Mediterranean ancestry. Approximately 90% of patients with FMF experience the onset of disease before the age of 20 years. FMF is characterized by short febrile attacks caused by neutrophil-induced serosal inflammation and a gradual accumulation of amyloid in the kidneys. These febrile attacks are associated with pain in the abdomen, chest, joints, muscles, scrotum, and/or skin. Colchicine is effective in preventing attacks, as well as preventing the development of amyloidosis; however, some patients do not experience sufficient relief with colchicine or have problematic side effects.

HIDS/MKD is an autosomal recessive disorder which is characterized by febrile attacks that last 3 to 7 days, and occur every 4 to 6 weeks. These attacks are often associated with abdominal pain, vomiting, diarrhea, headache, polyarthralgia, non-destructive arthritis, and/or skin lesions. HIDS, originally named based on the high serum levels of immunoglobulin D (IgD) in the first cases described, is caused by mutations in the gene encoding mevalonate kinase, a critical enzyme acting early in the isoprenoid pathway. Therefore, HIDS is also referred to as MKD and the two terms are often used interchangeably. This clinical overview consistently uses the terminology ‘HIDS/MKD’ to follow the current consensus among specialists to use HIDS for the phenotype of fever episodes and MKD as the overall disease name. No specific treatment exists. Corticosteroids have been used to treat some individuals; but such therapy has been noted to increase the frequency of febrile attacks in some individuals.

TRAPS is an autosomal dominant disorder that affects mostly people of northern European descent. The median age of onset is 3 years. TRAPS is characterized by febrile attacks that tend to last longer than those of FMF or HIDS. These attacks are associated with abdominal pain, severe myalgia, and painful erythema on the trunk or extremities. An estimated 14% to 25% of TRAPS patients develop reactive amyloidosis. Treatment with non-steroidal anti-inflammatory drug (NSAIDs) or glucocorticoids can reduce the severity of symptoms but does not affect the frequency of febrile attacks.

The scientific rationale for the use of canakinumab to treat FMF, HIDS/MKD, and TRAPS rests on the knowledge that:

1. IL-1 $\beta$  is the key mediator of inflammation in all the classical periodic fever syndromes.
2. The identified genes which are mutated in FMF, HIDS/MKD, and TRAPS lead to altered protein which activates IL-1 $\beta$  secretion and causes inflammation.

Canakinumab was designed to specifically inhibit IL-1 $\beta$  without interfering with other pathways of IL-1 signaling, such as interleukin-1 $\alpha$  (IL-1 $\alpha$ ). Thus, canakinumab represents a targeted therapy against the inflammatory process in FMF, HIDS/MKD, and TRAPS, and may represent a potential new therapy.

## 2.1 Product Information

Canakinumab (ACZ885; ILARIS®) is a high-affinity fully human monoclonal anti-human interleukin-1 $\beta$  (IL-1 $\beta$ ) antibody of the IgG1/ $\kappa$  isotype. IL-1 $\beta$  is a key mediator of the inflammatory response. Increased production of IL-1 $\beta$  has been shown to cause a number of autoinflammatory conditions. Canakinumab binds to human IL-1 $\beta$ , blocking the interaction of this cytokine to its receptors and functionally neutralizing the bioactivity of this cytokine.

Canakinumab is currently approved in more than 70 countries, including the United States (US) and European Union (EU), for the treatment of cryopyrin-associated periodic syndromes (CAPS) and systemic juvenile idiopathic arthritis (SJIA) in adults and children. The doses and regimens approved for these auto-inflammatory conditions vary by region, with weight-based dosing employed for patients with low body weight from 7.5 to 40 kg. The highest dose approved is 600 mg or 8 mg/kg administered as a subcutaneous (sc) injection every 8 weeks (q8w). Canakinumab is also approved to treat acute gouty arthritis attacks in the EU and other countries at a dose of 150 mg administered as a subcutaneous injection soon after the onset of an attack.

The current application is seeking approval of canakinumab doses of 2 mg/kg to 300 mg administered by subcutaneous injection every four weeks to treat children and adults 2 years of age and older with colchicine-resistant/intolerant crFMF, HIDS/MKD and TRAPS.

## 2.2 Currently Available Treatments for Proposed Indications

To date, there are no approved therapies for crFMF, HIDS/MKD or TRAPS. As discussed above, certain medications have been used to treat the symptoms of these periodic fever syndromes, but these provide limited control over the relapsing febrile attacks and none treat the underlying inflammation.

For patients with FMF, colchicine has shown to be effective in controlling febrile attacks and preventing secondary amyloidosis. However, 5% of FMF patients are intolerant to colchicine because of side effects. Additionally, 5-10% of FMF patients do not respond to colchicine treatment at all. This group of crFMF patients who do not respond to or are intolerant to colchicine has very few, if any, treatment options.

And while there are agents approved for the treatment of the periodic fever syndromes known as CAPS (the specific labeled indications being Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) for riloncept and canakinumab, and Neonatal-Onset Multisystem Inflammatory Disease (NOMID) for anakinra), there is no therapy supported by data from randomized, well-controlled clinical trials for patients with HIDS/MKD or TRAPS. Thus, there is a significant unmet medical need.

### **2.3 Availability of Proposed Active Ingredient in the United States**

ILARIS is commercially available in the United States. It is supplied in a sterile, single-use 6-ml, glass vial containing 180 mg of drug product as a lyophilized powder for reconstitution. Subcutaneous injection of canakinumab is approved for the treatment of adults and children 4 years of age or older with CAPS at doses of 150 mg for patients weighing >40 kg or 2 mg/kg for patients weighing 15 kg to ≤40 kg, and adults and children 2 years of age or older with SJIA.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Drugs that block IL-1 interfere with the normal immune response and are likely to induce a certain degree of immunosuppression. Currently, IL-1 inhibitors approved in the United States include canakinumab (Ilaris), anakinra (Kineret), and riloncept (Arcalyst). Data from clinical studies and reports from the literature have shown that the use of IL-1 blockers have been associated with increased risk of infections. The ILARIS package insert states that canakinumab has been associated with an increased incidence of serious infections and cautions against the administration of live vaccines while on canakinumab therapy. The most common adverse reactions reported by patients with CAPS treated with canakinumab were nasopharyngitis, diarrhea, influenza, headache, and nausea. The most common adverse drug reactions reported by patients with SJIA treated with canakinumab were nasopharyngitis and upper respiratory tract infections, abdominal pain and injection site reactions.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The Phase 3 clinical study (N2301) submitted in the current application was conducted under IND 100040, which was opened with the Division of Anesthesia, Analgesia, and Rheumatology Products in 2006. The following Agency-sponsor interactions occurred subsequent to the submission of N2301:

- Orphan designation for TRAPS (September 2012), HIDS/MKD (December 2013), and crFMF (December 2013)
- Pre-Phase 3 meeting (May 13, 2013)
  - FDA refused to accept (b) (4)
  - FDA suggested randomized withdrawal period following the initial 16-week randomized period
    - Responders would continue canakinumab or placebo withdrawal with assessment of disease flares as an efficacy outcome
    - To be used as supportive evidence
  - FDA disagreed with (b) (4)
    - TRAPS, HIDS/MKD, crFMF to be treated as individual disorders
    - Efficacy to be based on results derived from each treatment arm.
- Type C written responses (October 11, 2013)
  - (b) (4)
  - Reasonable to bridge LYO to vial based on analytical comparisons
- FDA Advice Letter (February 10, 2014)
  - Concern with study design: endpoint and lead-in phase length
- Pre-sBLA meeting (June 02, 2015)
  - Reasonable to submit vial in separate submission
  - Submit randomized withdrawal and placebo controlled data
  - FDA reiterated its position that canakinumab should be assessed in the broader FMF population
- Type C WRO (February 12, 2016)
  - Provide justification for primary endpoint
- Breakthrough therapy designation for TRAPS, HIDS/MKD, FMF (February 26, 2016)
- While it may be optimal to include pediatric patients less than age 2 years in Study N2301, age expectations for CAPS were provided by FDA. In Study D2306, safety and efficacy for FCAS, MWS, NOMID, subjects were at least 3 years of age; however, the labeled indication for FCAS and MWS is for 4 years of age and over. The Agency considered age expectations for labeling during the review of this application.

## 2.6 Other Relevant Background Information

- There is no other relevant background information.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

In general, the data quality and integrity of the studies were adequate. The amount of missing data did not interfere with reaching conclusions on the safety and efficacy of the product. A number of statistical issues were identified during the review but did not interfere with the final interpretation of the data.

#### 3.2 Compliance with Good Clinical Practices

All studies were conducted in accordance with the ethical principles in the Declaration of Helsinki and Good Clinical Practice. The studies were conducted in compliance with the prespecified protocols. Informed consent, protocol amendments, and administrative letters for each study received Institutional Review Board/Independent Ethics Committee approval prior to implementation.

#### 3.3 Financial Disclosures

The sponsor has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry. Three investigators were identified with a potential conflict of interest. See the Appendix for the financial disclosure template.

(b) (6), (b) (4) for Protocol (b) (6), received in excess of \$25,000 from Novartis for a research grant used to study patients with inflammatory syndromes. (b) (6) for Protocol (b) (6), received in excess of \$25,000 from Novartis for research grants. (b) (6), (b) (4) for Protocol (b) (6), has not received funds from Novartis, but does have a patent on the (b) (4), (b) (6), one of the patient evaluation tools used in Protocol (b) (6). It is unlikely that the participation of the aforementioned investigators in the clinical development program adversely impacted the outcome of the study given their limited involvement. Potential for bias was further minimized by using multiple investigators in this randomized, double-blind, placebo-controlled study.

### 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

There were no significant efficacy or safety issues related to other review disciplines for the current submission.

## 4.1 Chemistry Manufacturing and Controls

Canakinumab is available as powder for solution for injection, as a lyophilisate form that is reconstituted with Water for Injections for subcutaneous administration at 150 mg/mL. <sup>(b) (4)</sup>

<sup>(b) (4)</sup> A new presentation solution for injection in vial has been developed and used in Study N2301. Based on the comparability between the presentations, irrespective of market image, <sup>(b) (4)</sup> can be used across the indications. The new formulation, 150 mg/mL solution for injection in vial, has been reviewed in a separate supplement (BLA 125319/88) to this BLA. Based on CMC and PK data, the solution for injection in vial and lyophilized powder appeared comparable. The supplement received a complete response on July 29, 2016, for microbiology deficiencies.

## 4.2 Clinical Pharmacology

- The PK characteristics of canakinumab observed in colchicine-resistant/intolerant Familial Mediterranean Fever (crFMF), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) and Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) patients are consistent with those observed in other approved indications. Serum clearance of canakinumab and its volume of distribution were dependent only on body weight. No clinically significant impact of age, gender or ethnicity on canakinumab pharmacokinetics was identified. No dose adjustment is needed in patients with renal or hepatic impairment.
- Baseline IL-1 $\beta$  levels were generally higher in HIDS/MKD patients. An increase in total IL-1 $\beta$  was observed in crFMF, HIDS/MKD and TRAPS patients, indicating successful binding of canakinumab to its target.
- An exposure-response model for the probability of flare suggested a difference in drug sensitivity between disease cohorts, especially in HIDS/MKD and TRAPS patients.
- There was no observed association between hematology abnormalities (CTCAE grade > 1) and canakinumab concentrations in crFMF, HIDS/MKD and TRAPS patients.
- The incidence of treatment-emergent anti-drug antibodies (ADA) in crFMF, HIDS/MKD and TRAPS patients was very low (< 1%) and not associated with AEs, loss of efficacy or change in PK.

### 4.2.1 Pharmacodynamics

Canakinumab binding to human IL-1 $\beta$  neutralizes its bioactivity and results in the formation of a canakinumab-IL-1 $\beta$  complex. Since the complex is cleared slower than the free IL-1 $\beta$ , an

increase in total IL-1 $\beta$  indicating successful binding is observed in crFMF, HIDS/MKD and TRAPS patients in Study N2301.

With the small sample size, variability in time to up-titration and up-titration being driven by clinical responsiveness, direct assessment of the doses against each other is not appropriate in this trial. Canakinumab treatment was associated with a decrease of IL-1 $\beta$ -induced downstream mediators, including the acute phase proteins CRP and SAA. This adds to the evidence that canakinumab neutralizes the activity and down-regulates the production of IL-1 $\beta$  in vivo.

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 ADA were detected in any patient in Study N2301. Two patients (one crFMF and one TRAPS) in the Phase 2 studies had treatment-emergent ADA, with no link to adverse events (AEs), loss of efficacy or change in PK.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials Table 1: Pivotal phase 3 study

| Study                                      | Design                                                                                                                                                                                                       | Treatments & Durations                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Main safety variables                                                                                                                                                                                                          |
|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal Phase 3 study (controlled)*</b> |                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                |
| <b>N2301</b><br>(28 mo)                    | Placebo-controlled, randomized double-blind, efficacy/safety study in crFMF, HIDS/MKD, and TRAPS (Epochs 1 and 2), then randomized withdrawal or lower dosing (Epoch 3), then open label treatment (Epoch 4) | <p><b>Epoch 1: screening</b> (12 wks):<br/>N=280</p> <p><b>Epoch 2: randomized treatment **</b> (16 wks) (completed):<br/>150 mg (2mg/kg if ≤40 kg) sc q4 wks or placebo (blinded)<br/>N=185*</p> <p><b>Epoch 3: randomized withdrawal</b> (24 wks) (ongoing):<br/>150 mg (2mg/kg if ≤40 kg) sc q8 wks or placebo (blinded)<br/>N=170 from Epoch 2 + 18 TRAPS roll-over</p> <p><b>Epoch 4: open label treatment***</b> (72 wks) (ongoing):<br/>150 mg or 300 mg sc q4 or q8 wks (open-label)</p> | <p>-rate/type/severity/causality of AEs</p> <p>- rates/types of deaths/serious adverse events (SAEs)/AE discontinuations</p> <p>- laboratory, vital sign &amp; ECG data</p> <p>- subgroup analyses</p> <p>- immunogenicity</p> |

Patients ≤40 kg were dosed by kg of body weight, patients >40 kg received a fixed dose.

\* Study is ongoing; data cut-off date was 25-Aug-2015 (last patient last visit for the Week 16 primary endpoint analysis). Safety variables were assessed through the end of Epoch 2. N=185 in Epoch 2 (181 randomized patients and 4 non-randomized patients).

\*\*During Epoch 2, patients who experienced persistent mild, moderate or severe disease activity (PGA ≥2 or CRP >10 mg/L with less than 40% reduction from baseline from day 8 to day 14, then 70% reduction from baseline from day 15 to day 28) were able to receive a single add-on sc injection of 150 mg canakinumab (or 2 mg/kg for patients ≤40 kg) as blinded escape option from Day 8 to Day 28. For these patients, up-titration to 300 mg canakinumab q4w was initiated from Day 29 onward. At the discretion of the investigator, they were permitted to remain in the study and receive 300 mg canakinumab (or 4 mg/ kg for patients weighing ≤ 40 kg) q4w.

\*\*\* Number of patients who entered Epoch 4 is not yet available as Epoch 3 is ongoing at the time of reporting.

Source: [Study N2301 Week 16-Section 9.1]

Source: Sponsor's submission

### 5.2 Review Strategy

There are three sBLA supplements being provided by Novartis to the ILARIS® BLA 125319 in close sequence to support registration of three periodic fever syndromes:

- Supplement 85: New indication, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)
- Supplement 86: New indication, Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD)

- Supplement 87: New Indication, colchicine-resistant Familial Mediterranean Fever (crFMF)

As discussed above, the periodic fevers are severe conditions for which few treatments are available, with only FMF having an FDA-approved therapy, colchicine, available. Otherwise, at the time that this pivotal study was initiated, the standard of care for patients consisted largely of non-approved therapies including NSAIDs and high-dose corticosteroids. However, as described below, the sponsor was able to conduct a single-dose, placebo-controlled study that was adequately designed to demonstrate a clinically meaningful difference between canakinumab and placebo. In general, the data contained in the sponsor's submission, including the design, conduct, and analyses of the study are acceptable. Nonetheless, as most placebo subjects, as well as many canakinumab subjects, underwent "blinded escape" as early as Day 8, the extent of treatment comparison is limited, especially at later time points. Thus, in addition to the pre-specified primary and secondary analyses, the FDA review team examined endpoints at time points earlier than 16 weeks. Given the limitations in the data at 16 weeks, when the vast majority of patients were on canakinumab, an argument can be made that any efficacy summarized in the proposed label should be limited to the Resolution of Index Flare.

One pivotal Phase 3 trial was conducted to support the current submission. As discussed in greater detail below, Study N2301 was a randomized, placebo-controlled study (Epoch 2), comparing subjects treated with canakinumab 150 mg (2 mg/kg if  $\leq 40$  kg) and subjects treated with placebo in children and adults with active crFMF, HIDS/MKD, or TRAPS a 24-week randomized withdrawal phase (Epoch 3), with subjects re-randomized to placebo or canakinumab 150 mg q 8 weeks, and a 72-week open-label treatment phase (Epoch 4). In the current submission, the sponsor provided efficacy data from Epoch 2 (16 weeks).

A dosing schedule of 150 mg sc q4w (or 2 mg/kg sc q4w for patients weighing  $\leq 40$  kg) has been demonstrated to be highly effective in three PoC open-label studies: one study in patients with TRAPS (Study D2203) and two studies in patients with crFMF (Study DTR01, adult and pediatric patients; Study D2204, pediatric patients) (Table 2). In addition, a higher dose (300 mg or 4 mg/kg) with a longer dosing interval (every 6 weeks) was shown to be effective in HIDS/MKD patients (Study D2402). In Study N2301, the initial dosing regimen of 150 mg sc (or 2 mg/kg sc for patients weighing  $\leq 40$  kg) q4w was utilized to harmonize exposure between the three conditions while allowing for up-titration to a maximal dose of canakinumab 300 mg (or 4 mg/kg for patients weighing  $\leq 40$  kg) q4w to optimize the regimen and achieve efficacy in difficult cases. The sponsor hypothesizes that dose regimens used for open-label treatment (across Epochs 2 to 4) were considered to constitute the lowest clinically efficacious doses to maintain clinical efficacy in individual patients. 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  $\leq 40$  kg) at a reduced frequency of every 8 weeks (q8w) was evaluated during the randomized withdrawal epoch (Epoch 3); Epoch 3 will be reported separately when the data become available.

Given that the aforementioned pilot studies were not designed as dose-ranging studies, and that no data were used to support efficacy, formal review of these studies will not be included in this document. However, the subjects from these studies were included in the safety evaluation.

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

| <b>Study</b><br><i>Dates</i>             | <b>Patients</b>             | <b>Dose/Study design</b>                                                                                                                                            | <b>N</b> | <b>Duration</b> | <b>Results</b>                                                                                                                                                                                                              |
|------------------------------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| DTR01<br><i>Dec 2010-<br/>Oct 2011</i>   | crFMF (ages 12 to 75 years) | <b>canakinumab 150 mg</b> (2mg/kg if <40 kg) scq4 wks or 300 mg (4 mg/kg if <40 kg) s.c. if $\geq 1$ new flare during treatment period (3 mo)<br>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.<br><br>5/9 patients experienced an attack within the 2-month follow-up period (median time to flare was 71 days) |
| D2204<br><i>Dec 2010-<br/>Feb 2012</i>   | crFMF (4 to 20 years)       | <b>canakinumab 150 mg</b> (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)<br>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<br><br>5/7 patients experienced a relapse during the withdrawal period (median time to flare was 25 days)          |
| D2402<br><i>March 2011-<br/>Jul 2014</i> | HIDS/MKD ( $\geq 2$ years)  | <b>canakinumab 300 mg</b> (4mg/kg if $\leq 40$ kg) sc q6 wks* (6 mo)<br>Withdrawal (6 mo)<br><b>canakinumab 300 mg</b> (4mg/kg if $\leq 40$ 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<br><br>7/9 patients flared during the withdrawal period (median time to flare 110 days) |
| D2203<br><i>Oct 2010-</i>                | TRAPS ( $\geq 4$ years)     | <b>canakinumab 150 mg</b> (2mg/kg if $\leq 40$ kg) sc q4 wks in addition to a single dose escalation                                                                | 20       | 33 mo           | 19/20 (95%) of patients achieved complete or almost complete response at Day 15                                                                                                                                             |

|                         |  |                                                                                                                                                                                  |  |                                                                                                               |
|-------------------------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|---------------------------------------------------------------------------------------------------------------|
| <p><i>June 2014</i></p> |  | <p>up to 300 mg (4 mg/kg if <math>\leq 40</math> kg) in nonresponders at Day 8 (4 mo)<br/>         Withdrawal (5 mo)<br/> <b>canakinumab 150 or 300 mg</b> sc q4 wks (24 mo)</p> |  | <p>20/20 (100%) of patients relapsed during the 5-month follow-up period (median time to flare 91.5 days)</p> |
|-------------------------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|---------------------------------------------------------------------------------------------------------------|

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  $\leq 40$  kg) dose at the moment of flare, and would have received 450 mg (6 mg/kg for patients  $\leq 40$  kg) every 6 weeks thereafter starting at Week 6.

The safety of canakinumab at the doses utilized in Study N2301 is supported by clinical and post-marketing safety data from CAPS using doses up to 600 mg (or 8 mg/kg) q8w and from SJIA clinical trials which utilized higher starting doses of 4 mg/kg q4w. This study included patients as young as 2 years old in the randomized population and > 28 days but < 2 years old in the non-randomized group in Epoch 2. Study N2301 used the same initial dosing schedule as recommended for CAPS pediatric patients but with a shorter interval of administration (150 mg or 2 mg/kg q4w), with the possibility to up-titrate based on the early assessment of clinical response.

The study utilized the following clinical endpoints and measures of disease activity to assess subjects' response to treatment:

- Primary Endpoint
  - Proportion of responders within each cohort.
    - Responders: patients who had resolution of their index flare at Day 15 and did not experience a new flare from the time of the resolution of the index flare until the end of Epoch 2.
    - Resolution of index flare: PGA < 2, and CRP  $\leq 10$  mg/L, or reduction  $\geq 70\%$  from baseline  
 (New flare: PGA  $\geq 2$  and CRP  $\geq 30$  mg/L)
- Secondary Endpoints
  - %patients who achieved a PGA < 2 at Week 16
  - %patients with serologic remission at Week 16 (CRP  $\leq 10$  mg/L)
  - %patients with a normalized SAA level at Week 16 (SAA  $\leq 10$  mg/L)

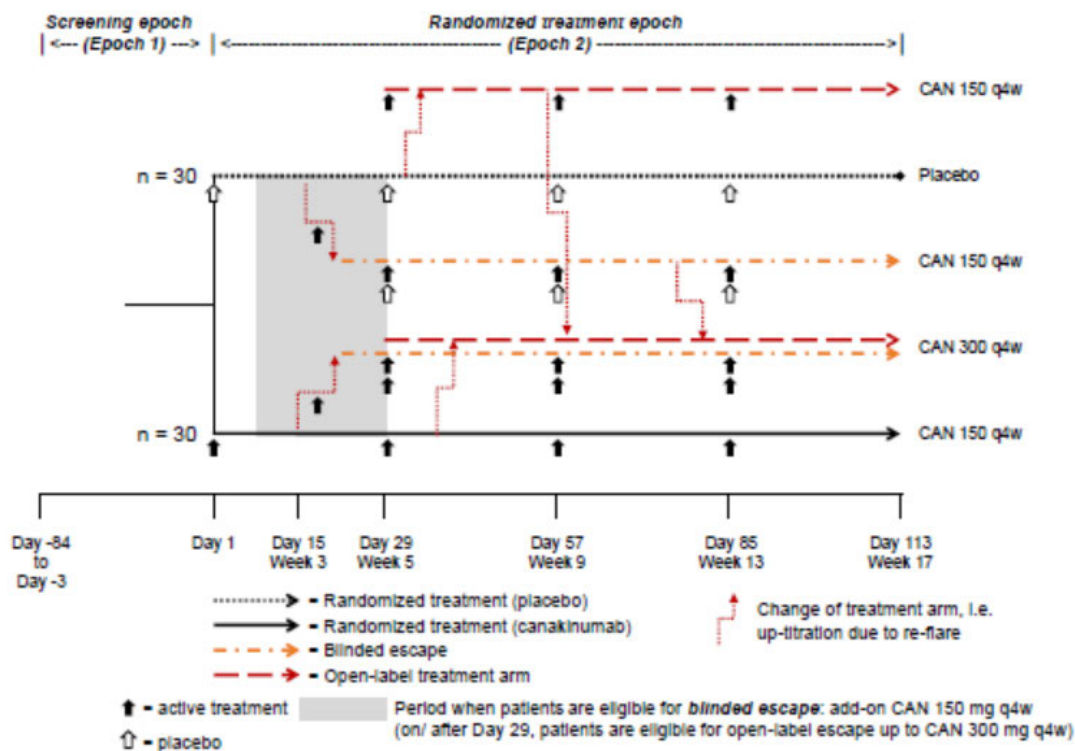
While these endpoints are acceptable, statistical issues were identified during the review that potentially limited interpretation of endpoints, such that, as most placebo subjects, as well as many canakinumab subjects, underwent “blinded escape” as early as Day 8, the extent of treatment comparison is limited, and an argument can be made that any efficacy summarized in the proposed label should be limited to the Resolution of Index Flare. For a detailed review of the statistical limitations, the reader is referred to the Division of Biometrics review for this application.

### **5.3 Discussion of Individual Studies/Clinical Trials**

One pivotal Phase 3 trial, CACZ885N2301 (N2301), was conducted to support all three clinical supplements. Study N2301 was a randomized, double-blind, placebo-controlled study comparing subjects treated with canakinumab 150 mg (2 mg/kg if  $\leq 40$  kg) and subjects treated with placebo in children with active crFMF, HIDS/MKD, or TRAPS (Epoch 2), a 24-week randomized withdrawal phase, with subjects re-randomized to placebo or canakinumab 150 mg q 8 weeks (Epoch 3), and a 72-week open-label treatment phase (Epoch 4). A total of 181 patients were randomized (46 TRAPS, 72 HIDS, and 63 crFMF) in sites in Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, Russia, Spain, Switzerland, Turkey, United Kingdom, and United States. The study was initiated in June 2014 and is ongoing at the cutoff date of August 25, 2015.

External, independent, and respective Malignancy Adjudication and Infection Adjudication committees were formed on the program level to review pertinent data from this trial. A Data Monitoring Committee was not required. An overview of the study is shown (Figure 1):

**Figure 1: Design of Study N2301**



Source: Sponsor's submission

Subjects who experienced persistent “mild,” “moderate,” or “severe” disease activity (i.e.,  $PGA \geq 2$  [clinical flare]) or CRP persistently  $> 10$  mg/L with less than 40% reduction from baseline from Day 8 to Day 14 were able to receive a single add-on sc injection of canakinumab (150 mg sc [or 2 mg/kg for patients  $\leq 40$  kg]) as a blinded escape option. Patients whose index flare did not resolve, or who had persistent disease activity from Day 15 up to Day 28 ( $PGA \geq 2$  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  $\leq 40$  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 was used until Day 29. Of note, any patient who received blinded add-on canakinumab was considered a non-responder 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  $\leq 40$  kg) q4w was initiated from Day 29 onward (these patients were also considered non-responders for the purpose of the primary analysis). These patients were not eligible for further up-titration. However, at the discretion of the investigator, they were permitted to remain in the study and receive canakinumab 300 mg (or 4 mg/kg for patients weighing  $\leq 40$  kg) q4w.

**Study population:**

The study population consisted of male and female patients  $\geq 2$  years of age at the time of the screening visit for the randomized cohorts, and patients  $> 28$  days but  $< 2$  years old for the nonrandomized treatment arm.

For randomized crFMF patients: diagnosis of type 1 FMF disease according to Tel Hashomer criteria but no active flare at the time of screening, at least one of the known MEFV gene exon 10 mutations, and one of the following two criteria: documented active disease despite colchicine therapy or documented intolerance to effective doses of colchicine. At randomization, patients must have had acute crFMF flare characterized by inflammation and serositis, and active clinical crFMF flare as evidenced by  $\text{PGA} \geq 2$ , and  $\text{CRP} > 10 \text{ mg/L}$ .

For randomized HIDS patients: clinical diagnosis of HIDS but no active flare at the time of screening, genetic/enzymatic diagnosis of HIDS, and prior documented history of  $\geq 3$  febrile acute HIDS flares in a six-month period when not receiving prophylactic treatment. At randomization, patients must have had active clinical HIDS flare as evidenced by  $\text{PGA} \geq 2$  and  $\text{CRP} > 10 \text{ mg/L}$ .

For randomized TRAPS patients: clinical diagnosis of TRAPS but no active flare at the time of screening, mutation of the TNFRSF1A gene, and chronic or recurrent disease activity periodicity. At randomization, patients must have had active clinical TRAPS flare as evidenced by  $\text{PGA} \geq 2$  and  $\text{CRP} > 10 \text{ mg/L}$ .

Major exclusion criteria for the study included:

- Use of the following therapies (within varying protocol defined timeframes): Corticosteroids (oral prednisone)  $> 0.2 \text{ mg/kg/day}$  (or greater than the maximum of  $15 \text{ mg/day}$  for children over  $60 \text{ kg}$ ), anakinra, canakinumab, rilonacept, tocilizumab, TNF inhibitors, abatacept, tofacitinib, rituximab, leflunomide, thalidomide, cyclosporine, intravenous immunoglobulin, 6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil, intraarticular, peri-articular or intramuscular corticosteroid injections, any other investigational biologics
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated
- Significant medical diseases, including but not limited to the following:
  - a. History of organ transplantation
  - b. Elevated alanine aminotransferase (ALT)  $\geq 2 \times 3 \times \text{ULN}$
  - c. Elevated aspartate aminotransferase (AST)  $\geq 2 \times 3 \times \text{ULN}$
  - d. Increase in total bilirubin defined as per Common Terminology Criteria (CTC) Grade  $\geq 2$
  - e. Serious hepatic disorder (Child-Pugh scores B or C)
  - f. Chronic Kidney Disease as per NKF stages  $\geq 4$
  - g. Thyroid disease

- h. Diagnosis of active peptic ulcer disease
- i. Coagulopathy
- j. Significant CNS effects including vertigo and dizziness
- Any conditions or significant medical problems which immunocompromise the patient and/ or places the patient at unacceptable risk for immunomodulatory therapy, e.g.
  - a. Absolute neutrophil count decreased as per CTC Grade  $\geq 1$
  - b. Thrombocytopenia CTC Grade  $\geq 1$
  - c. Any active or recurrent bacterial, fungal (with exception of onychomycosis) or viral infection
  - d. HIV infection, Hepatitis B or Hepatitis C infections
  - e. Presence of tuberculosis
  - f. Requirement for administration of antibiotics against latent TB
  - g. Clinical evidence or history of multiple sclerosis or other demyelinating diseases, or Felty's syndrome
- Live vaccinations within 3 months prior to the start of the trial, during the trial, and up to 3 months following the last dose

### **Endpoints:**

The primary endpoint of the trial was predefined as the proportion of responders within each cohort, responders defined as subjects who had resolution of their index flare at Day 15 and did not experience a new flare from the time of the resolution of the index flare until the end of Epoch 2. Resolution of index flare was defined as PGA  $< 2$ , and CRP  $\leq 10$  mg/L, or reduction  $\geq 70\%$  from baseline. (New flare was defined as PGA  $\geq 2$  and CRP  $\geq 30$  mg/L.)

Major secondary efficacy endpoints were prespecified and analyzed in the following order:

- % subjects who achieved a PGA  $< 2$  at Week 16
- % subjects with serologic remission at Week 16 (CRP  $\leq 10$  mg/L)
- % subjects with a normalized SAA level at Week 16 (SAA  $\leq 10$  mg/L)

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-acute 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)

### ***Brief Description of Efficacy Endpoints***

#### ***Physician 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  $\geq 38^{\circ}\text{C}$  [ $100.4^{\circ}\text{F}$ ]), 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 ( $\leq 10$  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  $\geq 2$  (clinical flare)
- CRP  $\geq 30$  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,  $\geq 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ); (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<sup>1</sup> 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<sup>®</sup> 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).

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<sup>1</sup> Piram M, et al (2014) Ann Rheum Dis; 73:2168-73.

These endpoints were assessed at time points as presented in Table 3 below.

**Table 3: Table of assessments.**

**Screening epoch (Epoch 1) and randomized treatment epoch (Epoch 2)**

| Epoch                                                                                                                                                        | Screening (Epoch 1) | Randomized treatment epoch (Epoch 2) |     |     |     |     |                 |                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------|-----|-----|-----|-----|-----------------|------------------------------------------------------|
| Visit                                                                                                                                                        | 1                   | 101                                  | 102 | 103 | 104 | 105 | 199 and/ or PSW | Safety follow-up                                     |
| Week                                                                                                                                                         |                     | 1                                    | 3   | 5   | 9   | 13  | 17              |                                                      |
| Day                                                                                                                                                          | -84 to -3           | 1                                    | 15  | 29  | 57  | 85  | 113             | PSW +30 or 8 weeks after last injection <sup>1</sup> |
| Informed consent                                                                                                                                             | X                   |                                      |     |     |     |     |                 |                                                      |
| Informed consent for pharmacogenetic sampling <sup>2</sup>                                                                                                   | X                   |                                      |     |     |     |     |                 |                                                      |
| Participation in previous study CACZ885D2203/ MPP treatment plan CAC/885D2207M                                                                               | X                   |                                      |     |     |     |     |                 |                                                      |
| Demography                                                                                                                                                   | X                   |                                      |     |     |     |     |                 |                                                      |
| Inclusion/Exclusion Criteria                                                                                                                                 | X                   | X                                    |     |     |     |     |                 |                                                      |
| Relevant medical history/ current medical conditions                                                                                                         | X                   |                                      |     |     |     |     |                 |                                                      |
| Prior and concomitant medications (including vaccination status)                                                                                             | X                   | X                                    | X   | X   | X   | X   | X               |                                                      |
| Surgical and medical procedures                                                                                                                              | X                   | X                                    | X   | X   | X   | X   | X               |                                                      |
| Disease characteristics                                                                                                                                      | X                   |                                      |     |     |     |     |                 |                                                      |
| Determination of TB status: QuantiFERON <sup>®</sup> -TB Gold in Tube (QFT-GIT) assay, PPD skin test and/ or chest X-ray (as stipulated by local guidelines) | X                   |                                      |     |     |     |     |                 |                                                      |
| Hepatitis B and C screen                                                                                                                                     | X                   |                                      |     |     |     |     |                 |                                                      |
| HIV screen                                                                                                                                                   | X                   |                                      |     |     |     |     |                 |                                                      |
| Pregnancy test – Serum*                                                                                                                                      | X                   |                                      |     |     |     |     |                 |                                                      |

| Epoch                                                                               | Screening (Epoch 1) | Randomized treatment epoch (Epoch 2) |     |     |                |     |                 |                                                      |
|-------------------------------------------------------------------------------------|---------------------|--------------------------------------|-----|-----|----------------|-----|-----------------|------------------------------------------------------|
| Visit                                                                               | 1                   | 101                                  | 102 | 103 | 104            | 105 | 199 and/ or PSW | Safety follow-up                                     |
| Week                                                                                |                     | 1                                    | 3   | 5   | 9              | 13  | 17              |                                                      |
| Day                                                                                 | -84 to -3           | 1                                    | 15  | 29  | 57             | 85  | 113             | PSW +30 or 8 weeks after last injection <sup>1</sup> |
| (for females of child bearing potential)                                            |                     |                                      |     |     |                |     |                 |                                                      |
| Pregnancy test – Urinalysis (for females of child bearing potential)                |                     | X                                    |     |     |                |     |                 |                                                      |
| Physical examination*                                                               | S                   | S                                    |     | S   | S              | S   | S               |                                                      |
| Height                                                                              | X                   |                                      |     |     | X <sup>3</sup> |     | X <sup>3</sup>  |                                                      |
| Weight*                                                                             | X                   | X                                    | X   | X   | X              | X   | X               |                                                      |
| Blood pressure and pulse*                                                           | X                   | X                                    | X   | X   | X              | X   | X               |                                                      |
| Body temperature*                                                                   | X                   | X                                    | X   | X   | X              | X   | X               |                                                      |
| ECG*                                                                                | X                   |                                      |     |     |                |     | X               |                                                      |
| Index flare onset                                                                   |                     | X                                    |     |     |                |     |                 |                                                      |
| PGA                                                                                 | X                   | X                                    | X   | X   | X              | X   | X               |                                                      |
| Physician's severity assessment of key disease-specific signs and symptoms          |                     | X                                    | X   | X   | X              | X   | X               |                                                      |
| Review eDiary instructions                                                          | S                   |                                      |     |     |                |     |                 |                                                      |
| PPGA <sup>4</sup>                                                                   | X                   | X                                    | X   | X   | X              | X   | X               |                                                      |
| AIDAI <sup>4</sup>                                                                  | X                   | X                                    | X   | X   | X              | X   | X               |                                                      |
| SF-12 <sup>®</sup> (to be completed by patients ≥18 years of age at Baseline)       |                     | X                                    |     | X   |                |     | X               |                                                      |
| CHQ-PF50 <sup>®</sup> (to be completed by patients >5 <18 years of age at Baseline) |                     | X                                    |     | X   |                |     | X               |                                                      |
| SDS v3                                                                              |                     | X                                    |     |     |                |     | X               |                                                      |

| Epoch                                                      | Screening<br>(Epoch 1) | Randomized treatment epoch<br>(Epoch 2) |     |     |     |     |                 |                                                            |
|------------------------------------------------------------|------------------------|-----------------------------------------|-----|-----|-----|-----|-----------------|------------------------------------------------------------|
| Visit                                                      | 1                      | 101                                     | 102 | 103 | 104 | 105 | 199 and/<br>PSW | Safety<br>follow-up                                        |
| Week                                                       |                        | 1                                       | 3   | 5   | 9   | 13  | 17              |                                                            |
| Day                                                        | -84 to -3              | 1                                       | 15  | 29  | 57  | 85  | 113             | PSW +30 or 8<br>weeks after last<br>injection <sup>1</sup> |
| Hematology*                                                | X                      | X                                       | X   | X   | X   | X   | X               |                                                            |
| Blood chemistry*                                           | X                      | X                                       | X   | X   | X   | X   | X               |                                                            |
| Urinalysis*                                                | X                      | X                                       | X   | X   | X   | X   | X               |                                                            |
| CRP (local lab)*                                           | X                      | X                                       | X   | X   | X   | X   | X               |                                                            |
| SAA*                                                       | X                      | X                                       | X   | X   | X   | X   | X               |                                                            |
| PD sample (total IL-1β)*<br>(pre-dose)                     |                        | X                                       | X   | X   | X   | X   | X               |                                                            |
| PK sample (canakinumab)*<br>(pre-dose)                     |                        | X                                       | X   | X   | X   | X   | X               |                                                            |
| IG sample* (pre-dose)                                      |                        | X                                       |     | X   |     |     | X               |                                                            |
| Pharmacogenetic sample <sup>2</sup>                        |                        | X                                       |     |     |     |     |                 |                                                            |
| Contact IRT*                                               | X                      | X                                       | X   | X   | X   | X   | X               |                                                            |
| Administration of double-blind randomized<br>treatment     |                        | X                                       |     | X   | X   | X   |                 |                                                            |
| Administration of blinded-escape<br>treatment <sup>3</sup> |                        |                                         | X   | X   | X   | X   |                 |                                                            |
| Administration of open-label treatment <sup>4</sup>        |                        |                                         |     | X   | X   | X   |                 |                                                            |
| Adverse events*                                            |                        | X                                       | X   | X   | X   | X   | X               |                                                            |
| Local tolerability*                                        |                        | X                                       | X   | X   | X   | X   | X               |                                                            |
| Screening phase disposition form                           |                        | X                                       |     |     |     |     |                 |                                                            |
| Study phase completion form                                |                        |                                         |     |     |     |     | X               |                                                            |
| Follow-up visit or phone call for SAEs*                    |                        |                                         |     |     |     |     |                 | X                                                          |

TD = Investigational treatment discontinuation

PSW = Premature subject withdrawal

X = assessment to be recorded on clinical data base

S = assessment to be recorded on source documentation

\*These assessments are also to be conducted for patients who discontinue

<sup>#</sup>These assessments are source documentation only and will not be entered into the CRF

<sup>1</sup> To be performed 30 days following Day 113 or PSW or 8 weeks after last injection of investigational drug, whichever is later for all patients **not** entering Epoch 3

<sup>2</sup> Only applicable for patients > 16 years of age

<sup>3</sup> Only applicable for pediatric patients

<sup>4</sup> The AIDAI and PPGA will be completed by the patient on an electronically diary daily from Screening till TD or PSW

<sup>5</sup> Applicable for patients whose index flare has not resolved by Day 15. Blinded-escape add-on treatment may be initiated between Day 8 and Day 28

<sup>6</sup> Applicable for patients on randomized treatment who flare on/ after Day 29 or patients on blinded-escape who will still have "mild", "moderate" or "severe" disease activity (PGA ≥2 [clinical flare] and CRP ≥30 mg/L [serological flare]) or re-flare

Source: Sponsor's submission

### Sample Size Considerations:

A Fisher's exact test with a 2.5% one-sided significance level would have 90% power to detect a between-treatment difference of 45%, assuming that the proportion of responders for the canakinumab treatment group is 0.65 and the proportion of placebo responders is 0.2 when the sample size per treatment arm is 28, rounded to 30 per treatment arm and per disease cohort (i.e., a total of total 180 patients). Since a 20% screening failure rate was expected, it was estimated that approximately 225 patients would have to be screened. A full review of the statistical methods is contained in the Division of Biometrics review.

### Protocol Amendments:

Protocol Amendments were made for the study as outlined below:

- Protocol Amendment #1 notified the Agency of a new investigator at Center 1206.

- Protocol Amendment #2 was written to address the request From the Pediatric Committee (PDCO) at the European Medicines in the framework of respective Pediatric Investigational Plans to include patients > 28 days in the clinical trial compared to the previously  $\geq 2$  years of age. Patients > 28 days but < 2 years old were allowed to enter the study directly into the open-label arm of Epoch 2, but would not be considered toward the total number of patients enrolled for the primary efficacy and safety analyses. The amendment also provided clarity on the management of randomized and non-randomized cohorts in accordance with clinical practice. (Further, the cover letter for this amendment noted that “Amendment 1” was a “non-substantial” amendment first implemented in the United Kingdom and was not submitted to the Agency, issued to address the request from the Medicines and Healthcare Products Regulatory Agency in the United Kingdom to refer to local label requirements for birth control in females of child-bearing potential when treated with canakinumab.)
- Protocol Amendment #3 notified the Agency of a new investigator at Center 1204.
- Protocol Amendment #4 notified the Agency of Form 1572 changes.

Overall, these amendments are not expected to bias or affect the interpretation of the results of the study.

## 6 Review of Efficacy

### Efficacy Summary

The primary efficacy data derives from the phase 3 study N2301. Study N2301 was a four-part study, consisting of a screening period (Epoch 1), a 16-week, randomized, double-blind, placebo-controlled treatment phase (Epoch 2) comparing a single dose of canakinumab 150 mg (2 mg/kg if  $\leq 40$  kg) versus placebo in children and adults with active crFMF, HIDS/MKD, or TRAPS, a 24-week randomized withdrawal phase (Epoch 3) with subjects re-randomized to placebo or canakinumab 150 mg q 8 weeks, and a 72-week open-label treatment phase (Epoch 4). In this submission, the sponsor provided data from the 16-week randomized, double-blind placebo-controlled treatment phase (Epoch 2). The study was adequately designed and conducted to allow for interpretation of the effect of canakinumab in patients with crFMF, HIDS/MKD, or TRAPS.

Review of the data demonstrated that the study met the pre-specified primary endpoint with a greater proportion of canakinumab-treated subjects responders compared to placebo in each cohort. The results were consistent regardless of age, gender, prior use of biologics and concomitant use of colchicine (for the crFMF cohort). Specifically, more subjects achieved a complete response with canakinumab than with placebo: TRAPS, 45% versus 8%; HIDS/MKD, 35% versus 6%; crFMF, 61% versus 6%. Also, more subjects in the canakinumab group

resolved their index flare at Day 15 compared with placebo: TRAPS, 64% versus 23%; HIDS/MKD, 65% versus 37%; crFMF, 81% versus 31%.

These data demonstrated a significant and clinically meaningful therapeutic effect of canakinumab in subjects with active TRAPS, HIDS/MKD, and crFMF. The data were further supported by subgroup and sensitivity analyses and testing of the major secondary endpoints, which showed that canakinumab's therapeutic effect was consistent across subgroups and measures of disease activity.

However, as switching and up-titration was allowed, there is a concern surrounding treatment comparison. Blinded escape was allowed before Day 29, and most placebo subjects switched to canakinumab 150 mg every 4 weeks: TRAPS, 75%; HIDS/MKD, 32%; crFMF, 16%.

There was in fact a high proportion of patients initially randomized to placebo who crossed over to canakinumab, an indication that this limits efficacy (and safety) comparisons given the lack of comparator group. Patients who crossed over from placebo to canakinumab, or who up-titrated the dose of canakinumab, or who discontinued the study, were considered non-responders in the primary analysis.

In terms of the efficacy of increasing the dose from 150 mg to 300 mg, this study was not designed to reliably evaluate the potential benefit of up-titration, as there was no control group of patients who had persistent disease activity/flare but remained on the 150 mg dose. Therefore, it is difficult to determine if differences over time in patients who up-titrated were due to differences between the doses. Nonetheless, there was supportive evidence of efficacy for canakinumab, as compared to placebo, for the components of the primary endpoint, CRP and PGA score, as well as for the secondary endpoint, SAA level.

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).

## 6.1 Indication

The current submission for canakinumab is to support the following orphan indications:

- 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 Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in patients aged 2 years and older.
- Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS) in patients aged 2 years and older.

### **6.1.1 Methods**

Refer to Section 5.3 for discussion of Study N2301 trial design. Study N2301 served as the critical trial for the evaluation of the efficacy of canakinumab in the treatment of FMF, HIDS/MKD, and TRAPS. This study was well-controlled and utilized endpoints that assessed clinically important manifestations of the disease.

### **6.1.2 Demographics**

The patients included in this trial are representative of the typical respective periodic fever patient populations. Baseline disease characteristics were also consistent with active disease. The baseline demographics and background characteristics for the pivotal study are summarized below (Table 4).

**Table 4: Baseline demographics and background characteristics for Study N2301**

| Characteristic                          | TRAPS<br>ACZ885<br>N=22 | TRAPS<br>Placebo<br>N=24 | HIDS<br>ACZ885<br>N=37 | HIDS<br>Placebo<br>N=35 | crFMF<br>ACZ885<br>N=31 | crFMF<br>Placebo<br>N=32 | Total<br>ACZ885<br>N=90 | Total<br>Placebo<br>N=91 |
|-----------------------------------------|-------------------------|--------------------------|------------------------|-------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
| <b>Age group (years) - n (%)</b>        |                         |                          |                        |                         |                         |                          |                         |                          |
| >=2 - <4                                | 1 (4.5)                 | 2 (8.3)                  | 4 (10.8)               | 1 (2.9)                 | 1 (3.2)                 | 0                        | 6 (6.7)                 | 3 (3.3)                  |
| >=4 - <6                                | 2 (9.1)                 | 2 (8.3)                  | 3 (8.1)                | 9 (25.7)                | 1 (3.2)                 | 1 (3.1)                  | 6 (6.7)                 | 12 (13.2)                |
| >=6 - <12                               | 6 (27.3)                | 4 (16.7)                 | 11 (29.7)              | 9 (25.7)                | 7 (22.6)                | 3 (9.4)                  | 24 (26.7)               | 16 (17.6)                |
| >=12 - <18                              | 5 (22.7)                | 5 (20.8)                 | 10 (27.0)              | 7 (20.0)                | 5 (16.1)                | 11 (34.4)                | 20 (22.2)               | 23 (25.3)                |
| >=18 - <65                              | 7 (31.8)                | 11 (45.8)                | 9 (24.3)               | 9 (25.7)                | 17 (54.8)               | 16 (50.0)                | 33 (36.7)               | 36 (39.6)                |
| >=65                                    | 1 (4.5)                 | 0                        | 0                      | 0                       | 0                       | 1 (3.1)                  | 1 (1.1)                 | 1 (1.1)                  |
| <b>Age (years)</b>                      |                         |                          |                        |                         |                         |                          |                         |                          |
| n                                       | 22                      | 24                       | 37                     | 35                      | 31                      | 32                       | 90                      | 91                       |
| Mean                                    | 21.0                    | 23.6                     | 13.0                   | 13.9                    | 22.5                    | 21.8                     | 18.2                    | 19.3                     |
| SD                                      | 19.22                   | 18.25                    | 8.49                   | 11.64                   | 15.02                   | 13.38                    | 14.56                   | 14.71                    |
| Min                                     | 3.0                     | 2.0                      | 2.0                    | 3.0                     | 2.0                     | 4.0                      | 2.0                     | 2.0                      |
| Median                                  | 13.5                    | 16.5                     | 12.0                   | 9.0                     | 18.0                    | 18.0                     | 14.5                    | 15.0                     |
| Max                                     | 76.0                    | 57.0                     | 43.0                   | 47.0                    | 60.0                    | 69.0                     | 76.0                    | 69.0                     |
| <b>Sex - n (%)</b>                      |                         |                          |                        |                         |                         |                          |                         |                          |
| Female                                  | 10 (45.5)               | 13 (54.2)                | 24 (64.9)              | 19 (54.3)               | 14 (45.2)               | 15 (46.9)                | 48 (53.3)               | 47 (51.6)                |
| Male                                    | 12 (54.5)               | 11 (45.8)                | 13 (35.1)              | 16 (45.7)               | 17 (54.8)               | 17 (53.1)                | 42 (46.7)               | 44 (48.4)                |
| <b>Race - n (%)</b>                     |                         |                          |                        |                         |                         |                          |                         |                          |
| Caucasian                               | 20 (90.9)               | 18 (75.0)                | 34 (91.9)              | 31 (88.6)               | 27 (87.1)               | 27 (84.4)                | 81 (90.0)               | 76 (83.5)                |
| Black or<br>African<br>American         | 0                       | 0                        | 0                      | 0                       | 0                       | 0                        | 0                       | 0                        |
| Asian                                   | 2 (9.1)                 | 4 (16.7)                 | 0                      | 1 (2.9)                 | 0                       | 1 (3.1)                  | 2 (2.2)                 | 6 (6.6)                  |
| Other                                   | 0                       | 2 (8.3)                  | 3 (8.1)                | 3 (8.6)                 | 4 (12.9)                | 4 (12.5)                 | 7 (7.8)                 | 9 (9.9)                  |
| <b>Weight group at baseline - n (%)</b> |                         |                          |                        |                         |                         |                          |                         |                          |
| <=40 kg                                 | 11 (50.0)               | 9 (37.5)                 | 19 (51.4)              | 21 (60.0)               | 9 (29.0)                | 6 (18.8)                 | 39 (43.3)               | 36 (39.6)                |
| >40 - <75 kg                            | 5 (22.7)                | 10 (41.7)                | 14 (37.8)              | 11 (31.4)               | 14 (45.2)               | 21 (65.6)                | 33 (36.7)               | 42 (46.2)                |
| >=75 kg                                 | 6 (27.3)                | 5 (20.8)                 | 4 (10.8)               | 3 (8.6)                 | 8 (25.8)                | 5 (15.6)                 | 18 (20.0)               | 13 (14.3)                |
| <b>Weight (kg)</b>                      |                         |                          |                        |                         |                         |                          |                         |                          |
| n                                       | 22                      | 24                       | 37                     | 35                      | 31                      | 32                       | 90                      | 91                       |
| Mean                                    | 49.0                    | 50.7                     | 44.2                   | 39.1                    | 55.3                    | 56.8                     | 49.2                    | 48.4                     |
| SD                                      | 26.22                   | 23.93                    | 26.39                  | 21.77                   | 27.12                   | 22.40                    | 26.74                   | 23.64                    |
| Min                                     | 13.2                    | 13.7                     | 11.6                   | 11.4                    | 16.5                    | 16.3                     | 11.6                    | 11.4                     |
| Median                                  | 40.6                    | 54.0                     | 39.9                   | 33.8                    | 56.0                    | 54.0                     | 47.3                    | 49.4                     |
| Max                                     | 92.0                    | 84.7                     | 126.3                  | 86.0                    | 122.0                   | 115.3                    | 126.3                   | 115.3                    |

| Characteristic                       | TRAPS<br>ACZ885<br>N=22 | TRAPS<br>Placebo<br>N=24 | HIDS<br>ACZ885<br>N=37 | HIDS<br>Placebo<br>N=35 | crFMF<br>ACZ885<br>N=31 | crFMF<br>Placebo<br>N=32 | Total<br>ACZ885<br>N=90 | Total<br>Placebo<br>N=91 |
|--------------------------------------|-------------------------|--------------------------|------------------------|-------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
| <b>CRP (mg/L)</b>                    |                         |                          |                        |                         |                         |                          |                         |                          |
| n                                    | 22                      | 24                       | 37                     | 35                      | 31                      | 32                       | 90                      | 91                       |
| Mean                                 | 183.4                   | 133.1                    | 162.6                  | 181.5                   | 163.9                   | 118.2                    | 168.1                   | 146.5                    |
| SD                                   | 195.41                  | 127.89                   | 141.84                 | 153.78                  | 134.75                  | 112.68                   | 152.79                  | 135.26                   |
| Min                                  | 13.0                    | 0.8                      | 16.0                   | 10.2                    | 20.0                    | 10.5                     | 13.0                    | 0.8                      |
| Median                               | 135.1                   | 84.6                     | 98.0                   | 121.6                   | 120.0                   | 79.7                     | 122.1                   | 97.0                     |
| Max                                  | 855.0                   | 532.1                    | 562.0                  | 613.6                   | 503.1                   | 480.0                    | 855.0                   | 613.6                    |
| <b>Region</b>                        |                         |                          |                        |                         |                         |                          |                         |                          |
| North America (US, Canada)           | 4 (18.2)                | 1 (4.2)                  | 1 (2.7)                | 0                       | 0                       | 1 (3.1)                  | 5 (5.6)                 | 2 (2.2)                  |
| Japan                                | 2 (9.1)                 | 4 (16.7)                 | 0                      | 1 (2.9)                 | 0                       | 1 (3.1)                  | 2 (2.2)                 | 6 (6.6)                  |
| Other                                | 16 (72.7)               | 19 (79.2)                | 36 (97.3)              | 34 (97.1)               | 31 (100.0)              | 30 (93.8)                | 83 (92.2)               | 83 (91.2)                |
| <b>Dose level (cumulative in mg)</b> |                         |                          |                        |                         |                         |                          |                         |                          |
| <=600 mg                             | 12 (54.5)               | 22 (91.7)                | 18 (48.6)              | 26 (74.3)               | 21 (67.7)               | 27 (84.4)                | 51 (56.7)               | 75 (82.4)                |
| >600 mg                              | 10 (45.5)               | 2 (8.3)                  | 19 (51.4)              | 9 (25.7)                | 10 (32.3)               | 5 (15.6)                 | 39 (43.3)               | 16 (17.6)                |

Including Epoch 2 and available data from Epochs 3 and 4

ACZ885=canakinumab

Source: Sponsor's submission

The median duration of disease and median number of flares per year at randomization reflected chronic severe disease (crFMF: 14.7 years, 18 flares per year; HIDS/MKD: 9.8 years, 12 flares per year; TRAPS: 8.2 years, 9 flares per year).

Concomitant medications were used by 93% of subjects exposed to canakinumab, and 88% of subjects only exposed to placebo. Most (87%) of crFMF subjects were taking concomitant colchicine during Epoch 2.

A small proportion of subjects had prior exposure to biologics (24% of crFMF subjects, 18% of HIDS/MKD subjects, and 35% of TRAPS subjects).

### **6.1.3 Subject Disposition**

A total of 180 patients (60 per cohort, 30 per treatment arm) were planned to be randomized. A total of 181 patients were randomized and four patients entered the non-randomized open-label treatment arm. In the crFMF cohort, 100 patients were screened and 63 patients were randomized (31 to 150 mg q4w canakinumab and 32 to placebo). In the HIDS/MKD cohort, 98 patients were screened and 72 patients were randomized (37 to 150 mg q4w canakinumab and 35 to placebo). In the TRAPS cohort, 82 patients were screened and 46 patients were randomized (22 to 150 mg q4w canakinumab and 24 to placebo). All randomized patients were included in the Full Analysis Set (for efficacy analysis) and the Safety set (for safety analysis). Four non-randomized patients (two crFMF patients with non-exon 10 mutations and two HIDS/MKD patients > 28 days but < 2 years old) received open-label treatment.

As previously noted, the vast majority of patients randomized to placebo crossed over to canakinumab and patients frequently up-titrated from canakinumab 150 mg to 300 mg (Table 5).

**Table 5: Patient disposition in study N2301 by disease cohort**

| crFMF                        |                   |                            |                    |                              |                              |              |
|------------------------------|-------------------|----------------------------|--------------------|------------------------------|------------------------------|--------------|
| Initial randomized treatment | 150mg (N=31)      |                            | Placebo (N=32)     |                              |                              | Total (N=63) |
| Actual treatment sequence    | 150mg<br>21 (68%) | 150mg to 300mg<br>10 (32%) | Placebo<br>5 (16%) | Placebo to 150mg<br>22 (69%) | Placebo to 300mg<br>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 | 150mg (N=37)      |                            | Placebo (N=35)     |                              |                              | Total (N=72) |
| Actual treatment sequence    | 150mg<br>18 (49%) | 150mg to 300mg<br>19 (51%) | Placebo<br>4 (12%) | Placebo to 150mg<br>19 (54%) | Placebo to 300mg<br>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 | 150mg (N=22)      |                            | Placebo (N=24)     |                              |                              | Total (N=46) |
| Actual treatment sequence    | 150mg<br>11 (50%) | 150mg to 300mg<br>11 (50%) | Placebo<br>3 (13%) | Placebo to 150mg<br>19 (79%) | Placebo to 300mg<br>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 Zeng, Biometrics Reviewer

#### 6.1.4 Analysis of Primary Endpoint(s)

In Study N2301, the primary efficacy variable of the randomized treatment epoch (Epoch 2) and for the overall study was the proportion of responders within each cohort, whereby a responder was defined as a patient who had resolution of his/her index disease flare (i.e., PGA < 2 and CRP either ≤ 10 mg/L or ≥ 70% reduction from baseline) at Day 15 and did not experience a new flare (i.e., PGA ≥ 2 and CRP ≥ 30 mg/L) before the end of Epoch 2 (end of Week 16). In the primary analysis, patients who needed dose escalation in the canakinumab 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 as non-responders.

The primary objective was met in all three disease cohorts. Canakinumab demonstrated superior efficacy over placebo. All treatment differences in the proportion of responders were statistically significant in favor of canakinumab vs. placebo (Table 6). In crFMF patients, there were 55% more responders on canakinumab vs. placebo (OR=23.75, p<0.0001). In HIDS/MKD patients, there were 29% more responders on canakinumab vs. placebo (OR=8.94, p=0.0020). In TRAPS patients, there were 37% more responders on canakinumab vs. placebo (OR=9.17, p=0.0050). However, as most placebo subjects, as well as many canakinumab subjects, underwent “blinded escape” as early as Day 8, the extent of treatment comparison is limited. Thus, additional efficacy analyses were performed at earlier time points.

**Table 6: Comparison between treatment groups of patients who responded at Week 16 by cohort, Study N2301, full analysis set**

|          | Canakinumab 150mg Q4W |          | Placebo  |         | Treatment Comparison |             |                   |
|----------|-----------------------|----------|----------|---------|----------------------|-------------|-------------------|
|          | n/M (%)               | 95% CI   | n/M (%)  | 95% CI  | Odds Ratio           | (95% CI)    | One-sided p-value |
| TRAPS    | 10/22 (46)            | (24, 68) | 2/24 (8) | (1, 27) | 9.17                 | (1.5, 94.6) | 0.0050*           |
| HIDS/MKD | 13/37 (35)            | (20, 53) | 2/35 (6) | (1, 19) | 8.9                  | (1.7, 86.4) | 0.0020*           |
| crFMF    | 19/31 (61)            | (42, 78) | 2/32 (6) | (1, 21) | 23.8                 | (4.4, 228)  | <0.0001*          |

\* Indicates statistical significance (one-sided) at p-value of 0.025 level based on Fisher exact test

Source: Adapted from sponsor’s submission

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 who remained 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.

**Table 7: 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<br>n/M (%)           | Placebo<br>n/M (%) | 150mg q4w<br>n/M (%)                | Placebo<br>n/M (%) | Treatment Comparison<br>Odds Ratio (95% CI) | P-value |
| crFMF    | 0/31<br>(0.0)                  | 6/32<br>(18.8)     | 25/31<br>(80.7)                     | 10/32<br>(31.3)    | 9.2<br>(2.5, 35.2)                          | 0.0001* |
| HIDS/MKD | 2/37<br>(5.4)                  | 11/35<br>(31.4)    | 24/37<br>(64.9)                     | 13/35<br>(37.1)    | 3.1<br>(1.1, 9.2)                           | 0.0168* |

|              |                |                |                 |                |                    |         |
|--------------|----------------|----------------|-----------------|----------------|--------------------|---------|
| <b>TRAPS</b> | 4/22<br>(18.2) | 9/24<br>(37.5) | 14/22<br>(63.6) | 5/24<br>(20.8) | 6.7<br>(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: Biometrics Review

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 ( $\leq 10$  mg/L) or reduction by at least 70% from baseline. The efficacy of canakinumab at Day 15 was observed in all 3 disease cohorts; however, the results should be interpreted with caution as 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 7).

### 6.1.5 Analysis of Secondary Endpoints(s)

Study N2301 also had three secondary efficacy endpoints in Epoch 2: the percentage of patients who achieved a PGA < 2 (“minimal” or “absent” disease activity); the percentage of patients with serologic remission (defined as CRP  $\leq 10$  mg/L); and the percentage of patients with normalized SAA (defined as SAA  $\leq 10$  mg/L), all assessed at the end of Week 16. The primary endpoint and the three secondary endpoints were assessed in a hierarchical testing strategy designed to protect the family-wise type 1 error rate at  $\alpha=2.5\%$  (one-sided tests). If the primary objective of the study was met, the superiority of canakinumab 150 mg q4w over placebo in each secondary endpoint was then assessed in the closed testing procedure.

Overall, canakinumab provided greater improvements in clinical and serological responses, as assessed by PGA < 2 (absent or minimal disease), serological remission per CRP  $\leq 10$  mg/L and normalization of SAA to  $\leq 10$  mg/L at the end of Week 16, compared with placebo across all cohorts of crFMF, HIDS/MKD and TRAPS patients.

Results of the closed testing procedure, which was performed after the primary objective was met, demonstrated the superiority of canakinumab to placebo for PGA < 2 and CRP  $\leq 10$  mg/L after 16 weeks of treatment in all cohorts of crFMF, HIDS/MKD and TRAPS patients. For SAA  $\leq 10$  mg/L after 16 weeks, canakinumab was superior to placebo in TRAPS patients and showed similar trend of greater improvements relative to placebo in crFMF and HIDS/MKD patients. Taken together, canakinumab demonstrated greater benefit in crFMF, HIDS/MKD and TRAPS patients compared with placebo in all primary and secondary efficacy endpoints, reflecting rapid and sustained flare control, absent to minimal disease activity, normalization of CRP and normalization of SAA (Table 8).

**Table 8: Results of the secondary endpoints at Week 16 by cohort, Study N2301, full analysis set**

|                 | Canakinumab<br>150mg Q4W |          | Placebo  |            | Treatment Comparison |            |                   |
|-----------------|--------------------------|----------|----------|------------|----------------------|------------|-------------------|
|                 | n/M (%)                  | 95% CI   | n/M (%)  | 95% CI     | Odds Ratio           | (95% CI)   | One-sided p-value |
| <b>TRAPS</b>    |                          |          |          |            |                      |            |                   |
| PGA <2          | 10/22 (45)               | (24, 68) | 1/24 (4) | (0.1, 21)  | 24                   | (3, 225)   | 0.0028*           |
| CRP ≤10mg/L     | 8/22 (36)                | (17, 59) | 2/24 (8) | (1, 27)    | 7                    | (1, 37)    | 0.0149*           |
| SAA ≤10mg/L     | 6/22 (27)                | (11, 50) | 0/24 (0) | (0, 14)    | 17                   | (1, 269)   | 0.0235*           |
| <b>HIDS/MKD</b> |                          |          |          |            |                      |            |                   |
| PGA <2          | 17/37 (50)               | (29, 63) | 2/35 (6) | (0.7, 19)  | 14                   | (3, 66)    | 0.0006*           |
| CRP ≤10mg/L     | 15/37 (41)               | (25, 58) | 2/35 (6) | (0.7, 19)  | 13                   | (3, 64)    | 0.0010*           |
| SAA ≤10mg/L     | 5/37 (14)                | (5, 29)  | 1/35 (3) | (0.07, 15) | 5                    | (1, 52)    | 0.0778            |
| <b>crFMF</b>    |                          |          |          |            |                      |            |                   |
| PGA <2          | 20/31 (65)               | (45, 81) | 3/32 (9) | (2, 25)    | 17                   | (4, 69)    | <0.0001*          |
| CRP ≤10mg/L     | 21/31 (68)               | (49, 83) | 2/32 (6) | (0.8, 21)  | 30                   | (6, 151)   | <0.0001*          |
| SAA ≤10mg/L     | 8/31 (26)                | (12, 45) | 0/32 (0) | (0, 11)    | 17                   | (0.9, 333) | 0.0286            |

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 p-value of 0.025 level based on Fisher exact test

Source: Adapted from Sponsor's submission

### 6.1.6 Other Endpoints

Rapid and sustained improvements in PGA scores were observed in crFMF, HIDS/MKD and TRAPS subjects treated with canakinumab. In the total group of canakinumab-treated subjects across all three cohorts, a high proportion of patients shifted from moderate or severe (PGA > 2) to no or minimal (PGA < 2) disease activity as early as Day 15, and this improvement was maintained through the end of Epoch 2 (Week 17/Day 113).

The distribution of baseline PGA scores was similar between the randomized canakinumab and placebo groups. Most patients improved to no or minimal disease activity after 16 weeks of canakinumab treatment. In canakinumab-treated patients (150 mg or 300 mg q4w), the proportion of patients with moderate or severe disease decreased from 90.3% at baseline to 3.2% after 16 weeks of treatment in crFMF patients, from 73.0% to 2.7% in HIDS/MKD patients, and from 59.1% to 4.5% in TRAPS patients. The proportion of canakinumab-treated patients with no or minimal disease activity increased from 0% at baseline to 93.6% after 16 weeks in crFMF patients, from 0% to 91.9% in HIDS/MKD patients, and from 0% to 81.8% in TRAPS patients. Shifts in PGA scores after 16 weeks are not shown for the randomized placebo group, as the majority of placebo patients switched to active treatment starting at Day 8.

Rapid and sustained decreases in CRP levels were observed in crFMF, HIDS/MKD and

TRAPS patients treated with canakinumab. Large reductions from baseline were observed by Day 15 and continued through end of Epoch 2 (Week 17/Day 113).

The proportion of canakinumab-treated patients (150 mg or 300 mg q4w) with CRP  $\leq 10$  mg/L after 16 weeks increased from 0% at baseline to 93.5% at Week 17 for crFMF patients, from 0% to 62.2% for HIDS/MKD patients, and from 0% to 77.3% for TRAPS patients.

Rapid and sustained decreases in SAA levels were observed in crFMF, HIDS/MKD and TRAPS patients treated with canakinumab. Large reductions from baseline were observed by Day 15 and continued through end of Epoch 2 (Week 17/Day 113). The proportion of canakinumab-treated patients (150 mg or 300 mg q4w) with SAA  $\leq 10$  mg/L after 16 weeks increased from 0% at baseline to 25.8% at Week 17 for crFMF patients, from 0% to 21.6% for HIDS/MKD patients, and from 4.5% to 36.4% for TRAPS patients.

The median time to first resolution of fever ( $< 38.0^{\circ}\text{C}$ ) was 1 to 1.5 days shorter for patients randomized to canakinumab 150 mg q4w compared with placebo in all 3 disease cohorts. This analysis was performed in a small subset of patients (15/63 (24%) crFMF patients, 42/72 (58%) HIDS/MKD patients and 19/46 (41%) TRAPS patients) who had fever (as assessed by daily diary) at baseline. While these results suggest the efficacy of canakinumab, the clinical significance of 1 to 1.5 days less fever is unclear. For each cohort the results for resolution of fever were:

- In crFMF patients, the median time to first resolution of fever ( $< 38.0^{\circ}\text{C}$ ) was 2.0 days for canakinumab 150 mg q4w group vs. 3.0 days for the placebo group (Hazard ratio=2.48; 95% CI: 0.79-7.73;  $p=0.0589$ ).
- In HIDS/MKD patients, the median time to first resolution of fever ( $< 38.0^{\circ}\text{C}$ ) was 2.0 days for canakinumab 150 mg q4w group vs. 3.5 days for the placebo group (Hazard ratio=3.32; 95% CI: 1.60-6.88;  $p=0.0006$ ).
- In TRAPS patients, the median time to first resolution of fever ( $< 38.0^{\circ}\text{C}$ ) was 2.0 days for canakinumab 150 mg q4w group vs. 3.5 days for the placebo group (Hazard ratio=2.55; 95% CI: 0.90-7.25;  $p=0.0393$ ).

### 6.1.7 Subpopulations

Canakinumab showed greater efficacy compared to placebo with the respect to the proportion of responders after 16 weeks in both age subgroups across all 3 disease cohorts. Similar results were also observed for the secondary efficacy endpoints of PGA  $< 2$  and CRP  $\leq 10$  mg/L in crFMF, HIDS/MKD and TRAPS patients. For SAA  $\leq 10$  mg/L, canakinumab was more efficacious than placebo in both age subgroups in crFMF patients, while in HIDS/MKD and TRAPS patients this effect was apparent in patients  $< 18$  years old but not in the very small number of HIDS/MKD and TRAPS patients  $\geq 18$  years old (Table 9).

**Table 9: Proportion of responders after 16 weeks by age group (full analysis set)**

| Cohort       | < 18 years            |                    |                                        | ≥ 18 years            |                    |                                        |
|--------------|-----------------------|--------------------|----------------------------------------|-----------------------|--------------------|----------------------------------------|
|              | 150 mg q4w<br>n/M (%) | Placebo<br>n/M (%) | Treatment<br>comparison<br>OR (95% CI) | 150 mg q4w<br>n/M (%) | Placebo<br>n/M (%) | Treatment<br>comparison<br>OR (95% CI) |
| <b>FMF</b>   | 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)                      |
| <b>HIDS</b>  | 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)                         |
| <b>TRAPS</b> | 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: Biometrics Reviewer

For patients with an inadequate response after the first dose, an up-titration to 300 mg (or 4 mg/kg) further improved flare control, reduced disease activity and normalized CRP and SAA levels. In the exploratory analysis, patients randomized to canakinumab 150 mg q4w who were up-titrated to 300 mg q4w before Day 29 were considered responders if they had resolution of flare at Day 29 and no flare after Day 29 for the primary endpoint of the proportion of responders and in addition if they had  $PGA < 2$ ,  $CRP \leq 10$  mg/L or  $SAA \leq 10$  mg/L after 16 weeks for each of the secondary endpoints.

Overall, results of this analysis suggest that the individualized up-titration is beneficial for crFMF patients and especially HIDS/MKD and TRAPS patients to achieve sufficient control of clinical and serological parameters. The improvements in flare control, disease activity and levels of CRP and SAA observed with up - titration from 150 mg to 300 mg q4w were most pronounced in the disease cohorts (i.e., HIDS/MKD and TRAPS patients) who most needed up-titration. However, given that most placebo subjects switched to canakinumab and some patients required up-titration as early as Day 8, the comparison between canakinumab and placebo is difficult to interpret.

#### 6.1.7.1 crFMF subjects

Dose escalation further improved flare control, reduction of PGA scores to no or minimal disease and return of CRP to normal levels in crFMF patients treated with canakinumab. The proportion of canakinumab-treated crFMF patients who resolved their index flare by Day 29 and had no new flare up to the end of Epoch 2 increased to 70.97% when patients received an add-on dose if needed before Day 29, representing a 9.7% higher responder rate with up-titration to 300 mg q4w. The response rates for  $PGA < 2$  (74.19%) and  $CRP \leq 10$  mg/L (74.19%) after 16 weeks also improved with up-titration to 300 mg q4w before Day 29, reflecting an increase of 9.7% and 6.5%, respectively. There was no change in the rate of  $SAA \leq 10$  mg/L (remained at 25.81%).

For the crFMF subjects who were taking concomitant colchicine during Epoch 2, canakinumab showed greater efficacy than placebo with respect to the proportion of responders after 16 weeks (62% versus 0%); the risk difference in favor of canakinumab versus placebo (62%) in subjects taking concomitant colchicine was of similar magnitude as that in the overall population (55%), indicating the added benefit of canakinumab beyond that provided by colchicine therapy. Both the canakinumab and placebo group received comparable daily colchicine doses, and treatment responders did not receive higher doses of colchicine versus non-responders.

Among those with prior exposure to biologics (24% of crFMF subjects), there were more responders in Epoch 2 in the canakinumab group than in the placebo group for the crFMF cohort (57% for canakinumab versus 0% for placebo). The responder profile among subjects without prior exposure to biologics was similar to the overall population, with a higher proportion of subjects on canakinumab compared to placebo achieving a complete response.

#### 6.1.7.2 HIDS/MKD subjects

Dose escalation further improved flare control, reduction of PGA scores to no or minimal disease and return of CRP and SAA to normal levels in HIDS/MKD patients treated with canakinumab. The proportion of canakinumab-treated HIDS/MKD patients who resolved their index flare by Day 29 and had no new flare up to the end of Epoch 2 increased to 56.76% when patients received an add-on dose if needed before Day 29, representing a 21.6% higher responder rate with up-titration to 300 mg q4w. The response rates for PGA < 2 (67.57%), CRP ≤ 10 mg/L (48.65%) and SAA ≤ 10 mg/L (18.92%) after 16 weeks also improved with up-titration to 300 mg q4w before Day 29, reflecting an increase of 21.6%, 8.1% and 5.4%, respectively, for these secondary endpoints.

Among those with prior exposure to biologics (18% of HIDS/MKD subjects), there was one subject in the canakinumab group who was a responder compared with 0 subjects in the placebo group. The responder profile among subjects without prior exposure to biologics was similar to the overall population, with a higher proportion of subjects on canakinumab compared to placebo achieving a complete response.

#### 6.1.7.3 TRAPS subjects

Dose escalation further improved flare control, reduction of PGA scores to no or minimal disease and return of CRP and SAA to normal levels in TRAPS patients treated with canakinumab. The proportion of canakinumab-treated TRAPS patients who resolved their index flare by Day 29 and had no new flare up to the end of Epoch 2 increased to 72.73% when patients received an add-on dose if needed before Day 29, representing a 27.3% higher responder rate with up-titration to 300 mg q4w. The response rates for PGA < 2 (68.18%), CRP ≤ 10 mg/L (63.64%) and SAA ≤ 10 mg/L (31.82%) after 16 weeks also improved with up-

titration to 300 mg q4w before Day 29, reflecting an increase of 22.7%, 27.3% and 4.6%, respectively, for these secondary endpoints.

Among those with prior exposure to biologics (35% of TRAPS subjects), there were more responders in Epoch 2 in the canakinumab group than in the placebo group for the TRAPS cohort (50% versus 13%). The responder profile among subjects without prior exposure to biologics was similar to the overall population, with a higher proportion of subjects on canakinumab compared to placebo achieving a complete response.

### **Analyses at Day 15**

Canakinumab provided flare control, as indicated by the majority of patients in all three disease cohorts resolving their index flare by Day 15. Overall, 80.65%, 64.86% and 63.64% of crFMF, HIDS/MKD and TRAPS patients, respectively, achieved flare control with 150 mg or 2 mg/kg canakinumab. Approximately two to three times more patients resolved their index flare at Day 15 with canakinumab treatment compared to placebo: 80.65% for canakinumab vs. 31.25% for placebo in the crFMF cohort, 64.86% vs. 37.14% in the HIDS/MKD cohort, and 63.64% vs. 20.83% in the TRAPS cohort. This corresponds to 49.4%, 27.7% and 42.8% more crFMF, HIDS/MKD and TRAPS patients, respectively, who resolved their index flare by Day 15 with canakinumab treatment compared to placebo.

The results at Day 15 should be interpreted with caution, as some patients had received add-on injection of canakinumab before Day 15. However, compared to the evaluation of treatment effect at Week 16, the short-term results at Day 15, as discussed by the Biometrics reviewer, appear more reliable because less cross-over and up-titration had occurred at Day 15 compared to later time points.

### **6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

For those patients who did not achieve resolution of their index flare by Day 15 with the first dose of 150 mg (or 2 mg/kg), administration of a second dose of 150 mg (or 2 mg/kg) was effective for resolution of the index flare at Day 29 in 60.0% of crFMF patients and 62.5% of TRAPS patients, but in only 26.7% of HIDS/MKD patients.

For patients on placebo who did not resolve their index flare by Day 15, an add-on dose with canakinumab 150 mg (or 2 mg/kg) led to resolution by Day 29 for 77.8%, 55.6% and 62.5% of crFMF, HIDS/MKD and TRAPS patients, respectively. These responder rates are similar to those in patients randomized to and receiving canakinumab 150 mg (or 2 mg/kg) q4w from Day 1 (i.e., 80.65%, 64.86% and 63.64%, respectively), providing additional evidence of efficacy for canakinumab in patients initially exposed to placebo.

For all three randomized cohorts of crFMF, HIDS/MKD and TRAPS patients, the proportion of patients who needed blinded escape with an add-on injection of canakinumab 150 mg

(or 2 mg/kg) between Days 8 and 28 was lower in the randomized canakinumab group than in the placebo group. However, 16% of crFMF patients, and even more HIDS/MKD patients (32%) and TRAPS patients (36%), were up-titrated from 150 mg to 300 mg q4w (Table 10).

**Table 10: Patients with blinded escape at Days 8 to 28 (Full analysis set)**

| Cohort | Canakinumab 150 mg q4w |                | Placebo       |                |
|--------|------------------------|----------------|---------------|----------------|
|        | n/M (%)                | 95% CI         | n/M (%)       | 95% CI         |
| crFMF  | 5/31 (16.13)           | (5.45, 33.73)  | 20/32 (62.50) | (43.69, 78.90) |
| HIDS   | 12/37 (32.43)          | (18.01, 49.79) | 22/35 (62.86) | (44.92, 78.53) |
| TRAPS  | 8/22 (36.36)           | (17.20, 59.34) | 18/24 (75.00) | (53.29, 90.23) |

n=number of patients with blinded escape; M=total number of patients evaluated

Source: [\[Study N2301 Week 16-Table 14.2-3.11\]](#)

\* Adapted from Sponsor's submission

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The majority of crFMF, HIDS/MKD and TRAPS patients did not re-flare over 16 weeks of treatment in Epoch 2. Among canakinumab-treated patients (150 mg or 300 mg q4w), 90.3%, 64.9% and 77.3% of crFMF, HIDS/MKD and TRAPS patients, respectively, had no new flare (i.e., PGA  $\geq$  2 and CRP  $\geq$  30 mg/L) after resolution of the index flare up to the end of Week 16. While data are only available from 16 weeks of treatment, it is reasonable to assume that these results would be maintained, especially given the lack of anti-drug antibody development. There was no evidence of drug tolerance.

#### 6.1.10 Additional Efficacy Issues/Analyses

The primary objective of the study was achieved for all three cohorts: canakinumab was superior to placebo in the proportion of patients who resolved their index disease flare at Day 15 and had no new flare before the end of Epoch 2. Canakinumab also demonstrated superior efficacy compared to placebo on the secondary endpoints of PGA < 2 and CRP  $\leq$  10 mg/L after 16 weeks in all 3 cohorts. Higher proportions of patients had normalized SAA ( $\leq$  10 mg/L) after 16 weeks with canakinumab treatment compared to placebo in all 3 cohorts, with a statistically significant difference observed in TRAPS patients. These improvements in the clinical and serological parameters of disease were accompanied by increased health-related mQoL for patients as assessed by CHQ-PF50 (Child Health Questionnaire – Parent Form 50) and SF-12 (Medical Outcome Short Form 12 Health Survey) physical component summary scores.

Reductions in AIDAI score were observed by Weeks 1 – 2 and continued through Week 16, with subjects who were up-titrated from 150 mg to 300 mg q4w having higher baseline median AIDAI scores and exhibiting comparable or larger median reductions compared to subjects who continued on 150 mg q4w. Improvements in the physical and psychological component summary scores of the CHQ-PF50 were observed after 16 weeks of treatment with canakinumab; median changes in the CHQ-PF50 physical component summary scores after 16 weeks in the randomized 150 mg q4w group reflected moderate to large benefits of canakinumab treatment to health-related quality of life in crFMF, HIDS/MKD and TRAPS pediatric subjects > 5 to < 18 years, but no change in the group of HIDS/MKD pediatric subjects who were up-titrated to 300 mg q4.

Overall, improvements in SF-12 physical and mental component summary scores (PCS and MCS) were observed as early as Day 29, and for PCS further improved after 16 weeks of treatment with canakinumab in subjects at least 18 years of age. Median changes in SF-12 PCS scores in the randomized 150 mg q4w group after 16 weeks reflected benefits of canakinumab treatment of quality of life in crFMF, HIDS/MKD and TRAPS subjects at least 18 years of age, with no relevant change in the group of crFMF subjects who were up-titrated to 300 mg q4w. In addition, improvements in the SDS global function impairment score were observed after 16 weeks of canakinumab treatment, based on three interrelated domains of work/school, social life and family life.

Again, comparisons to placebo from Day 15 onward are limited by the high proportion of subjects switching from placebo to canakinumab starting at Day 8.

There was no pooling of efficacy data from the randomized, placebo-controlled pivotal Phase 3 studies and the four open-label, uncontrolled Phase 2 studies, as the study design, efficacy variables and dosing regimens differ across the studies.

## 7 Review of Safety

### Safety Summary

ILARIS® (canakinumab) is approved in more than 70 countries, including the European Union and United States, to treat CAPS and SJIA in adults, adolescents and children. The doses and regimens approved for these two autoinflammatory conditions vary by region, with weight-based dosing employed for the low-body weight patients where dosing down to age 2 is approved. The highest doses are approved in SJIA, where patients receive 4 mg/kg (maximum of 300 mg) administered every 4 week.

ILARIS® is additionally approved outside the US for use in acute gouty arthritis attacks at a dose of 150 mg given as a single subcutaneous injection as soon as possible following onset of an attack.

With approval in many markets for use across the above-mentioned indications, there is a large body of evidence supporting the safety of canakinumab in pediatric and adult patients.

My review of the data did not identify new safety signals and the overall safety profile of canakinumab in crFMF, HIDS/MKD, and TRAPS appears to provide an acceptable degree of risk given the severity of the disease and the demonstrated efficacy of canakinumab.

## 7.1 Methods

Study N2301 was a randomized, multicenter, double-blind, placebo controlled study of canakinumab in patients with crFMF, HIDS/MKD, or TRAPS. The primary objective was to demonstrate that canakinumab treatment at a dose of 150 mg (or 2 mg/kg in subjects weighing  $\leq 40$  kg) administered subcutaneously 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 is ongoing; the original cut-off date was August 25, 2015 (last patient last visit for the Week 16 primary endpoint analysis).

The cut-off date for safety data from ongoing studies included in the sBLA submissions was November 06, 2015. The cut-off date for safety data for the 120-Day Safety Update was March 31, 2016. Therefore, the 120-Day Safety Update provided new safety data for canakinumab studies in TRAPS, HIDS/MKD, FMF and other more related indications: CAPS and SJIA. Overall, 21 SAEs were reported for 17 patients. Four patients reported five SAEs in the crFMF cohort of which two were suspected to be related to study treatment (infectious colitis and acute sinusitis). Nine patients reported 12 SAEs in the HIDS/MKD cohort of which 3 were suspected to be related to study treatment (hyper Immunoglobulin D [IgD] syndrome, anal abscess and herpes virus infection). Four patients reported four SAEs in the TRAPS cohort of which none were suspected to be related to treatment. A review of these cases did not alter the safety profile of canakinumab. There were no new cases of neutropenia, thrombocytopenia, vertigo/dizziness, immunogenicity, autoimmunity or malignancy in any of the cohorts. Canakinumab demonstrated a similar safety profile in TRAPS, HIDS/MKD and crFMF to that observed in the already approved CAPS indication.

Given the short duration of the trial and the limited number of subjects who continued on placebo during the study, comparisons between the canakinumab and placebo groups based on proportions are very limited. Interpretation of the safety data for canakinumab, as it relates specifically to subjects exposed to canakinumab, is severely limited in the current application due to the lack of subjects exposed to placebo during the same time period as patients exposed to canakinumab, as well as the small number of subjects in each treatment group.

The sponsor's presentation of safety data was found to be reasonable and the sponsor's safety tables are presented.

### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

This submission is supported by efficacy and safety data from the recently completed randomized, double-blind, placebo-controlled treatment phase (Epoch 2) of the ongoing pivotal confirmatory Phase 3 study (Study N2301), with additional safety data from the ongoing randomized withdrawal phase (Epoch 3) and the open-label treatment phase (Epoch 4) of this study. Additionally, four completed Phase 2 studies in the three indications support this application, in conjunction with supportive safety data from five completed Phase 2 and 3 studies in the approved indication of CAPS.

### **7.1.2 Categorization of Adverse Events**

All safety evaluations were conducted and reported according to Good Clinical Practice guidelines with data collected for AEs, clinical laboratory test results, and vital signs. Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries and predefined lists of preferred terms (PTs) were developed by the sponsor and used to analyze the data for safety events.

Adverse events were included in the safety analysis if the onset date was on or after the first dose start date of a specified period. Subject listings included all AEs, even those that occurred more than 60 days after the last dose of study medication.

### **7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

All AEs were coded and grouped into PTs by system organ class (SOC). As studies completed at various times, it is likely that AEs have been coded with different Medical Dictionary for Regulatory Activities (MedDRA) versions. For the pooled analyses, low level term codes are mapped to the latest MedDRA version available at the time of analysis.

## **7.2 Adequacy of Safety Assessments**

### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

The key safety population supporting canakinumab in crFMF, HIDS/MKD, and TRAPS is the N2301 Epoch 2 Safety set presented in the pivotal CSR (“N2301 Epoch 2”), which included a total of 181 randomized patients (63 crFMF patients, 72 HIDS/MKD patients, and 46 TRAPS patients) with a median duration of exposure of 113 days in this Any ACZ group (which includes all patients who took at least one dose of canakinumab during Epoch 2) and a cumulative exposure of 47.6 patient-years. This safety population reflects the safety results for each patient

up to Week 16 (end of Epoch 2). The median placebo exposure in the Total placebo group (which includes exposure up to when each patient switched to canakinumab in Epoch 2) was 14.0 days.

Presented as supportive safety data were two additional data pools:

The N2301 pool ( N2301 Epochs 2-4), which includes all safety data up to the 25-Aug-2015 data cut-off (including events that occurred in the completed Epoch 2 and the ongoing Epochs 3 and 4 up to the cut-off date) for the crFMF, HIDS/MKD and TRAPS patient cohorts from Study N2301. For the N2301 Epochs 2-4 Safety set, the Total ACZ group includes all data collected from randomization to canakinumab or the day of each patient's first dose of canakinumab for each cohort (crFMF, TRAPS, or HIDS/MKD) combined. Due to the long half-life of canakinumab, all data collected in Epochs 3 and 4 (including all events occurring under placebo) are counted within this Total ACZ group. While this pool provides a longer-term safety assessment, it should be noted that the duration of exposure to placebo (9.39 patient-years) is much shorter than the duration of exposure to canakinumab (114.85 patient-years) since all data collected in Epochs 3 and 4 are counted within the canakinumab treatment group. There were 139 subjects who received treatment of at least 24 weeks duration; 25 subjects received treatment for at least 48 weeks. Median duration of canakinumab exposure was 260 days, while that of placebo (this Total placebo group only includes data collected until the patient switched to canakinumab in Epoch 2) remained that of Epoch 2 (14.0 days). Patient exposure was highest in the crFMF ACZ group, with a median of 302 days. The HIDS/MKD ACZ group had a median exposure of 221 days and the TRAPS ACZ group had a median exposure of 215 days.

The CAPS pool presented consists of patients enrolled in the five completed CAPS studies A2102, D2304, D2306, D2308 and D2201, and provides long-term safety information from a closely-related periodic fever syndrome that is an approved indication for comparison.

Data are drawn from an age group that ranged from 2 to 76 years when starting treatment with canakinumab. This included 102 pediatric patients ranging from 2 years to 17 years of age exposed to canakinumab. There were also two non-randomized patients under 2 years of age with HIDS/MKD and two non-randomized adult patients with crFMF with non-exon 10 mutations.

The sponsor also presented safety data from the Phase 2 crFMF, HIDS/MKD and TRAPS studies as additional supportive data. These data were not pooled with each other or with data from the pivotal Phase 3 N2301 study because these Phase 2 studies were small (range of patients: 7 to 20), uncontrolled, open-label trials with different dosing regimens and treatment durations.

It should be noted that, according to the submission, the number of subjects eligible for Epoch 3 included <sup>(b) (4)</sup>



### **7.2.3 Special Animal and/or In Vitro Testing**

Not applicable.

### **7.2.4 Routine Clinical Testing**

The types and frequencies of safety tests used to assess AEs, vital signs, labs, and other tests were adequate to assess the safety of canakinumab in FMF, HIDS/MKD, and TRAPS. These safety tests were adequate to evaluate the known IL-1 associated AEs.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Not applicable.

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Study N2301 incorporated monitoring for toxicities associated with IL-inhibitors, such as infections, hypersensitivity, and injection site reactions. Details of these analyses are found in Section 7.3.4 (Submission Specific Primary Safety Concerns).

## **7.3 Major Safety Results**

Overall, the incidence and profile of AEs in the crFMF, HIDS/MKD, and TRAPS cohorts was comparable across the treatment groups within each cohort and across the cohorts. The profile of AEs in canakinumab-treated patients was also comparable between Study N2301 Epoch 2 and Epochs 2-4. The most frequently affected SOC in crFMF, HIDS/MKD, and TRAPS patients was infections and infestations, with the most common infections being those of the upper respiratory tract. All infections were mild or moderate in severity; the majority were not considered related to study drug and resolved, and few were SAEs. Other frequently observed AEs in crFMF, HIDS/MKD, and TRAPS subjects were pyrexia, headache, diarrhea, abdominal pain, and injection site reaction.

The profile of AEs in the Study N2301 groups was comparable to that of the CAPS group. The SOC with the highest frequency of AEs in the CAPS pool was infections and infestations. Similar to what was reported in the N2301 study population, the most frequently reported AEs in the CAPS group were nasopharyngitis, headache, upper respiratory tract infection, rhinitis, diarrhea, and arthralgia.

In Epoch 2, the most commonly reported AEs by preferred term (PT) in the crFMF Any ACZ Group (all patients who took at least one dose of canakinumab during Epoch 2) were FMF (22.4%), injection site reaction (13.8%), and diarrhea (12.1%). The most commonly reported AEs in the HIDS/MKD Any ACZ group were pyrexia (23.5%), headache (17.6%), and diarrhea and oropharyngeal pain (each 11.8%). The most commonly reported AEs in the TRAPS Any ACZ group were pyrexia (14.0%), and abdominal pain, injection site reaction, and nasopharyngitis (each 11.6%). All injection site reactions were mild and none were SAEs or AEs that led to discontinuation. In Study N2301 Epochs 2-4, comparable to what was observed in Epoch 2, the most frequently affected primary SOC in the Total ACZ group was infections and infestations (59.2%), with nasopharyngitis (10.7%) and upper respiratory tract infection (10.1%) being the most common infection events. Other SOCs with AEs reported for more than 25% of patients in the Total ACZ group were: general disorders & administration site conditions (40.8%), gastrointestinal disorders (37.3%), and musculoskeletal and connective tissue disorders (26.6%).

When adjusted for exposure per 100 patient-years, the most commonly occurring SOC of infections and infestations showed a comparable rate between the Total ACZ group (which includes all data collected from randomization to canakinumab or the day of each patient's first dose of canakinumab) and the lower-exposed Total placebo group (204.6 vs. 202.3). Similarly, all other SOCs showed comparable or lower exposure-adjusted event rates for the Total ACZ group compared with the Total placebo group from Study N2301.

Similar to what was observed in canakinumab-treated patients in Epoch 2, in the N2301 Epochs 2-4 Safety set, the most commonly reported AEs in the Total ACZ group were pyrexia (21.3%), headache (17.8%), diarrhea (13.0%), abdominal pain, and injection site reaction.

Overall, the frequency and type of SAEs observed during the clinical trials of canakinumab in TRAPS, HIDS/MKD and crFMF subjects was similar and consistent with data from prior trials for current indications, with no new safety signals identified.

### **7.3.1 Deaths**

There were no deaths in any studies of periodic fever syndrome patients, no deaths in the CAPS safety populations, and no deaths in study N2301 as of the cut-off date.

### **7.3.2 Nonfatal Serious Adverse Events**

In the N2301 Epoch 2 crFMF cohort, the incidence of SAEs was low in the Any ACZ group (five subjects, 8.6%). No SAE was reported in more than one subject. The SAEs considered by the investigator to be possibly related to study drug were granulomatous liver disease, pharyngotonsillitis, and atypical pneumonia. In the N2301 Epoch 2 HIDS/MKD cohort, the

incidence of SAEs was 11.8% (eight subjects) in the Any ACZ group. With the exception of pneumonia, reported in two subjects in the placebo to 150 mg group, no SAE was reported in more than one subject. One SAE, neutropenia, which occurred in a subject in the placebo group, was considered by the investigator to be related to study drug. In the N230 1 Epoch 2 TRAPS cohort, the incidence of SAEs was low, affecting 4.7% (two subjects) in the Any ACZ group. No SAE was reported in more than one subject. No SAE was considered by the investigator to be related to study drug.

In Epochs 2-4, the incidence of SAEs in the Total ACZ group was 10.7% (18 subjects). No SAE was reported in more than one patient in any particular cohort except umbilical hernia (two subjects (3.4%) in crFMF ACZ group) and pneumonia (three subjects (4.4%) in HIDS/MKD ACZ group). The SOC with the highest frequency of SAEs was infections and infestations (4.1% in the Total ACZ group).

The exposure-adjusted SAE rate per 100 patient-years was 30.5 in the Total ACZ group and 85.2 in the Total placebo group.

In the CAPS pooled population, the frequency of SAEs was comparable (28 patients, 14.4%) **to that of the Total ACZ group (18 patients, 10.7%). SAEs occurred most commonly in the infections and infestations SOC (7.2%). SAEs reported in > 1 patient in the CAPS pooled group were: vertigo, appendicitis, pneumonia, tonsillitis, headache, pregnancy, and abortion induced. The exposure-adjusted SAE rate per 100 patient-years in the CAPS pool was 15.9, compared with 30.5 in the Total ACZ group and 85.2 in the Total placebo group. Although the exposure-adjusted SAE rate was higher in the Total ACZ group vs. the CAPS pool, this was partly driven by the disease-specific SAEs of FMF, HIDS, and MKD and by a small number of individual patients who experienced a unique set of multiple SAEs. In addition, a slightly higher percentage of patients in the N2301 Total ACZ group reported > 1 SAE (approximately 50%) vs. the CAPS group (approximately 40%). Overall, the profile of SAEs in Study N2301 was similar to that reported in the CAPS pooled population, and are summarized below (**

Table 11):

**Table 11: Serious Adverse Events by Primary SOC and PT regardless of relation to treatment in N2301 and CAPS Safety Set**

| Primary system organ class<br>Preferred term                 | N2301                                            |                                   |                                 |                                  |                                  |                                   |                                   |                                   |                                  |
|--------------------------------------------------------------|--------------------------------------------------|-----------------------------------|---------------------------------|----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
|                                                              | TRAPS<br>ACZ885<br>N=43<br>n (%)                 | TRAPS<br>Placebo<br>N=24<br>n (%) | HIDS<br>ACZ885<br>N=68<br>n (%) | HIDS<br>Placebo<br>N=35<br>n (%) | crFMF<br>ACZ885<br>N=58<br>n (%) | crFMF<br>Placebo<br>N=32<br>n (%) | Total<br>ACZ885<br>N=169<br>n (%) | Total<br>Placebo<br>N=91<br>n (%) | CAPS<br>ACZ885<br>N=194<br>n (%) |
|                                                              | <b>-Number of patients with at least one SAE</b> | <b>1 (2.3)</b>                    | <b>1 (4.2)</b>                  | <b>9 (13.2)</b>                  | <b>4 (11.4)</b>                  | <b>8 (13.8)</b>                   | <b>2 (6.3)</b>                    | <b>18(10.7)</b>                   | <b>7 (7.7)</b>                   |
| <b>Blood and lymphatic system disorders</b>                  | 0                                                | 0                                 | 0                               | 1 (2.9)                          | 0                                | 0                                 | 0                                 | 1 (1.1)                           | 0                                |
| Neutropenia                                                  | 0                                                | 0                                 | 0                               | 1 (2.9)                          | 0                                | 0                                 | 0                                 | 1 (1.1)                           | 0                                |
| <b>Cardiac disorders</b>                                     | 0                                                | 0                                 | 1 (1.5)                         | 0                                | 0                                | 0                                 | 1 (0.6)                           | 0                                 | 1 (0.5)                          |
| Pericarditis                                                 | 0                                                | 0                                 | 1 (1.5)                         | 0                                | 0                                | 0                                 | 1 (0.6)                           | 0                                 | 0                                |
| <b>Congenital, familial and genetic disorders</b>            | 0                                                | 1 (4.2)                           | 2 (2.9)                         | 0                                | 1 (1.7)                          | 1 (3.1)                           | 3 (1.8)                           | 2 (2.2)                           | 1 (0.5)                          |
| Familial mediterranean fever                                 | 0                                                | 0                                 | 1 (1.5)                         | 0                                | 1 (1.7)                          | 1 (3.1)                           | 2 (1.2)                           | 1 (1.1)                           | 0                                |
| Hyper IgD syndrome                                           | 0                                                | 0                                 | 1 (1.5)                         | 0                                | 0                                | 0                                 | 1 (0.6)                           | 0                                 | 0                                |
| Mevalonate kinase deficiency                                 | 0                                                | 0                                 | 1 (1.5)                         | 0                                | 0                                | 0                                 | 1 (0.6)                           | 0                                 | 0                                |
| Tumour necrosis factor receptor-associated periodic syndrome | 0                                                | 1 (4.2)                           | 0                               | 0                                | 0                                | 0                                 | 0                                 | 1 (1.1)                           | 0                                |
| <b>Ear and labyrinth disorders</b>                           | 0                                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 2 (1.0)                          |
| <b>Gastrointestinal disorders</b>                            | 1 (2.3)                                          | 0                                 | 0                               | 1 (2.9)                          | 3 (5.2)                          | 0                                 | 4 (2.4)                           | 1 (1.1)                           | 1 (0.5)                          |
| Abdominal pain                                               | 0                                                | 0                                 | 0                               | 1 (2.9)                          | 0                                | 0                                 | 0                                 | 1 (1.1)                           | 0                                |
| Ascites                                                      | 0                                                | 0                                 | 0                               | 0                                | 1 (1.7)                          | 0                                 | 1 (0.6)                           | 0                                 | 0                                |
| Dysphagia                                                    | 1 (2.3)                                          | 0                                 | 0                               | 0                                | 0                                | 0                                 | 1 (0.6)                           | 0                                 | 0                                |
| Inguinal hernia                                              | 0                                                | 0                                 | 0                               | 0                                | 1 (1.7)                          | 0                                 | 1 (0.6)                           | 0                                 | 0                                |
| Umbilical hernia                                             | 0                                                | 0                                 | 0                               | 0                                | 2 (3.4)                          | 0                                 | 2 (1.2)                           | 0                                 | 0                                |
| Vomiting                                                     | 1 (2.3)                                          | 0                                 | 0                               | 0                                | 0                                | 0                                 | 1 (0.6)                           | 0                                 | 0                                |
| <b>General disorders and administration site conditions</b>  | 0                                                | 0                                 | 1 (1.5)                         | 0                                | 1 (1.7)                          | 0                                 | 2 (1.2)                           | 0                                 | 2 (1.0)                          |
| Polyserositis                                                | 0                                                | 0                                 | 1 (1.5)                         | 0                                | 0                                | 0                                 | 1 (0.6)                           | 0                                 | 0                                |
| Pyrexia                                                      | 0                                                | 0                                 | 0                               | 0                                | 1 (1.7)                          | 0                                 | 1 (0.6)                           | 0                                 | 1 (0.5)                          |

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|                                                        |         |   |         |         |         |         |         |         |          |
|--------------------------------------------------------|---------|---|---------|---------|---------|---------|---------|---------|----------|
| <b>Hepatobiliary disorders</b>                         | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| Bile duct stone                                        | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| Granulomatous liver disease                            | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| Hepatic cirrhosis                                      | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| <b>Infections and infestations</b>                     | 0       | 0 | 5 (7.4) | 1 (2.9) | 2 (3.4) | 1 (3.1) | 7 (4.1) | 2 (2.2) | 14 (7.2) |
| Atypical pneumonia                                     | 0       | 0 | 0       | 0       | 0       | 1 (3.1) | 0       | 1 (1.1) | 0        |
| Cellulitis                                             | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 1 (0.5)  |
| Conjunctivitis                                         | 0       | 0 | 1 (1.5) | 0       | 0       | 0       | 1 (0.6) | 0       | 0        |
| Diarrhoea infectious                                   | 0       | 0 | 0       | 1 (2.9) | 0       | 0       | 0       | 1 (1.1) | 0        |
| Gastroenteritis rotavirus                              | 0       | 0 | 1 (1.5) | 0       | 0       | 0       | 1 (0.6) | 0       | 0        |
| Pelvic abscess                                         | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| Pharyngitis                                            | 0       | 0 | 1 (1.5) | 0       | 0       | 0       | 1 (0.6) | 0       | 0        |
| Pharyngotonsillitis                                    | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| Pneumonia                                              | 0       | 0 | 3 (4.4) | 0       | 0       | 0       | 3 (1.8) | 0       | 3 (1.5)  |
| <b>Injury, poisoning and procedural complications</b>  | 0       | 0 | 0       | 0       | 0       | 0       | 0       | 0       | 3 (1.5)  |
| <b>Metabolism and nutrition disorders</b>              | 0       | 0 | 0       | 0       | 2 (3.4) | 0       | 2 (1.2) | 0       | 0        |
| Dehydration                                            | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| Hypokalaemia                                           | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| Obesity                                                | 0       | 0 | 0       | 0       | 1 (1.7) | 0       | 1 (0.6) | 0       | 0        |
| <b>Nervous system disorders</b>                        | 0       | 0 | 0       | 1 (2.9) | 0       | 0       | 0       | 1 (1.1) | 4 (2.1)  |
| Seizure                                                | 0       | 0 | 0       | 1 (2.9) | 0       | 0       | 0       | 1 (1.1) | 0        |
| <b>Pregnancy, puerperium and perinatal conditions</b>  | 0       | 0 | 0       | 0       | 0       | 0       | 0       | 0       | 2 (1.0)  |
| <b>Psychiatric disorders</b>                           | 0       | 0 | 1 (1.5) | 0       | 0       | 0       | 1 (0.6) | 0       | 1 (0.5)  |
| Self injurious behavior                                | 0       | 0 | 1 (1.5) | 0       | 0       | 0       | 1 (0.6) | 0       | 0        |
| Suicide attempt                                        | 0       | 0 | 1 (1.5) | 0       | 0       | 0       | 1 (0.6) | 0       | 0        |
| <b>Renal and urinary disorders</b>                     | 0       | 0 | 0       | 0       | 0       | 0       | 0       | 0       | 1 (0.5)  |
| <b>Respiratory, thoracic and mediastinal disorders</b> | 1 (2.3) | 0 | 0       | 0       | 0       | 1 (3.1) | 1 (0.6) | 1 (1.1) | 1 (0.5)  |
| Cough                                                  | 0       | 0 | 0       | 0       | 0       | 1 (3.1) | 0       | 1 (1.1) | 0        |
| Laryngeal stenosis                                     | 1 (2.3) | 0 | 0       | 0       | 0       | 0       | 1 (0.6) | 0       | 0        |

|                                               |         |   |         |   |   |   |         |   |         |
|-----------------------------------------------|---------|---|---------|---|---|---|---------|---|---------|
| Oropharyngeal pain                            | 1 (2.3) | 0 | 0       | 0 | 0 | 0 | 1 (0.6) | 0 | 0       |
| <b>Skin and subcutaneous tissue disorders</b> | 0       | 0 | 1 (1.5) | 0 | 0 | 0 | 1 (0.6) | 0 | 0       |
| Granulomatous rosacea                         | 0       | 0 | 1 (1.5) | 0 | 0 | 0 | 1 (0.6) | 0 | 0       |
| <b>Surgical and medical procedures</b>        | 0       | 0 | 0       | 0 | 0 | 0 | 0       | 0 | 2 (1.0) |

Study N2301 Week-16 IA, including Epoch 2 and available data from Epochs 3 and 4, CAPS Studies A2102, D2304, D2306, D2201, D2308.

A patient with multiple AEs within a primary SOC is counted only once in the total row.

A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment. Primary SOC are presented in alphabetical order; PTs are sorted within SOC in alphabetical order.

Patients switching from Placebo to ACZ885 are counted in both treatment arms. AEs reported in patients switching from Placebo to ACZ885 are counted once. The onset start date of the AE is used to define if AE is counted under Placebo or ACZ885.

Note that rows which contain SAEs by PT in only CAPS patients have been cut to shorten the in text table. Refer to the post-text table for these additional SAEs.

ACZ885=canakinumab

Source: Sponsor's submission

### 7.3.3 Dropouts and/or Discontinuations

There was a >90% completion rate overall and across crFMF, HIDS, and TRAPS cohorts. There were very few discontinuations; the most common reasons for discontinuation were lack of efficacy and subject/guardian decision (Table 12).

**Table 12: Discontinuations in study N2301**

| Disposition/Reason                      | N2301                            |                                   |                                 |                                  |                                  |                                   |                                   |                                   |                                  |
|-----------------------------------------|----------------------------------|-----------------------------------|---------------------------------|----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|
|                                         | TRAPS<br>ACZ885<br>N=43<br>n (%) | TRAPS<br>Placebo<br>N=24<br>n (%) | HIDS<br>ACZ885<br>N=68<br>n (%) | HIDS<br>Placebo<br>N=35<br>n (%) | crFMF<br>ACZ885<br>N=58<br>n (%) | crFMF<br>Placebo<br>N=32<br>n (%) | Total<br>ACZ885<br>N=169<br>n (%) | Total<br>Placebo<br>N=91<br>n (%) | CAPS<br>ACZ885<br>N=194<br>n (%) |
| Completed                               | 42<br>(97.7)                     | 22<br>(91.7)                      | 66<br>(97.1)                    | 33<br>(94.3)                     | 58<br>(100.0)                    | 31<br>(96.9)                      | 166<br>(98.2)                     | 86<br>(94.5)                      | 175<br>(90.2)                    |
| Discontinued                            | 1 (2.3)                          | 2 (8.3)                           | 2 (2.9)                         | 2 (5.7)                          | 0                                | 1 (3.1)                           | 3 (1.8)                           | 5 (5.5)                           | 19 (9.8)                         |
| <b>Primary reason for discontinuing</b> |                                  |                                   |                                 |                                  |                                  |                                   |                                   |                                   |                                  |
| Adverse event                           | 0                                | 0                                 | 1 (1.5)                         | 1 (2.9)                          | 0                                | 0                                 | 1 (0.6)                           | 1 (1.1)                           | 3 (1.5)                          |
| Death                                   | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 0                                |
| Lack of efficacy                        | 1 (2.3)                          | 1 (4.2)                           | 1 (1.5)                         | 1 (2.9)                          | 0                                | 0                                 | 2 (1.2)                           | 2 (2.2)                           | 5 (2.6)                          |
| Lost to follow-up                       | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 2 (1.0)                          |
| New therapy for<br>study indication     | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 0                                |
| No longer requires<br>treatment         | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 1 (0.5)                          |
| Non-compliance<br>with study treatment  | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 0                                |
| Physician decision                      | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 0                                |
| Pregnancy                               | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 0                                |
| Protocol deviation                      | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 1 (0.5)                          |
| Study terminated<br>by sponsor          | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 0                                |
| Subject/guardian<br>decision            | 0                                | 1 (4.2)                           | 0                               | 0                                | 0                                | 1 (3.1)                           | 0                                 | 2 (2.2)                           | 6 (3.1)                          |
| Technical<br>problems                   | 0                                | 0                                 | 0                               | 0                                | 0                                | 0                                 | 0                                 | 0                                 | 1 (0.5)                          |

Study N2301 Week-16 IA, including Epoch 2 and available data from Epochs 3 and 4, CAPS Studies A2102, D2304, D2306, D2201, D2308.

ACZ885=canakinumab

Source: Sponsor's submission

### 7.3.4 Significant Adverse Events

There were two non-randomized HIDS/MKD subjects, both > 28 days but < 2 years of age. One subject reported multiple non-serious AEs, with the most frequently reported being diarrhea, aphthous ulcer, nasopharyngitis, and pyrexia, in addition to increased liver function tests. The other subject had a history of immune thrombocytopenic purpura (ITP), and had an active medical condition of abnormal hepatic function reported during a first screening, which was ongoing at the beginning of open-label treatment.

This latter subject reported AEs of upper respiratory tract infection, hepatic failure, hypocalcemia, hypophosphatemia, and pancytopenia. In addition, this subject experienced the SAEs of pancytopenia and hepatic failure. Both SAEs were considered to be related to study

treatment due to their occurrence after the start of study treatment. The hepatic failure SAE was considered severe and led to study discontinuation; but was reported as resolved after the last assessment in the study.

The Novartis response to our July 14, 2016, Information Request states that the investigator suspected abnormal hepatic function due to an unspecified viral infection. The subject had elevated liver function tests at the time of screening in early January of 2015, and experienced an upper respiratory infection a couple of weeks later. In the second week of February, 2015, the patient was diagnosed with ITP, and about a week after that, the alkaline phosphatase was above 600, the investigator suspecting abnormal hepatic function since early January being due to a viral infection.

At the end of March, 2015, the patient had another episode of increased liver function tests, and the investigator deemed the patient a screening failure. But a week later, the patient underwent re-screening (at which time the transaminases were elevated—with an ALT of 172, and alkaline phosphatase of 345, and the investigator enrolled the patient into the study), and shortly after that the patient was thought to have completely recovered from ITP.

On May 12, 2015, the alkaline phosphatase was 346; prednisolone was tapered and the now-subject received open-label canakinumab on May 13—at which time AST and ALT were 15 and 24, respectively, and platelets were 387,000. Two weeks later, AST was 258, ALT was 370, alkaline phosphatase was 576, and platelets were 195,000. On June 08, ALT was 922, AST was 504, and platelets 90,000; on June 11, alkaline phosphatase was 1622 and total bilirubin 2.8, rising to 4.9 on June 15; platelet count was 67,000.

Bilirubin increased to 12.5 on June 21, 2015, AST and ALT had gone down to 278 and 175, respectively, with a platelet count of 38,000. Ammonia level was 89 on June 24, and a few days after that liver transplant was considered, as prothrombin time had been worsening. Bone marrow biopsy revealed a relatively hypoplastic bone marrow—which responded well to G-CSF. While the subject had also received famotidine, due to the temporal relation to canakinumab administration, the investigator suspected this as the cause of the pancytopenia. Liver biopsy on September 18 showed 50% loss of hepatocytes/necrosis.

The pancytopenia recovered on August 31, 2015. On September 15, the ALT was 162, AST was 56 and bilirubin was 2.3; the investigator considered HIDS/MKD as a contributory factor for the reported events.

It is my opinion that this subject had pre-existing conditions, and no conclusions can be drawn that canakinumab contributed to the aforementioned events.

### *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 higher 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

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2 Hinson DD, et al (1998) American Journal of Medical Genetics; 78:408-12.

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.<sup>2</sup>

## 7.4 Supportive Safety Results

The profile of AEs and SAEs in the Phase 2 TRAPS, HIDS/MKD and crFMF studies was similar to that observed in Study N2301.

### 7.4.1 Common Adverse Events

The table below (Table 13) displays adverse events by primary SOC. Overall, the rates and types of the AEs reported in the clinical trials of canakinumab for the treatment of SJIA are similar to those observed in the clinical development program of canakinumab for CAPS and no new safety signals were identified.

#### *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%).

**Table 13: Adverse events by primary SOC regardless of study treatment relationship by dose level**

| Primary system organ class                                          | TRAPS<br>ACZ885<br>N=12<br>n (%) | HIDS<br>ACZ885<br>N=28<br>n (%) | crFMF<br>ACZ885<br>N=15<br>n (%) | Total<br>ACZ885<br>N=55<br>n (%) |
|---------------------------------------------------------------------|----------------------------------|---------------------------------|----------------------------------|----------------------------------|
| -Number of patients with at least one AE                            | 11 (91.7)                        | 25 (89.3)                       | 15 (100.0)                       | 51 (92.7)                        |
| Blood and lymphatic system disorders                                | 4 (33.3)                         | 6 (21.4)                        | 2 (13.3)                         | 12 (21.8)                        |
| Cardiac disorders                                                   | 0                                | 1 (3.6)                         | 0                                | 1 (1.8)                          |
| Congenital, familial and genetic disorders                          | 2 (16.7)                         | 3 (10.7)                        | 3 (20.0)                         | 8 (14.5)                         |
| Ear and labyrinth disorders                                         | 1 (8.3)                          | 2 (7.1)                         | 2 (13.3)                         | 5 (9.1)                          |
| Eye disorders                                                       | 3 (25.0)                         | 4 (14.3)                        | 1 (6.7)                          | 8 (14.5)                         |
| Gastrointestinal disorders                                          | 8 (66.7)                         | 9 (32.1)                        | 11 (73.3)                        | 28 (50.9)                        |
| General disorders and administration site conditions                | 6 (50.0)                         | 17 (60.7)                       | 7 (46.7)                         | 30 (54.5)                        |
| Immune system disorders                                             | 0                                | 0                               | 1 (6.7)                          | 1 (1.8)                          |
| Infections and infestations                                         | 9 (75.0)                         | 22 (78.6)                       | 12 (80.0)                        | 43 (78.2)                        |
| Injury, poisoning and procedural complications                      | 2 (16.7)                         | 2 (7.1)                         | 1 (6.7)                          | 5 (9.1)                          |
| Investigations                                                      | 2 (16.7)                         | 3 (10.7)                        | 1 (6.7)                          | 6 (10.9)                         |
| Metabolism and nutrition disorders                                  | 1 (8.3)                          | 0                               | 0                                | 1 (1.8)                          |
| Musculoskeletal and connective tissue disorders                     | 7 (58.3)                         | 9 (32.1)                        | 8 (53.3)                         | 24 (43.6)                        |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0                                | 0                               | 1 (6.7)                          | 1 (1.8)                          |
| Nervous system disorders                                            | 3 (25.0)                         | 11 (39.3)                       | 5 (33.3)                         | 19 (34.5)                        |
| Psychiatric disorders                                               | 0                                | 3 (10.7)                        | 1 (6.7)                          | 4 (7.3)                          |
| Renal and urinary disorders                                         | 0                                | 0                               | 1 (6.7)                          | 1 (1.8)                          |
| Reproductive system and breast disorders                            | 1 (8.3)                          | 2 (7.1)                         | 0                                | 3 (5.5)                          |
| Respiratory, thoracic and mediastinal disorders                     | 5 (41.7)                         | 11 (39.3)                       | 4 (26.7)                         | 20 (36.4)                        |
| Skin and subcutaneous tissue disorders                              | 6 (50.0)                         | 6 (21.4)                        | 2 (13.3)                         | 14 (25.5)                        |

Study N2301 Week-16 IA, including Epoch 2 and available data from Epochs 3 and 4.

A patient with multiple AEs within a primary SOC is counted only once in the total row. A patient with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment. SOCs are presented in alphabetical order.

MedDRA Version 18.1 has been used for the reporting of AEs.

ACZ885=canakinumab  
Source: Sponsor's submission

#### **7.4.2 Laboratory Findings**

The potential drug-induced liver injury events consisted mainly of mild hepatic transaminase elevations and none was confirmed to reflect severe liver injury attributable to canakinumab and without other identified causes. Less than five percent of those subjects exposed to canakinumab experienced a neutropenia-related AE.

The rate of all biochemistry abnormalities was lower or comparable to patients in the pooled CAPS population. The increases in creatinine in the Total ACZ group (28.4%) were comparable to CAPS patients (26.6%).

#### **7.4.3 Vital Signs**

Overall, the majority of subjects exposed to canakinumab maintained normal vital sign measurements for crFMF, for HIDS/MKD, and for TRAPS.

#### **7.4.4 Electrocardiograms (ECGs)**

There were no abnormalities attributable to canakinumab.

#### **7.4.5 Special Safety Studies/Clinical Trials**

Not applicable.

#### **7.4.6 Immunogenicity**

The immunogenicity assay used was validated to detect anti-canakinumab antibodies in human serum. No samples were confirmed as being immunogenicity-positive, and thus titration and neutralizing antibody determinations were not performed.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

Subjects having a cumulative dose >600 mg over 16 weeks were uptitrated to canakinumab 300 mg and would not necessarily have the same characteristics as subjects in the ≤600 mg group (those who responded to canakinumab 150 mg); subjects in the two dose level groups may be at

different risks of experiencing AEs, confounding the interpretation of potential dose dependencies. Extrapolating the relative safety of a specific dose level of canakinumab becomes problematic.

Nonetheless, the incidence of AEs was generally higher (93% versus 79%) in subjects with a dose level >600 mg versus <600 mg in subjects exposed to canakinumab across all cohorts.

The most frequently affected primary SOC in those subjects exposed to canakinumab was infections and infestations, with a substantially higher incidence of AEs in subjects with cumulative doses >600 mg (50% versus 78% for those with cumulative doses ≤600 mg and >600 mg, respectively). Other SOCs with substantially higher incidence of AEs in subjects with higher doses were: blood and lymphatic system disorders (3% versus 22%), eye disorders (2% versus 14%^), general disorders and administration site conditions (34% versus 54%), gastrointestinal disorders (31% versus 51%), musculoskeletal and connective tissue disorders (18% versus 44%), nervous system disorders (17% versus 34%), respiratory, thoracic and mediastinal disorders (18% versus 36%), and skin and subcutaneous tissue disorders (15% versus 25%) for those with cumulative doses ≤600 mg and >600 mg, respectively.

The AEs with the higher incidence in subjects with cumulative doses >600 mg compared with subjects on doses ≤600 mg included abdominal pain, arthralgia, cough, diarrhea, headache, injection site reaction, nasopharyngitis, oropharyngeal pain, pyrexia, rhinitis, and vomiting.

### **7.5.2 Time Dependency for Adverse Events**

Exposure adjusted (per 100 patient-years) event rates of AEs were analyzed for Study N2301 by dose level, with the pattern of AEs following similar patterns by SOC and PT as AEs by dose level.

The most frequently affected primary SOC was infections and infestations in subjects exposed to canakinumab, with a similar incidence of AEs in subjects with cumulative doses ≤600 mg and >600 mg; there was no indication of a dose response.

### **7.5.3 Drug-Demographic Interactions**

Subgroup evaluation of AEs was limited due to small sample sizes in each subgroup and the small number of AEs; however, no consistent correlations between the types and frequency of AEs based on race, gender, or age (including children ages 2 to 4

years) were identified.

Clinically notable hematological abnormalities by weight were presented for subjects with weight  $\leq 40$  kg and  $>40$  kg at baseline. A higher percentage of subjects in the  $\leq 40$  kg group (who received 2 mg/kg in place of 150 mg canakinumab) showed a decrease in platelet count and neutrophil count compared with the  $>40$  kg group.

#### **7.5.4 Drug-Disease Interactions**

None noted.

#### **7.5.5 Drug-Drug Interactions**

None noted.

### **7.6 Additional Safety Evaluations**

n/a

#### **7.6.1 Human Carcinogenicity**

No specific trials were conducted to assess for carcinogenicity in humans.

#### **7.6.2 Human Reproduction and Pregnancy Data**

No studies of canakinumab were conducted in pregnant or lactating women.

#### **7.6.3 Pediatrics and Assessment of Effects on Growth**

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.

#### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

Not applicable.

## 7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120 day safety update. The safety cut-off used in the original submission was October 19, 2011. The safety cut-off used for the safety update was October 1, 2012. No new patients were enrolled in the study between October 19, 2011 and October 1, 2012. Data from this submission did not reveal any new issues not already commented on.

## 8 Postmarket Experience

The Sponsor submitted a periodic safety update report for canakinuamb for the reporting period of January 1, 2015 to June 30, 2015, to summarize the post-marketing experience. Canakinumab is currently approved in 74 countries for varying indications. In the United States, canakinumab is approved for the treatment of CAPS and SJIA.

For the reporting period from January 1, 2015 to June 30, 2015, the Sponsor estimated that the world-wide exposure to canakinumab was <sup>(b) (4)</sup> patient treatment years. The estimated cumulative patient exposure since June 30, 2015 is <sup>(b) (4)</sup> patient treatment years. No safety information was included in this submission that changed the known risks of canakinumab.

## 9 Appendices

### 9.1 Literature Review/References

Piram M, et al (2014) Ann Rheum Dis; 73:2168-73.

2 Hinson DD, et al (1998) American Journal of Medical Genetics; 78:408-12.

### 9.2 Labeling Recommendations

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.

### Dosage and administration

- Recommend changing the dosage, (b) (4)

### 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, the recommendation is to (b) (4) only include incidence rates.

### 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).

### 9.3 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.

Appendix:

Clinical Investigator Financial Disclosure  
 Review Template

Application Number: **BLA 125319 supplements 85/86/87**

Submission Date(s): **March 23, 2016**

Applicant: **Novartis**

Product: **Canakinumab**

Reviewer: **Mark Borigini, MD**

Date of Review: **August 29, 2016**

Covered Clinical Study (Name and/or Number): (b) (6)

|                                                                                                                                                                                                                              |                                         |                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                                                                                                                               | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from applicant) |
| Total number of investigators identified:                                                                                                                                                                                    | (b) (6)                                 |                                                           |
| Number of investigators who are sponsor employees (including both full-time and part-time employees):                                                                                                                        | <b>0</b>                                |                                                           |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):                                                                                                                                   | <b>3</b>                                |                                                           |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <b>N/A</b> |                                         |                                                           |
| Compensation to the investigator for conducting the study where the value could be                                                                                                                                           |                                         |                                                           |

|                                                                                                                                                                                                                                              |                                         |                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| influenced by the outcome of the study: 0<br>Significant payments of other sorts: 2<br>Proprietary interest in the product tested held by investigator: 1<br>Significant equity interest held by investigator in sponsor of covered study: 0 |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                  | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request details from applicant)     |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                     | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <b>0</b>                                                                                                                                                  |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                   | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from applicant) |

Reviewer's Comments: Any bias resulting from these arrangements is minimized by independent data monitoring by Novartis; multiple investigators used in the studies and double-blind placebo controlled trials.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARK BORIGINI  
08/30/2016

JANET W MAYNARD  
08/30/2016

## CLINICAL FILING CHECKLIST FOR BLA 125319

**BLA Number: 125319**

**Applicant: Novartis**

**Stamp Date: March 23 (s85),  
March 28 (s86), and March 29,  
2016 (s87)**

**Drug Name: Canakinumab  
(Ilaris®)**

**BLA Type: Supplemental**

On initial overview of the NDA/BLA application for filing:

|                                       | Content Parameter                                                                                                                                                                                                                                                                                                                                                               | Yes | No | NA | Comment                                                                                                                            |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|----|------------------------------------------------------------------------------------------------------------------------------------|
| <b>FORMAT/ORGANIZATION/LEGIBILITY</b> |                                                                                                                                                                                                                                                                                                                                                                                 |     |    |    |                                                                                                                                    |
| 1.                                    | Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).                                                                                                                                                                                                                                                          | X   |    |    |                                                                                                                                    |
| 2.                                    | Is the clinical section legible and organized in a manner to allow substantive review to begin?                                                                                                                                                                                                                                                                                 | X   |    |    |                                                                                                                                    |
| 3.                                    | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?                                                                                                                                                                                                                                                     | X   |    |    |                                                                                                                                    |
| 4.                                    | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?                                                                                                                                                                                                                    | X   |    |    |                                                                                                                                    |
| 5.                                    | Are all documents submitted in English or are English translations provided when necessary?                                                                                                                                                                                                                                                                                     | X   |    |    |                                                                                                                                    |
| <b>LABELING</b>                       |                                                                                                                                                                                                                                                                                                                                                                                 |     |    |    |                                                                                                                                    |
| 6.                                    | Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm</a> ) | X   |    |    |                                                                                                                                    |
| <b>SUMMARIES</b>                      |                                                                                                                                                                                                                                                                                                                                                                                 |     |    |    |                                                                                                                                    |
| 7.                                    | Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?                                                                                                                                                                                                                                                                                   | X   |    |    |                                                                                                                                    |
| 8.                                    | Has the applicant submitted the integrated summary of safety (ISS)?                                                                                                                                                                                                                                                                                                             | X   |    |    |                                                                                                                                    |
| 9.                                    | Has the applicant submitted the integrated summary of efficacy (ISE)?                                                                                                                                                                                                                                                                                                           | X   |    |    |                                                                                                                                    |
| 10.                                   | Has the applicant submitted a benefit-risk analysis for the product?                                                                                                                                                                                                                                                                                                            | X   |    |    |                                                                                                                                    |
| 11.                                   | Indicate if the Application is a 505(b)(1) or a 505(b)(2).                                                                                                                                                                                                                                                                                                                      | X   |    |    | 505(b)1                                                                                                                            |
| <b>505(b)(2) Applications</b>         |                                                                                                                                                                                                                                                                                                                                                                                 |     |    |    |                                                                                                                                    |
| 12.                                   | If appropriate, what is the relied upon listed drug(s)?                                                                                                                                                                                                                                                                                                                         |     |    | X  |                                                                                                                                    |
| 13.                                   | Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?                                                                                                                                                                                                                          |     |    | X  |                                                                                                                                    |
| 14.                                   | Describe the scientific bridge (e.g., BA/BE studies)                                                                                                                                                                                                                                                                                                                            |     |    | X  |                                                                                                                                    |
| <b>DOSAGE</b>                         |                                                                                                                                                                                                                                                                                                                                                                                 |     |    |    |                                                                                                                                    |
| 15.                                   | If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)?                                                                                                                                                                                                          | X   |    |    | While the applicant has not performed formal dose-ranging studies, dose considerations were explored in several open label phase 2 |

File name: Clinical Filing Checklist for BLA 125319

## CLINICAL FILING CHECKLIST FOR BLA 125319

|                 | Content Parameter                                                                                                                                                                                                                                           | Yes | No | NA | Comment                                                                                                                                                                                                                                                     |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                 |                                                                                                                                                                                                                                                             |     |    |    | studies (DTR01, D2204, D2402, D2203) and informed by previous dose considerations in other inflammatory conditions for which canakinumab is approved (sJIA and CAPS). The applicant's strategy for dose selection was reasonable for these rare conditions. |
| <b>EFFICACY</b> |                                                                                                                                                                                                                                                             |     |    |    |                                                                                                                                                                                                                                                             |
| 16.             | Do there appear to be the requisite number of adequate and well-controlled studies in the application?                                                                                                                                                      | X   |    |    | Pivotal Study:<br>CACZ885N2301<br><br>Indication: FMF, HIDS/MKD, TRAPS                                                                                                                                                                                      |
| 17.             | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X   |    |    |                                                                                                                                                                                                                                                             |
| 18.             | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.                                                                     | X   |    |    |                                                                                                                                                                                                                                                             |
| 19.             | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?                                                                                                         | X   |    |    |                                                                                                                                                                                                                                                             |
| <b>SAFETY</b>   |                                                                                                                                                                                                                                                             |     |    |    |                                                                                                                                                                                                                                                             |
| 20.             | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?                                                                                                          | X   |    |    |                                                                                                                                                                                                                                                             |
| 21.             | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?                                                                                                              |     |    | X  |                                                                                                                                                                                                                                                             |
| 22.             | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?                                                                                                                                            | X   |    |    |                                                                                                                                                                                                                                                             |
| 23.             | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dosage (or dosage range) believed to be efficacious?                                                       | X   |    |    |                                                                                                                                                                                                                                                             |

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

File name: Clinical Filing Checklist for BLA 125319

## CLINICAL FILING CHECKLIST FOR BLA 125319

|                                                                                  | <b>Content Parameter</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>Yes</b> | <b>No</b> | <b>NA</b> | <b>Comment</b>                                                           |
|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|-----------|--------------------------------------------------------------------------|
| 24.                                                                              | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?                                                                                                                                                                                                                                                                                                                                                                                                                            |            |           | X         |                                                                          |
| 25.                                                                              | Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            | X         |           |                                                                          |
| 26.                                                                              | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?                                                                                                                                                                                                                                                                                                                                                                                                                                        | X          |           |           |                                                                          |
| 27.                                                                              | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?                                                                                                                                                                                                                                                                                                                                                                                                                                             | X          |           |           |                                                                          |
| <b>OTHER STUDIES</b>                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |           |           |                                                                          |
| 28.                                                                              | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | X          |           |           |                                                                          |
| 29.                                                                              | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?                                                                                                                                                                                                                                                                                                                                                                                                         |            |           | X         |                                                                          |
| <b>PEDIATRIC USE</b>                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |           |           |                                                                          |
| 30.                                                                              | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | X          |           |           | The applicant has orphan designation for the three proposed indications. |
| <b>PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |           |           |                                                                          |
| 31.                                                                              | For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see <a href="http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm">http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm</a> )? | X          |           |           | PLLR labeling was submitted in supplement 84, which is under review      |
| <b>ABUSE LIABILITY</b>                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |           |           |                                                                          |
| 32.                                                                              | If relevant, has the applicant submitted information to assess the abuse liability of the product?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |            |           | X         |                                                                          |
| <b>FOREIGN STUDIES</b>                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |           |           |                                                                          |
| 33.                                                                              | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?                                                                                                                                                                                                                                                                                                                                                                                                                                                   | X          |           |           | All studies were globally conducted and, thus, included US sites.        |
| <b>DATASETS</b>                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |            |           |           |                                                                          |
| 34.                                                                              | Has the applicant submitted datasets in a format to allow reasonable review of the patient data?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | X          |           |           |                                                                          |
| 35.                                                                              | Has the applicant submitted datasets in the format agreed to previously by the Division?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | X          |           |           |                                                                          |

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: Clinical Filing Checklist for BLA 125319

## CLINICAL FILING CHECKLIST FOR BLA 125319

|                               | <b>Content Parameter</b>                                                                                                                                                | <b>Yes</b> | <b>No</b> | <b>NA</b> | <b>Comment</b> |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|-----------|----------------|
| 36.                           | Are all datasets for pivotal efficacy studies available and complete for all indications requested?                                                                     | X          |           |           |                |
| 37.                           | Are all datasets to support the critical safety analyses available and complete?                                                                                        | X          |           |           |                |
| 38.                           | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?                                                        | X          |           |           |                |
| <b>CASE REPORT FORMS</b>      |                                                                                                                                                                         |            |           |           |                |
| 39.                           | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?                                  | X          |           |           |                |
| 40.                           | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?    | X          |           |           |                |
| <b>FINANCIAL DISCLOSURE</b>   |                                                                                                                                                                         |            |           |           |                |
| 41.                           | Has the applicant submitted the required Financial Disclosure information?                                                                                              | X          |           |           |                |
| <b>GOOD CLINICAL PRACTICE</b> |                                                                                                                                                                         |            |           |           |                |
| 42.                           | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X          |           |           |                |

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_Yes\_\_**

If the Application is not fileable from the clinical 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.

1. We note the inclusion of multiple endpoints and analyses in the CLINICAL STUDIES sections of each of the proposed labels for the three indications. A focus of the review will be assessing the extent to which the proposed information adds to an understanding of the clinical effects of the drug and how the drug should be used. It is unclear whether the proposed amount of detail is necessary to inform this understanding.

3. We note your proposal to limit the intended FM indication to those patients in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response. As noted in the Advice letter dated February 7, 2014, and the meeting minutes dated July 1, 2015, it is unclear if it is reasonable to limit the proposed FMF indication since the efficacy of canakinumab might be similar regardless of colchicine response or intolerance.

File name: Clinical Filing Checklist for BLA 125319

# CLINICAL FILING CHECKLIST FOR BLA 125319

Mark Borigini, MD

Reviewing Medical Officer

Date

Janet Maynard, MD, MHS

Clinical Team Leader

Date



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

[www.fda.gov](http://www.fda.gov)

# BLA 125319 s85, 86, 87 Canakinumab (ACZ885) for FMF, HIDS/MKD, TRAPS

Filing Meeting  
May 03, 2015

## Introduction

- **Name:** Canakinumab (ILARIS®)
- **Class:** IL-1 $\beta$  inhibitor
  - Human monoclonal antibody against IL-1 $\beta$
- **Approved indications:**
  - Cryopyrin-Associated Periodic Syndromes (CAPS), including FCAS and MWS
  - Active Systemic JIA in patients aged 2 years and older
- **Proposed indications:**
  - FMF, HIDS/MKD, and TRAPS
- **Route:** lyophilized powder 180 mg (150 mg/mL)
- **Summary:** Fileable from a clinical perspective



## Proposed Indications

- 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 Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in patients aged 2 years and older.
- Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS) in patients aged 2 years and older.



## Approved and Proposed Doses

- **Approved doses:**
  - CAPS
    - >40 kg: 150 mg Q8wk
    - 15-40 kg: 2mg/kg (can increase to 3 mg/kg for inadequate response) Q8wk
  - SJIA
    - $\geq 7.5$  kg: 4 mg/kg (max 300mg) SC Q4wk
- **Proposed doses:**
  - TRAPS, HIDS/MKD, FMF
    - >40kg: 150 mg Q4wk (b) (4) and then increase to 300 mg q4wk)
    - <40 kg: 2mg/kg (can increase to 4 mg/kg for inadequate response) Q4wk



## Clinical Overview

- Autoinflammatory periodic fever syndromes include:
  - TRAPS, HIDS/MKD, CAPS, and Periodic Fever
- Common to all these is that each has a genetic mutation identified
- Manifested by episodic fever, myalgias, arthralgias, and serositis
  - Febrile episodes impact quality of life
  - Major source of morbidity is progressive secondary amyloidosis

## Clinical Overview—FMF

- Mutations in the MEFV gene identified in FMF lead to functional change in the pyrin protein which interacts with caspase 1 and PSTPIP, a protein causally involved in the syndrome of pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA syndrome), another autoinflammatory disease. These genetic alterations in the pyrin gene lead to enhanced IL-1  $\beta$  secretion and autoinflammation in an experimental mouse model
- Approximately 30% to 40% of cases of FMF are only partially responsive to colchicine and 5% are considered resistant
  - Only approved medication for treatment of FMF in US is colchicine



## Clinical Overview—HIDS/MKD

- Febrile attacks that last 3 to 7 days, every 4 to 6 weeks
  - Abdominal pain, vomiting, diarrhea, headache, arthralgia/arthritis
  - Rash
  - Continuous spectrum of disease phenotypes (including severe disorder, mevalonic aciduria, with cerebellar ataxia, mental retardation, failure to thrive, and early death)
- Mutations in gene encoding mevalonate kinase
  - originally named HIDS based on high serum levels of IgD
- MKD is overall disease name
  - specifying the type of disease with term, HIDS, for phenotype of fever episodes prospectively included in Study CACZ885N2301.



## Clinical Overview—TRAPS

- Characterized by febrile attacks that tend to last longer than those of FMF or HIDS.
  - Attacks are associated with abdominal pain, severe myalgia, and painful erythema on the trunk or extremities.
- An estimated 14% to 25% of TRAPS patients develop reactive amyloidosis.

## Regulatory History

- Orphan designation for TRAPS (Sept 2012), HIDS/MKD (Dec 2013), and FMF (Dec 2013)
- Pre-Phase 3 Meeting (05/13/13)
  - FDA refused to accept <sup>(b) (4)</sup> [REDACTED]
  - FDA suggested randomized withdrawal period following the initial 16-week randomized period
    - Responders to continue canakinumab or placebo withdrawal with assessment of disease flares as efficacy outcome
      - Used as supportive evidence
  - FDA disagreed with <sup>(b) (4)</sup> [REDACTED]
    - TRAPS, HIDS, FMF to be treated as individual disorders
      - Efficacy to be based on results from each treatment arm

## Regulatory History (cont)

- Type C written responses (10/11/13)
  - (b) (4)
  - Reasonable to bridge LYO to vial based on analytical comparisons
- FDA Advice Letter (2/10/14)
  - Concern with study design: endpoint and lead-in phase length
- Pre-sBLA meeting (6/2/15)
  - Reasonable to submit vial in separate submission
  - Submit randomized withdrawal and placebo controlled data
- Type C WRO (2/12/16)
  - Provide justification for primary endpoint
- Breakthrough therapy designation for TRAPS, HIDS/MKD, FMF (2/26/16)



## Clinical Program

- Phase 3 study CACZ885N2301 (N2301)
  - 16-week randomized, double blind, placebo controlled treatment phase (Epoch 2)
  - 24-week randomized withdrawal phase; re-randomized to placebo or canakinumab 150 mg q8wk (Epoch 3)
  - 72-wk open-label treatment phase (Epoch 4)
- 4 completed Phase 2 studies in the 3 indications
- 5 completed Phase 2 and 3 studies in the approved indication of CAPS

# Supportive Phase 2 Studies

**Table 1-2 Summary of earlier, uncontrolled studies in crFMF, HIDS/MKD and TRAPS**

| Study                                            | Design                                                                                                      | Treatments & Durations                                                                                                       | Main variables                                                                                                                                                                                                                                                             |
|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Open-label Phase 2 studies (uncontrolled)</i> |                                                                                                             |                                                                                                                              |                                                                                                                                                                                                                                                                            |
| <b>DTR01</b><br>N=9<br><b>(6 mo)</b>             | Open label, efficacy/safety study in <b>crFMF</b> patients ≥12 years old during treatment & follow up       | <b>150 mg</b> (2mg/kg if < 40 kg) sc q4w<br>(3 mo)<br>Follow up (2 mo)                                                       | <ul style="list-style-type: none"> <li>- Proportion with ≥ 50% less attacks on treatment vs. baseline (1°)</li> <li>- VAS assessment for change in severity (2°)</li> <li>- Reduction in inflammatory markers (SAA, CRP, ESR) (2°)</li> </ul>                              |
| <b>D2204</b><br>N=7<br><b>(6 mo)</b>             | Efficacy/safety study in <b>crFMF</b> patients ≥4 years old during treatment & follow up                    | <b>150 mg</b> (2mg/kg if < 40 kg) sc q4w<br>(3 mo)<br>Follow up (2 mo)                                                       | <ul style="list-style-type: none"> <li>- Proportion with ≥ 50% less attacks on treatment vs. baseline (1°)</li> <li>- Changes in severity and duration of acute attacks during treatment (2°)</li> <li>- Reduction in inflammatory markers (SAA, CRP, ESR) (2°)</li> </ul> |
| <b>D2402</b><br>N=9<br><b>(3 yr)</b>             | Efficacy/safety study in <b>HIDS/MKD</b> patients ≥ 2 years old during treatment, withdrawal & re-treatment | <b>300 mg</b> (4mg/kg if ≤ 40 kg) sc q6w<br>(6 mo)<br>Withdrawal (6 mo)<br><b>300 mg</b> (4mg/kg if ≤ 40 kg) sc. q6w (24 mo) | <ul style="list-style-type: none"> <li>- Flare frequency vs baseline (1°)</li> <li>- Physician &amp; patient global assessment of HIDS flare severity (2°)</li> <li>- Physician &amp; patient severity assessment of key HIDS symptoms (2°)</li> </ul>                     |
| <b>D2203</b><br>N=20<br><b>(33 mo)</b>           | Efficacy/safety study in <b>TRAPS</b> patients ≥ 4 years old during treatment, withdrawal & re-treatment    | <b>150 mg</b> (2 mg/kg if ≤ 40 kg) sc q4w<br>(4 mo)<br>Withdrawal (5 mo)<br><b>150 or 300 mg</b> sc q8w<br>(24 mo)           | <ul style="list-style-type: none"> <li>- Complete/Almost complete response (clinical &amp; SAA/CRP) (1°)</li> <li>- Proportion with Physician global assessment score ≤1 (2°)</li> <li>- Reduction in inflammatory markers (SAA, CRP) (2°)</li> </ul>                      |

N = total number of patients enrolled, 1° = primary variable, 2° = secondary variable(s); mo=months; yr=years, sc=subcutaneous; q4w=every 4 weeks; q8w=every 8 weeks  
Dose up-titration was permitted.

Source: [Synopses of Individual Studies], [Tabular Listing of All Clinical Studies]



## Supportive data from CAPS clinical program Phase 2 and 3 trials in CAPS

| Study                  | Design                   | Patient population                         |
|------------------------|--------------------------|--------------------------------------------|
| <b>Phase 2 studies</b> |                          |                                            |
| A2102                  | OL, dose titration study | MWS, NOMID, FCAS/FCU                       |
| D2201                  | OL                       | NOMID, CINCA                               |
| <b>Phase 3 studies</b> |                          |                                            |
| D2304                  | R, DB, PC 3 part study   | MWS                                        |
| D2306                  | OL, single treatment arm | FCAS, MWS, NOMID                           |
| D2308                  | OL                       | Japanese patients with FCAS,<br>MWS, NOMID |



# Pivotal Clinical Trial Summary: N2301

**Table 1-1 Summary of pivotal, controlled study in TRAPS, HIDS/MKD, crFMF**

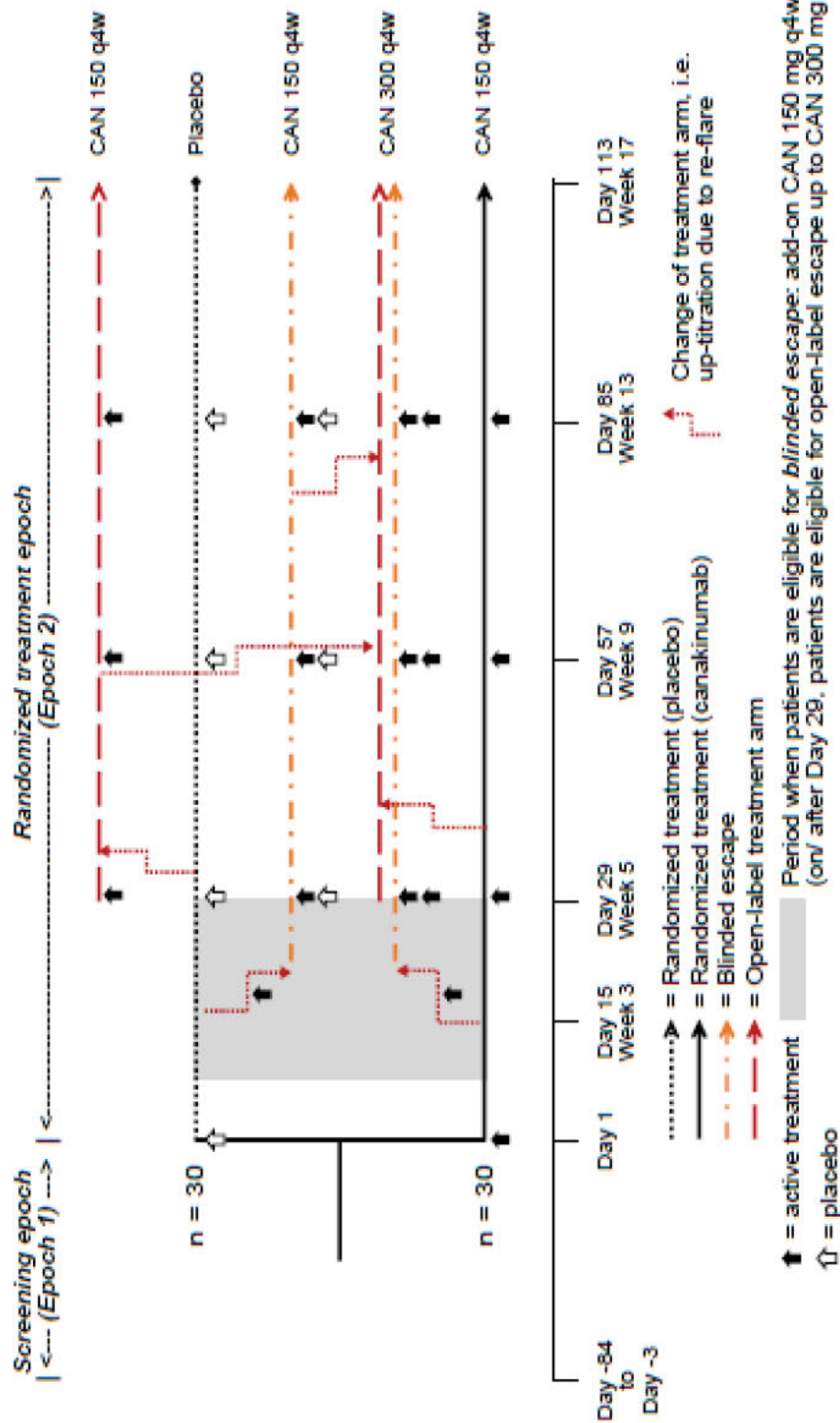
| Study                                     | Design                                                                                                                                                                            | Treatments & Durations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Main efficacy variables                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal Phase 3 study (controlled)</b> |                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| N2301 (28 mo)                             | Placebo-controlled, randomized double-blind, efficacy/safety study in crFMF, HIDS/MKD, TRAPS (Epoch 2), then randomized withdrawal (Epoch 3), then open label treatment (Epoch 4) | <p><b>Epoch 1</b> (12 wks): screening period</p> <p><b>Epoch 2</b> (16 wks) (completed): 150 mg (2mg/kg if ≤ 40 kg) sc q4w or placebo (<i>blinded</i>)</p> <p>N=185 (181 randomized patients: 63 crFMF, 72 HIDS/MKD and 46 TRAPS; and 4 non-randomized patients)</p> <p><b>Epoch 3</b> (24 wks) (ongoing): 150 mg (2mg/kg if ≤ 40 kg) sc q8w or placebo (<i>blinded</i>)</p> <p>N=170 from Epoch 2 + 18 TRAPS roll-over patients</p> <p><b>Epoch 4*</b> (72 wks) (ongoing): 150 mg or 300 mg sc q4w or q8w (<i>open-label</i>)</p> | <p><b>Primary:</b></p> <ul style="list-style-type: none"> <li>- Proportion with resolution of index flare and no new flare up to the end of Epoch 2</li> </ul> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>- Proportion with PGA score &lt; 2 at the end of Epoch 2</li> <li>- Proportion with CRP ≤ 10 mg/L at the end of Epoch 2</li> <li>- Proportion with SAA ≤ 10 mg/L at the end of Epoch 2</li> </ul> |

CRP=C-reactive protein; N = total number of patients enrolled; PGA=Physician's global assessment of disease activity; SAA=serum amyloid A; sc=subcutaneous, q4w=every 4 weeks; q8w=every 8 weeks  
 Patients ≤ 40 kg were dosed by kg of body weight, patients > 40 kg received a fixed dose.  
 Dose up-titration was permitted based on assessment of response.

\* Number of patients who entered Epoch 4 is not yet available as Epoch 3 is ongoing at the time of reporting.  
 Source: [Synopses of Individual Studies], [Tabular Listing of All Clinical Studies]

# N2301 Summary (cont)

**Figure 2-1 Cohort detail: Screening (Epoch 1) and randomized treatment (Epoch 2)**





## N2301: Baseline Demographics

- FMF: n=63
  - Mean age: 22 years, 3 patients <6 years
- HIDS/MKD: n=72
  - Mean age: 14 years, 17 patients <6 years
- TRAPS: n=46
  - Mean age: 22 years; 7 patients <6 years



## N2301: Primary Efficacy

- Proportion of responders within each cohort
  - Resolution of his/her index disease flare (i.e., PGA < 2 and CRP either  $\leq 10$  mg/L or  $\geq 70\%$  reduction from baseline) at Day 15 and did not experience a new flare (i.e., PGA  $\geq 2$  and CRP  $\geq 30$  mg/L) before the end of Epoch 2 (end of Week 16)
- In the primary analysis, patients who needed dose escalation in the canakinumab 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 as non-responders



## N2301: Secondary Efficacy Endpoints

- 3 secondary efficacy endpoints in Epoch 2:
  - % patients who achieved a PGA < 2 (“minimal” or “absent” disease activity)
  - % patients with serologic remission (defined as CRP  $\leq$  10 mg/L)
  - % patients with normalized SAA (defined as SAA  $\leq$  10 mg/L), all assessed at the end of Week 16

# N2301: Proportion of Responders

**Table 4-1 Primary analysis: comparison between treatment groups for the proportion of responders after 16 weeks by cohort (Full analysis set)**

| Cohort | ACZ885 150 mg q4w |                |                | Placebo       |                      |                         | Treatment comparison     |                     |                   |
|--------|-------------------|----------------|----------------|---------------|----------------------|-------------------------|--------------------------|---------------------|-------------------|
|        | n/M (%)           | 95% CI         | n/M (%)        | 95% CI        | n/M (%)              | 95% CI                  | Risk difference (95% CI) | Odds Ratio (95% CI) | One-sided p-value |
| crFMF  | 19/31<br>(61.29)  | (42.19, 78.15) | 2/32<br>(6.25) | (0.77, 20.81) | 0.55<br>(0.31, 0.73) | 23.75<br>(4.38, 227.53) |                          |                     | <0.0001*          |
| HIDS   | 13/37<br>(35.14)  | (20.21, 52.54) | 2/35<br>(5.71) | (0.70, 19.16) | 0.29<br>(0.06, 0.50) | 8.94<br>(1.72, 86.41)   |                          |                     | 0.0020*           |
| TRAPS  | 10/22<br>(45.45)  | (24.39, 67.79) | 2/24<br>(8.33) | (1.03, 27.00) | 0.37<br>(0.08, 0.61) | 9.17<br>(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: [Study N2301 Week 16-Table 11-7]

# N2301: Uptitration

**Table 4-7 Patients with blinded escape at Days 8 to 28 (Full analysis set)**

| Cohort | ACZ885 150 mg q4w |                |               | Placebo        |                |  |
|--------|-------------------|----------------|---------------|----------------|----------------|--|
|        | n/M (%)           | 95% CI         | n/M (%)       | 95% CI         | 95% CI         |  |
| crFMF  | 5/31 (16.13)      | (5.45, 33.73)  | 20/32 (62.50) | (43.69, 78.90) | (43.69, 78.90) |  |
| HIDS   | 12/37 (32.43)     | (18.01, 49.79) | 22/35 (62.86) | (44.92, 78.53) | (44.92, 78.53) |  |
| TRAPS  | 8/22 (36.36)      | (17.20, 59.34) | 18/24 (75.00) | (53.29, 90.23) | (53.29, 90.23) |  |

n=number of patients with blinded escape; M=total number of patients evaluated

Source: [Study N2301 Week 16-Table 14.2-3.11]

# N2301: Resolution of Index Flare

**Table 4-2 Resolution of index flare (Full analysis set)**

| Cohort | Resolution at Day 15* |                    | Resolution at Day 29*<br>for patients with no resolution at Day 15            |                                                                             |                                                                          |                                                                          |
|--------|-----------------------|--------------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
|        | 150 mg q4w<br>n/M (%) | Placebo<br>n/M (%) | Randomized to<br>150mg q4w<br>and received 300 mg<br>q4w by Day 29<br>n/M (%) | Randomized to<br>Placebo and<br>received 150 mg<br>q4w by Day 29<br>n/M (%) | Randomized to<br>Placebo and received<br>300 mg q4w by Day 29<br>n/M (%) | Randomized to<br>Placebo and received<br>300 mg q4w by Day 29<br>n/M (%) |
| crFMF  | 25/31 (80.65)         | 10/32 (31.25)      | 3/5 (60.0)                                                                    | 14/18 (77.8)                                                                | 1/3 (33.3)                                                               |                                                                          |
| HIDS   | 24/37 (64.86)         | 13/35 (37.14)      | 4/15 (26.7)                                                                   | 10/18 (55.6)                                                                | 3/6 (50.0)                                                               |                                                                          |
| TRAPS  | 14/22 (63.64)         | 5/24 (20.83)       | 5/8 (62.5)                                                                    | 10/16 (62.5)                                                                | 0/2                                                                      |                                                                          |

n=number of patients with the response; M=number of patients evaluated for that response in each cohort

\*Resolution of index disease flare (PGA <2 and CRP ≤ 10mg/L or reduction ≥ 70% from baseline)

Source: [Study N2301 Week 16-Table 11-12]

# Primary and Secondary Endpoints

**Table 4-3 Results for the primary and secondary efficacy variables after 16 weeks by cohort (Full analysis set)**

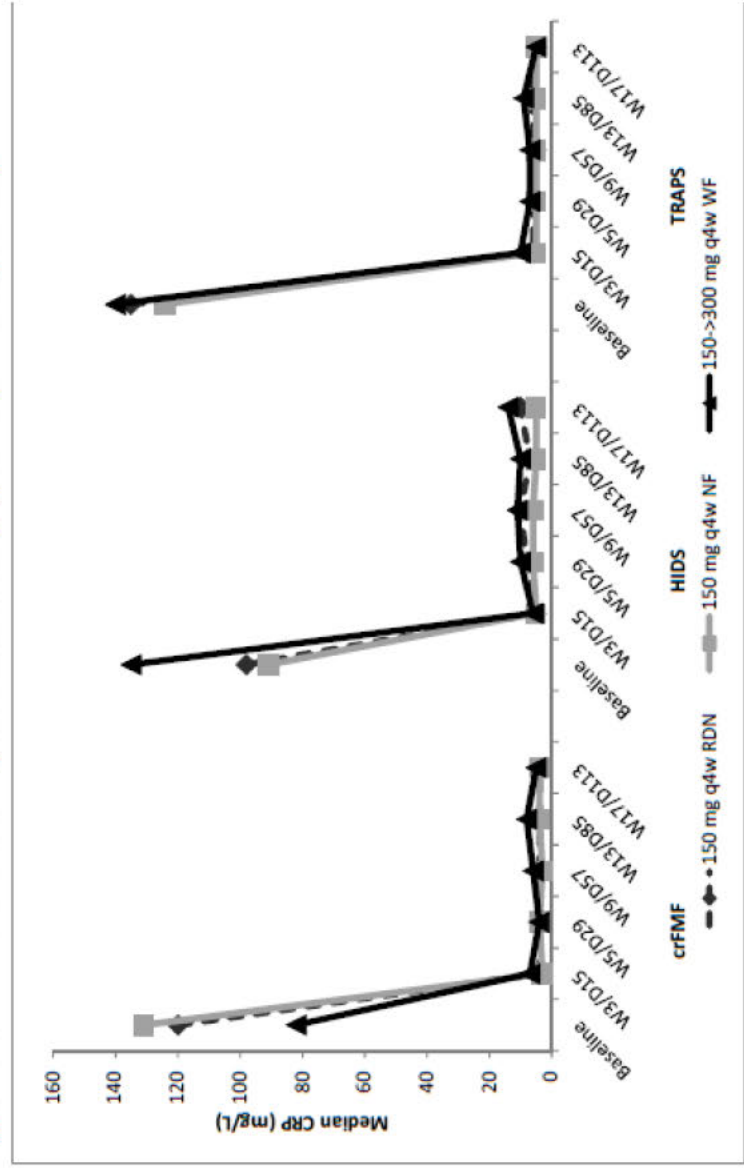
| Variable         | crFMF             |                    |          | HIDS/MKD          |                    |         | TRAPS             |                    |         |
|------------------|-------------------|--------------------|----------|-------------------|--------------------|---------|-------------------|--------------------|---------|
|                  | ACZ885<br>n/M (%) | Placebo<br>n/M (%) | p-value  | ACZ885<br>n/M (%) | Placebo<br>n/M (%) | p-value | ACZ885<br>n/M (%) | Placebo<br>n/M (%) | p-value |
| Responder        | 19/31<br>(61.29)  | 2/32<br>(6.25)     | <0.0001* | 13/37<br>(35.14)  | 2/35<br>(5.71)     | 0.0020* | 10/22<br>(45.45)  | 2/24<br>(8.33)     | 0.0050* |
| PGA < 2          | 20/31<br>(64.52)  | 3/32<br>(9.38)     | <0.0001* | 17/37<br>(45.95)  | 2/35<br>(5.71)     | 0.0006* | 10/22<br>(45.45)  | 1/24<br>(4.17)     | 0.0028* |
| CRP<br>≤ 10 mg/L | 21/31<br>(67.74)  | 2/32<br>(6.25)     | <0.0001* | 15/37<br>(40.54)  | 2/35<br>(5.71)     | 0.0010* | 8/22<br>(36.36)   | 2/24<br>(8.33)     | 0.0149* |
| SAA<br>≤ 10 mg/L | 8/31<br>(25.81)   | 0/32<br>(0.00)     | 0.0286   | 5/37<br>(13.51)   | 1/35<br>(2.86)     | 0.0778  | 6/22<br>(27.27)   | 0/24<br>(0.00)     | 0.0235* |

Results are shown for the randomized canakinumab 150 mg q4w and placebo groups in each cohort. n=number of protocol-defined responders or number of patients who had PGA < 2, CRP ≤ 10 mg/L or SAA ≤ 10 mg/L after 16 weeks; M=number of patients with evaluable data for each variable

\* Indicates statistical significance (one-sided) at the 0.025 level for the primary endpoint based on Fisher exact test, or statistical significance (one-sided) at the 0.025 level for each secondary endpoint based on the logistic regression model with treatment group and baseline PGA, CRP or SAA as explanatory variables. Source: [Study N2301 Week 16-Table 11-7, Table 11-14, Table 11-16 and Table 11-18]

# N2301: CRP

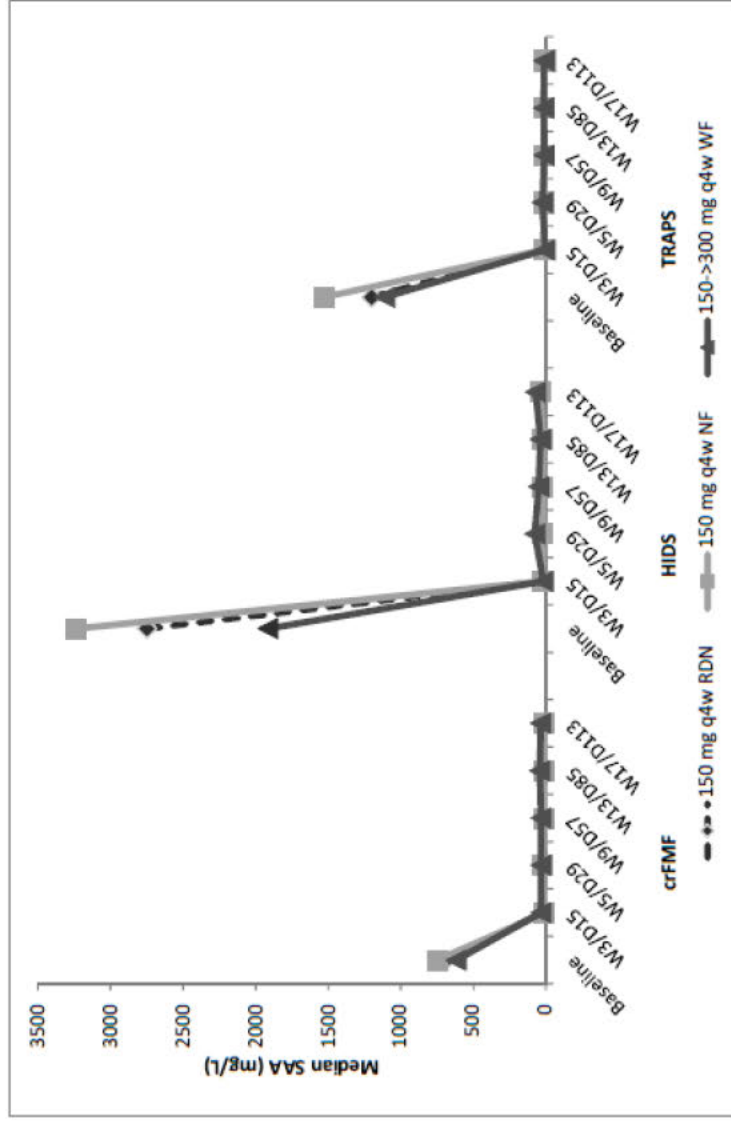
Figure 3-4 CRP values by visit and cohort, Epoch 2 (Full analysis set)



150 mg q4w RDN=initial randomized 150 mg q4w group (includes patients up-titrated to 300 mg q4w); 150 mg q4w NF=no flare 150 mg q4w group; 150 mg->300 mg q4w WF= $\geq$  1 flare 150 mg to 300 mg q4w group

# N2301: SAA

Figure 3-5 SAA values by visit and cohort, Epoch 2 (Full analysis set)



150 mg q4w RDN=initial randomized 150 mg q4w group (includes patients up-titrated to 300 mg q4w); 150 mg q4w NF=no flare 150 mg q4w group; 150 mg->300 mg q4w WF= $\geq$  1 flare 150 mg to 300 mg q4w group



## Canakinumab Safety

- Current Warnings
  - Serious infections
  - Immunosuppression
  - Hypersensitivity
  - Immunizations
  - Macrophage activation syndrome (SJIA)
- Common AEs
  - Nasopharyngitis, diarrhea, influenza, rhinitis, nausea, headache, bronchitis, gastroenteritis, pharyngitis, weight increased, musculoskeletal pain, vertigo

## HIDS/MKD Safety

- Most frequently affected SOC was infections and infestations (57.4%), with nasopharyngitis (10.3%) and upper respiratory tract infection (8.8%) being the most common infectious events
  - Most common AEs—pyrexia (23.5%), headache (17.6%), diarrhea (11.8%), oropharyngeal pain (11.8%)
  - SAEs (11.8%)
    - Pneumonia in 2 patients in placebo to 150 mg canakinumab group
    - Incidence of AEs leading to discontinuation in the canakinumab group in the HIDS/MKD 16-week treatment period cohort was 2.9%

## FMF Safety

- Safety set of the 16-week treatment period of Study N2301, the most frequently affected primary SOC in the canakinumab group was infections and infestations (39.7%), nasopharyngitis (10.3%), upper respiratory tract infection (8.6%)
  - Most commonly reported AEs by PT were FMF (22.4%), injection site reaction (13.8%), and diarrhea (12.1%)
- SAEs low (8.6%)—no discontinuations
  - Possibly related: gran liver disease, tonsillitis and atypical pneumonia

## TRAPS Safety

- Safety set of the 16-week treatment period of Study N2301, the most frequently affected SOC was infections and infestations (34.9%), with nasopharyngitis (11.6%), rhinitis (9.3%), and upper respiratory tract infection (9.3%) being the most common infectious events
  - Most commonly reported AEs were pyrexia (14.0%), abdominal pain (11.6%), injection site reaction (11.6%), and nasopharyngitis (11.6%)
- SAEs low (4.7%)
  - Thought not related to study drug

## Presentations

- Lyophilized powder (approved)
- Vial (Study N2301, supplement 88)
  - Used in the pivotal study
  - (b) (4)
  - Compared to the lyophilized powder, sucrose has been replaced by mannitol in vial (b) (4)

(b) (4)

–



## Summary and Conclusions

- Filable from a clinical perspective
- Priority review designation
- While efficacy appears robust, will have to consider optimal labeling and dose

## Midcycle Deliverables

- Efficacy Results
  - Confirmation of all results proposed for labeling
- Safety Results
  - Deaths, SAE, Discontinuations due to AE, Common AE
  - AEs of interest—As per labeled Warnings, as well as any new safety signals

## Consults

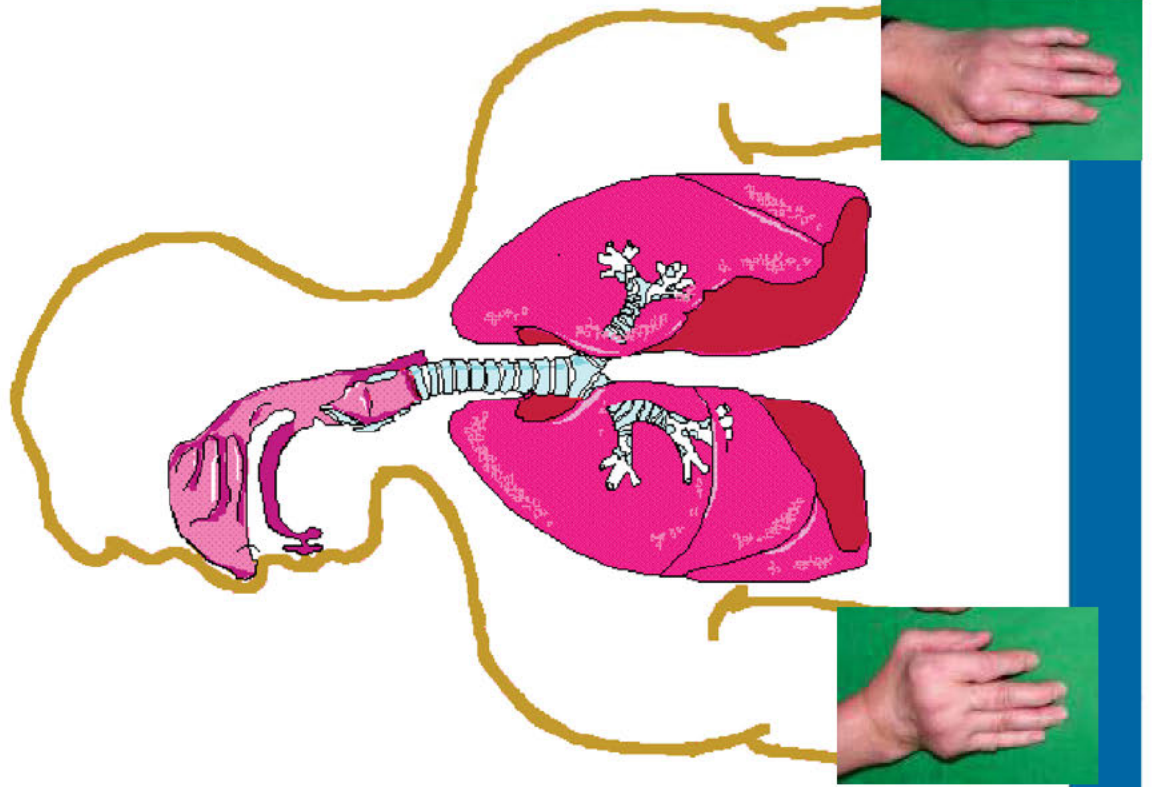
- Recommend foregoing routine OSI inspection
  - Approved product, two approved indications, long history



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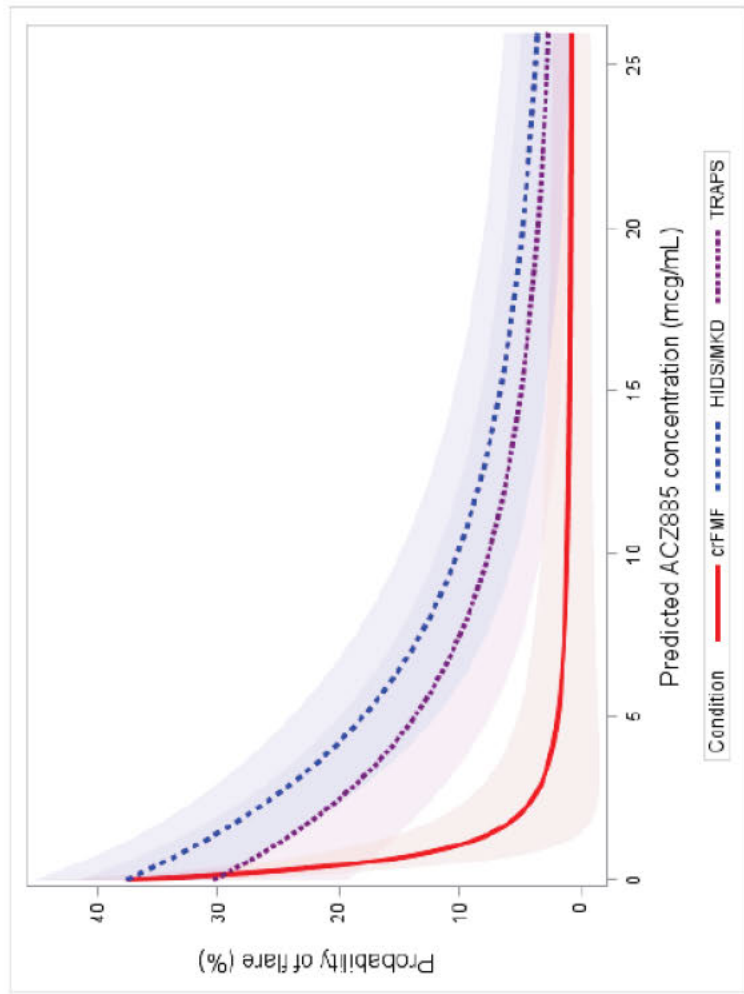
# Back-up Slides

## Clinical Overview (cont)

- Major source of mortality and most serious complication in FMF (autosomal recessive), HIDS/MKD (autosomal recessive) or TRAPS (autosomal dominant) is represented by progressive secondary amyloidosis
  - Can progress to CKD and renal failure
  - Renal amyloidosis seen in up to 60% of untreated FMF patients, up to 25% of TRAPS patients and in < 10% of HIDS/MKD patients

# Dose Considerations

**Figure 3-3** Probability of flare as a function of predicted canakinumab concentration for typical patients with crFMF, HIDS/MKD or TRAPS



The probability of flare with 95% CI is shown from the logistic model prediction as a function of predicted concentration for each disease condition.



## Therapies for HIDS/MKD

- *High-dose corticosteroids*
- *NSAIDs used during acute episodes for myalgias and fevers*
  - *No protection against future attacks*
  - *No impact on reducing SAA levels*



## TRAPS Treatment

- Non-steroidal anti-inflammatory drugs (NSAIDs) are often used during acute episodes for some symptomatic relief of the myalgias and fever, but offer no protection against future attacks and have no impact on reducing the SAA levels.
- High dose corticosteroids are often used to treat acute episodes
- The use of standard immunosuppressants has not been successful in reducing the frequency and the intensity of the inflammatory episodes.



## Four sBLA Supplements

- SN0211: New indication, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)
- SN0212: New indication, Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD)
- SN0213: New Indication, Familial Mediterranean Fever (FMF)
- SN0214: New formulation, 150 mg/mL solution for injection in vial



## Supportive Phase 2 Studies (cont)

- A dosing schedule of 150 mg or 2 mg/kg sc q4w was demonstrated to be effective in 3 open-label Phase 2 studies in FMF and TRAPS patients (Studies DTR01, D2204 and D2203).
- In a Phase 2 study, a higher dose with a longer interval (300 mg or 4 mg/kg q6w) was demonstrated to be effective in HIDS/MKD patients (Study D2402).



## Supportive Phase 2 Studies (cont)

- In all 4 studies, using various dosing regimens, results of the primary endpoint showed rates of responses  $\geq 85\%$  in each of the 3 conditions with clinically meaningful improvements observed across a spectrum of measures (physician and patient based), and in inflammatory biomarkers. In addition, no new safety signals emerged in the study populations.



# Pivotal Phase 3 study in FMF, HIDS/MKD, TRAPS

| Study | Epoch                           | Duration (wks) |
|-------|---------------------------------|----------------|
| N2301 | Epoch 1 (screening)             | --             |
|       | Epoch 2 (DB, PC, parallel arm)  | 16             |
|       | Epoch 3 (Randomized withdrawal) | 24             |
|       | Epoch 4 (OL)                    | 72             |



## Pivotal Clinical Trial Enrollment

- The protocol for Study N2301 allowed patients aged 2 years or older to be enrolled in the randomized population and very young patients aged > 28 days but < 2 years to be enrolled in the non-randomized population.
- Patients in Study N2301 received the same initial dosing schedule as recommended for CAPS pediatric patients, but with a shorter interval of administration (150 mg or 2 mg/kg q4w), with the possibility to up-titrate based on the early assessment of clinical response.



## Pivotal Clinical Trial Dosing

- An initial dose regimen of 150 mg or 2 mg/kg sc q4w for patients  $\leq$  40 kg was chosen for Study N2301 to harmonize exposure across the 3 conditions.
- Up-titration to a maximal dose of canakinumab 300 mg or 4 mg/kg sc q4w for patients  $\leq$  40 kg was allowed to optimize the regimen in order to achieve efficacy in difficult cases.



## Pivotal Clinical Trial Dosing (cont)

- The majority of patients achieved sufficient disease control with canakinumab 150 mg q4w.
- Approximately one-third of HIDS/MKD and TRAPS patients and 16% of FMF patients required up-titration to canakinumab 300 mg q4w between Day 8 and 28 for resolution of their index flare.



## Pivotal Clinical Trial Endpoints

- Study N2301 was designed with the defined primary efficacy endpoint at the end of Week 16 (end of Epoch 2) to provide placebo-controlled efficacy and safety data for the randomized population.

## Immunogenicity profile

- Incidence of anti-canakinumab antibody development during treatment in all indications remains very low ( $\leq 3\%$ ).
- No neutralizing antibodies detected in any study.
  - Low rate of loss of efficacy, not found related to patients with ADA. Similarly, there was no evidence of decreased canakinumab levels or target binding related to development of ADA.
- Potential immunogenicity-related AEs were also not associated with development of ADA.
- No anaphylaxis or anaphylactoid reactions were reported in any studies.

## Dose Recommendations

- 16% of FMF patients, 32% of HIDS/MKD patients and 36% of TRAPS patients required up-titration to 300 mg q4w (or 4 mg/kg) between Days 8 and 28 to achieve sufficient flare control
- Exploratory analyses on the primary and secondary endpoints showed that up-titration to 300 mg q4w further improved the efficacy of canakinumab in patients who did not achieve an adequate response after the first dose of 150 mg
- Based on these results, the recommended starting dose for canakinumab in FMF, HIDS/MKD and TRAPS patients is 150 mg (or 2 mg/kg) every 4 weeks, with the possibility to up-titrate to 300 mg (or 4 mg/kg) every 4 weeks for those patients who do not achieve sufficient control after the first dose of 150 mg.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARK BORIGINI  
05/09/2016

JANET W MAYNARD  
05/09/2016