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APPLICATION NUMBER:

125319Orig1s085, 086, 087

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	September 23, 2016
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
BLA Number:	125319, Supplements 85, 86, and 87
Applicant Name:	Novartis Pharmaceuticals
Date of Submission:	March 23, 2016 (85), March 28, 2016 (86), March 29, 2016 (87)
PDUFA Goal Date:	September 23, 2016 (85, as the earliest date)
Proprietary Name:	Ilaris
Established Name:	Canakinumab
Dosage form:	Glass vial containing Ilaris as a lyophilized powder for reconstitution
Strength:	Each glass vial contains 180 mg of Ilaris, and after reconstitution each vial contains 150 mg/mL of Ilaris
Proposed Indications:	(1) Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adults and children 2 years of age and older [Supplement 85]; (2) Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adults and children 2 years of age and older [Supplement 86]; (3) Familial Mediterranean Fever (FMF) in adults and children 2 years of age and older in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response [Supplement 87]
Action:	Approval

1. Introduction

Novartis submitted these supplemental biological license applications (sBLAs) to support the use of Ilaris (canakinumab) for the treatment of: (1) Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adults and children 2 years of age and older [Supplement 85]; (2) Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adults and children 2 years of age and older [Supplement 86]; (3) Familial Mediterranean Fever (FMF) in adults and children 2 years of age and older in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response [Supplement 87]. Ilaris is a recombinant, human anti-human IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass which was approved in the United States (U.S.) on June 17, 2009, for the indication of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults and children 4 years of age and older including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). It was subsequently approved on May 9, 2013, for systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older. In support of the new indications, Novartis submitted data from Epoch 2 of the ongoing study CACZ885N2301 (N2301).

2. Background

The periodic fever syndromes are rare disorders of innate immunity characterized by recurring episodes of fever and systemic inflammatory symptoms, affecting the serosal surfaces, joints, skin, and eyes. The attacks of fever and localized inflammation occur periodically or irregularly and are not explained by usual infections. Generally, the periodic fever syndromes are considered autoinflammatory diseases. Periodic fever syndromes include tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulin D and periodic fever syndrome (HIDS)/mevalonate kinase deficiency (MDK), familial Mediterranean fever (FMF), the cryopyrin-associated periodic syndromes (CAPS), and periodic fevers with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome. There are currently no approved treatments for TRAPS and HIDS/MKD. Colchicine is approved for the treatment of FMF.

Despite similarities, the periodic fever syndromes have differing etiologies, inheritance, duration and frequency of attacks, and clinical characteristics (Table 1).

Table 1. Characteristics of periodic fever syndromes TRAPS, HIDS/MKD, and FMF

	Gene	Inheritance	Predominant ethnic groups	Usual age of onset	Potential attack precipitants	Typical attack duration	Typical attack frequency
TRAPS	*TNFRSF1A* Chromosome 12	Autosomal dominant, can be *de novo*	Northern Europa but reported in many ethnic groups	Childhood/ early adult	Usually none. Often travel, stress, fasting, menstrual cycle	>1 week, or very prolonged	Variable, may be continuous or q6w
HIDS/ MKD	*MVK* Chromosome 12	Autosomal recessive	Northern European	Infancy	Immunizations	3-7 days	1-2 monthly
FMF	*MEVF* Chromosome 16	Autosomal recessive (dominant in rare families)	Eastern Mediterranean	Childhood/ early adult	Usually none Occasionally menstruation, fasting, stress, trauma	1-3 days	Variable

TRAPS patients are frequently of northern European descent. More than half of patients develop symptoms in the first decade of life, but the age ranges from 2 weeks to 53 years. Generally, flares occur every 6 weeks and last more than 1 week. Flares are characterized by conjunctivitis, periorbital edema, localized myalgias, rash, abdominal pain, and, arthralgias.

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

Mevalonate kinase is a key enzyme in the cholesterol and isoprenoid synthesis pathway. Deficiency in this enzyme leads to accumulation of mevalonate, and further downstream in the pathway to a shortage of isoprenoids. It has been demonstrated that, when unprenylated, the GTP-bound levels of the GTPase RhoA decrease, causing a reduction in GTPase activity and increased protein kinase B phosphorylation. Cells expressing unprenylated RhoA produce increased levels of interleukin 1β mRNA. The mechanism by which activated small GTPases regulate pro-inflammatory gene expression is still not fully understood, but may also involve activation of caspase I as well as elevation of IL-1β.

FMF is the most common of the monogenic periodic fever syndromes. FMF is an autosomal recessive disorder in which there is a mutation in the FMF gene (*MEFV*) encoding the protein pyrin that helps regulate production of IL-1β. FMF predominantly affects populations living in the Mediterranean region. FMF is characterized by episodic attacks of fever lasting one to three days. Symptoms include abdominal pain, pleurisy, and arthralgias or arthritis. Colchicine (Colcrys) is approved for the treatment of FMF in adults and children 4 years and older.

PFAPA is of unknown etiology. While it is characterized by recurrent, unexplained fevers, it is unknown whether it is an autoinflammatory condition. There are autoinflammatory disorders that do not typically present with fever, such as Blau syndrome, deficiency of the interleukin (IL)-1-receptor antagonist (DIRA), pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA syndrome); and others that have associated fever, including chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature (CANDLE), deficiency of the interleukin-36 receptor antagonist (DITRA), familial cold autoinflammatory syndrome type 2 (FCAS2), and Majeed syndrome. There continues to be development in terms of our understanding of autoinflammatory disorders.

The Division of Pulmonary, Allergy, and Rheumatology Products (the Division) and Novartis had multiple regulatory meetings to discuss the development of canakinumab for periodic fever syndromes as discussed below.

At a pre-phase 3 meeting (May 13, 2013), Novartis proposed to (b) (4) [redacted]). Rather, the Division recommended performing a randomized controlled study that also incorporated a randomized withdrawal period after the randomized controlled period.

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

At a pre-sBLA meeting on June 2, 2015 (meeting minutes dated July 1, 2015), the Division stated that data from both the randomized placebo-controlled period (Epoch 2) and the randomized withdrawal period (Epoch 3) would be needed to support the submission of an application. In addition, there were concerns with the integrity of the randomized placebo-controlled period due to the provisions in the protocol allowing patients to escape and receive open-label active therapy after Day 29 in Epoch 2. Finally, the Division recommended that Novartis study a broader population of FMF patients, and not just those who are colchicine resistant since canakinumab would be expected to work for the broader FMF population.

In Type C written responses (February 12, 2016), Novartis proposed submitting 16-week data from the double-blind, placebo-controlled part of the pivotal phase 3 study (Study N2301 (Epoch 2)) to support applications for three indications: TRAPS, HIDS/MKD, and crFMF. The Division noted that the decision to only submit Epoch 2 data to support the proposed sBLAs was at the sponsor's discretion and the adequacy of the data would be a review issue.

On April 21, 2016, Ilaris was granted breakthrough designation for the treatment of patients with TRAPS, HIDS/MKD, and FMF, essentially based on the ongoing clinical study that is submitted to support approval of this application.

3. Chemistry, Manufacturing, and Controls

Ilaris is an approved marketed product and there are no CMC issues.

Ilaris is currently marketed as a lyophilized powder that needs to be reconstituted with water for injection prior to administration. The pivotal clinical study (N2301) that forms the basis of this supplement utilized a solution for injection in vial. Novartis proposed introduction of the 150 mg/ml solution for injection in vial in a different supplemental application. That supplement received a complete response on July 29, 2016, due to microbiology deficiencies. (b) (4) [redacted] Given that Novartis has bridged the

lyophilized powder and the solution for injection in vial with CMC and bioequivalence data, it is reasonable for the currently marketed lyophilized powder presentation to be utilized for the new proposed indications.

4. Nonclinical Pharmacology and Toxicology

No new non-clinical toxicology studies were required or performed for this application. The pharmacology and toxicology data were reviewed with the original application.

5. Clinical Pharmacology and Biopharmaceutics

The majority of the clinical pharmacology data were reviewed with the original application for Ilaris and subsequent supplement. In the current submission, canakinumab pharmacokinetic (PK) data was collected in the pivotal study (Study N2301) and early phase 2 studies. The PK parameters of Canakinumab in TRAPS, HIDS/MKD, and FMF patients were consistent with the approved indications such as CAPS. The exposure of canakinumab was not influenced by disease. Based on population PK analysis, canakinumab exposure (AUC and Cmin) were comparable across age groups (≥2 yrs) following subcutaneous administration of the same weight based dose in patients less than 40kg. In pediatric patients, of ages less than 2 years (n=5, age range = 0.2 to 1.2 years), the steady state trough concentrations of canakinumab were within the concentration range of older age groups with the same weight based dosing regimen.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical program consists of early phase 2 uncontrolled studies in TRAPS, HIDS/MKD, and FMF that provided proof of concept and some dose exploration (Table 2); and one pivotal study (Study N2301) that randomized 181 patients with TRAPS, HIDS/MKD, and FMF (Table 3).

Table 2: Summary of uncontrolled phase 2 studies in crFMF, HIDS/MKD, and TRAPS [source: CDTL review]

Study ***Dates***	**Patients**	**Dose/Study design**	**N**	**Duration**	**Results**
DTR01 *Dec 2010-Oct 2011*	crFMF (ages 12 to 75 years)	**canakinumab 150 mg** (2mg/kg if <40 kg) s.c. q4 wks or 300 mg (4 mg/kg if <40 kg) s.c. if ≥1 new flare during treatment period *(3 mo)* Follow up *(2 mo)*	9	6 mo	1) 100% of patients had at least a 50% reduction in the attack frequency during the 3 month treatment period. 2) 5/9 patients experienced an attack within the 2-month follow-up period (median time to flare was 71 days)
D2204 *Dec 2010-*	crFMF (4 to 20 years)	**canakinumab 150 mg** (2mg/kg if <40 kg) s.c q4 wks or 300 mg (4 mg/kg if <40 kg) s.c. at the second dosing if any new attacks occurred	7	6 mo	1) 6/7 (86%) of patients had at least 50% reduction in attack frequency during the 3 month treatment period 2) 5/5 patients experienced a relapse

Study *Dates*	Patients	Dose/Study design	N	Duration	Results
Feb 2012		*(3 mo)* Follow up *(2 mo)*			after the last dose of canakinumab (median time to flare was 25 days)
D2402 *March 2011-Jul 2014*	HIDS/MKD (≥2 years)	**canakinumab 300 mg** (4mg/kg if ≤40 kg) s.c. q6 wks* *(6 mo)* Withdrawal *(6 mo)* **canakinumab 300 mg** (4mg/kg if ≤40 kg) s.c. q6 wks *(24 mo)*	9	3 yrs	1) 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 2) 7/9 patients flared during the withdrawal period (median time to flare 110 days)
D2203 *Oct 2010-June 2014*	TRAPS (≥18 years)	**canakinumab 150 mg** (2mg/kg if ≤40 kg) s.c. q4 wks in addition to a single dose escalation up to 300 mg (4 mg/kg if <40 kg) in nonresponders at Day 8 *(4 mo)* Withdrawal *(5 mo)* **canakinumab 150 or 300 mg** s.c. q4 wks *(24 mo)*	20	33 mo	1) 19/20 (95%) of patients achieved complete or almost complete response at Day 15 2) 20/20 (100%) of patients relapsed during the 5-month follow-up period (median time to flare 91.5 days)

HIDS/MKD = Hyper IgD syndrome/Mevalonate Kinase Deficiency, TRAPS = TNF receptor-associated periodic syndrome, crFMF = colchicine-resistant familial Mediterranean fever, N = total number of subjects studied, yrs = years, mo = months, wks = weeks, qX wks = every X weeks, s.c. = sub-cutaneous
* Patients who experienced a new HIDS/MKD flare between baseline and Week 4 should have received an additional 150 mg (2 mg/kg for patients ≤40 kg) dose at the moment of flare, and would have received 450 mg (6 mg/kg for patients ≤40 kg) every 6 weeks thereafter starting at Week 6.

Table 3: Overview of Study N2301 [source: CDTL review]

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

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

b. Design and conduct of studies

Study N2301 was a randomized, double-blind, placebo-controlled study of canakinumab in patients with TRAPS, HIDS/MKD, or crFMF. It consisted of three randomized cohorts (TRAPS, HIDS/MKD, and crFMF), and 4 study Epochs (Figure 1). The study Epochs are: screening of up to 12 weeks duration to assess eligibility (Epoch 1); randomized and blinded treatment of 16 weeks duration (Epoch 2); randomized

withdrawal of 24 weeks duration (Epoch 3); and open-label treatment of 72 weeks duration to collect safety data (Epoch 4). This study is ongoing and the primary efficacy data available are from Epoch 2, the 16-week randomized treatment Epoch. The study population consisted of male and female patients with confirmed TRAPS, HIDS/MKD, or crFMF who were at least 2 years of age at the time of the screening visit. At randomization, patients had active disease, as defined by a Physician's Global assessment (PGA) of disease activity (PGA) ≥2 and CRP >10 mg/L.

The study treatment schedules in various treatment Epochs are shown in Figure 1. During Epoch 2, patients received either 150 mg canakinumab (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 4 weeks. Randomized patients in Epoch 2 treated with canakinumab whose disease flare did not resolve, or who had persistent disease activity from Day 8 up to Day 14 (PGA greater than or equal to 2 or CRP greater than 10 mg/L and no reduction by at least 40% from baseline) received an additional dose of 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg). Patients treated with canakinumab whose disease flare did not resolve, or who had persistent disease activity from Day 15 up to Day 28 (PGA greater than or equal to 2 or CRP greater than 10 mg/L and no reduction by at least 70% from baseline), also received an additional dose of 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg). On or after Day 29, patients treated with canakinumab in Epoch 2 with PGA greater than or equal to 2 and CRP greater than or equal to 30 mg/L were also up-titrated. Escape (cross-over or up-titration) after Day 29 was done in an open-label manner. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients weighing less than or equal to 40 kg) every 4 weeks. As noted earlier, the current submission is based on results form Epoch 2, the 16-week randomized treatment Epoch.

Figure 9-1 Overall study design

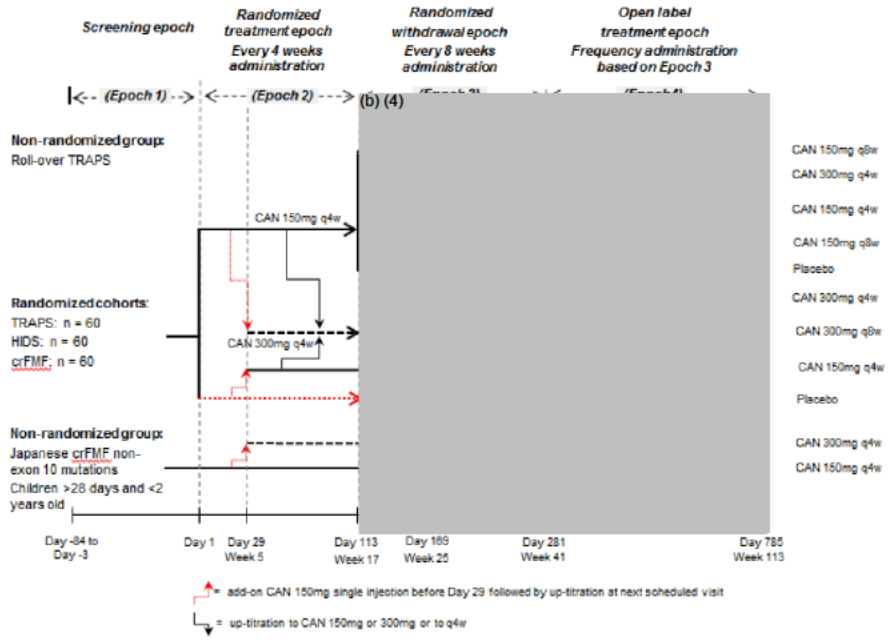

Figure 1. Schematic design of Study N2301.

Patients who completed 16 weeks of treatment and were classified as responders were then re-randomized into a 24-week, double-blind, withdrawal treatment period (Epoch 3) where they received either 150 mg canakinumab (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 8 weeks. (b) (4)

[redacted] were then entered into a 72-week open-label treatment extension period (Epoch 4).(b) (4) [redacted]

The primary efficacy endpoint of the randomized, 16-week treatment period (Epoch 2) was the proportion of complete responders within each cohort as defined by patients who had resolution of their index disease flare at Day 15 and did not experience a new disease flare during the remainder of the 16-week treatment period. Resolution of the index disease flare (initial flare at the time of the randomization) was defined at the Day 15 visit as a PGA score less than 2 ("minimal or no disease") and CRP within normal range (less than or equal to 10 mg/L) or reduction greater than or equal to 70% from baseline. A new flare was defined as a PGA score greater than or equal to 2 ("mild, moderate, or severe disease") and CRP greater than or equal to 30 mg/L. Of note, while there are differences between TRAPS, HIDS/MKD, and FMF, the choice of endpoint assessment and the timing of assessment are reasonable to evaluate the efficacy of canakinumab for the reduction of signs and symptoms of these diseases given that there are overlapping manifestations.

c. Efficacy findings and conclusions

The submitted data from 16 weeks of Study N2301 support efficacy of canakinumab for the treatment of TRPS, HIDS/MKD, and FMF. On the primary efficacy analysis of the comparison of responders between the randomized treatment groups the difference between canakinumab and placebo was statistically significant for each of the disease cohorts (Table 4). In this analysis, patients who needed dose escalation or crossed-over from placebo to canakinumab (blinded escape was allowed starting at Day 8), or who discontinued from the study prior to evaluating the primary endpoint were considered non-responders.

Secondary efficacy analyses of the comparison between canakinumab and placebo were also supportive for each disease cohort (Table 5). There were three predefined secondary efficacy endpoints in Study N2301 at Week 16 (end of Epoch 2): the percentage of patients who achieved a PGA < 2 ("minimal" or "none"), the percentage of patients with serologic remission (defined as CRP ≤ 10 mg/L), and the percentage of patients with

normalized Serum Amyloid A (SAA) level (defined as SAA ≤ 10 mg/L). Patients who needed dose escalation in the canakinumab treatment groups, or who escape from placebo arms to canakinumab in Epoch 2, or discontinued from the study due to any reason prior to evaluating the endpoint at Week 16, were considered as having PGA ≥ 2, CRP > 10 mg/L, and SAA > 10 mg/L, respectively.

The primary and secondary efficacy analyses shows efficacy of canakinumab for TRAPS, HIDS/MKD, and FMF. For FMF, although Novartis described the patients as colchicine resistant FMF (crFMF), there is no reason to believe that all FMF patients would not derive benefit from canakinumab. Further, there is no convincing way to define colchicine resistance as a binary disease classification as responsive or resistant.

One limitation of the data is the study design allowed patients on placebo to cross over to canakinumab prior to Week 16 and allowed dose titration. During the study, the vast majority of the patients crossed over from placebo to canakinumab, and approximately 44% of patients initially randomized to canakinumab 150 mg up-titrated to 300 mg q4w. Despite this limitation, the data are convincing because the primary analysis evaluates a composite endpoint of resolving the index flare by day 15 and remaining flare-free through week 16, and various sensitivity analyses using the worst-case scenario support efficacy.

Table 4. 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							

Table 5. Results of the secondary endpoints 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							
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*
HIDS/MKD							

	Canakinumab 150mg Q4W		Placebo		Treatment Comparison		
	n/M (%)	95% CI	n/M (%)	95% CI	Odds Ratio	(95% CI)	One-sided p-value
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
crFMF							
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

8. Safety

a. Safety database

The safety assessment of canakinumab for TRAPS, HIDS/MKD, and FMF patients is primarily based on studies submitted with the original application, subsequent supplement for sJIA, and data from Study N2301 discussed above.

b. Safety findings and conclusion

The safety data submitted and reviewed with this submission do not raise any new safety concerns in the TRAPS, HIDS/MKD, and FMF patients that would preclude approval or place any major limitation on the use of canakinumab for the new proposed indications. There were no deaths in the submitted study. The adverse event profile observed from patients enrolled in Study N2301 is consistent with the known safety profile for canakinumab.

c. REMS/RiskMAP

Ilaris does not have a REMS and no REMS is recommended based on the review of this application.

9. Advisory Committee Meeting

A meeting of the Arthritis Advisory Committee (AAC) was not convened or required for this submission as the efficacy and safety findings for canakinumab for TRAPS, HIDS/MKD, and FMF were clear enough that discussion at an advisory committee meeting was not felt to be necessary.

10. Pediatric

TRAPS, HIDS/MKD, and FMF are orphan diseases and not subject to PREA. Data submitted with this application include data in children as young as 2 years of age, and no further data in children are necessary. Although Novartis proposed indication for ages 2 years and older, the labeled indication will not be restricted to any age. For these rare genetic diseases it would be reasonable to use canakinumab for patients of any age. The currently marked Ilaris dosage form allows dosing of patients of any age, and the

appropriate dose can be derived based on available PK data and use in other pediatric diseases for which Ilaris is already approved.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audits were not conducted for this submission. During review of the submission no issues were identified to warrant inspection of clinical study sites.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. No investigator with significant equity interest in Novartis was involved in the Study N2301.

c. Other

There are no outstanding issues with consults received from the OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Ilaris was previously reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

Novartis submitted a label that contained information from Study N2301. The major issues for labeling were the extent of the efficacy data to be described in Section 14 of the label, lower age bound of approval, and restriction of use in FMF. Description of efficacy data described in Section 14 of the label is primarily limited to the first 16 weeks of treatment, as this submission is based on first 16 weeks of the study. While, the first 16 weeks provide controlled data that are informative, the label clarifies that patients who crossed over from placebo or who up-titrated the dose of canakinumab, or who discontinued the study early, were considered as non-responders in the primary analysis. Given that the majority of patients assigned to placebo crossed over to canakinumab prior to week 16, there are limitations to the interpretation of endpoints at week 16, and they are removed from the proposed labeling. The primary endpoint, which was resolution of index flare at Day 15 and no new flare over the 16 weeks of treatment from the time of resolution of the index flare was included in the labeling. In addition, supportive efficacy endpoints from Day 15 were included in the labeling. As discussed in section 10 above, there will be no lower bound of age for use of canakinumab for TRAPS, HIDS/MKD, and FMF. For FMF, although Novartis proposed restriction to those in whom colchicine is contraindicated, not tolerated, or does not provide adequate response, such restriction in the FMF patients is removed from the labeled indication as canakinumab is expected to be effective in FMF regardless of previous exposure to colchicine. Section 14 of the label describes the patients who were studied, including those for FMF. Novartis and the Division have agreed to final labeling language.

c. Carton and Immediate Container Labels

Ilaris is a marketed product and there were no major changes to the carton and immediate container labels with this application. On OSE request, updated Carton and Container labeling were submitted on August 12, 2016. The team finds the Carton and Container label acceptable.

d. Patient Labeling and Medication Guide

The Medication Guide will be updated to include information related to the new indications.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Novartis has submitted adequate data to support approval of canakinumab for the treatment of patients with TRAPS, HIDS/MKD, and FMF. The recommended starting dose is 150 mg sc for patients with body weight greater than 40 kg and 2 mg/kg sc for patients with body weight less than or equal to 40 kg; (b) (4) (b) (4) The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment of Ilaris supports its approval for the treatment of TRAPS, HIDS/MKD, and FMF. The safety profile of Ilaris for these diseases is consistent with the known safety profile of Ilaris. The submitted clinical data for these diseases did not show any new safety findings. The submitted efficacy data provides evidence of benefit of Ilaris for these three rare periodic fever syndromes.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

Novartis has agreed to conduct a post-marketing commitment study to submit data from the randomized withdrawal period (Epoch 3) of the ongoing phase 3 study, CACZ885N2301 (N2301). Novartis will include an assessment of the maintenance of efficacy of canakinumab at a reduced dosing frequency in the study.

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/s/

BADRUL A CHOWDHURY
09/23/2016