CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319

SUMMARY REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	June 17, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
BLA #	125319
Applicant Name	Novartis
Date of Submission	December 17, 2009
PDUFA Goal Date	June 17, 2009
Proprietary Name / Established (USAN) Name	Ilaris Canakinumab
Dosage Forms / Strength	Single-use vial for subcutaneous injection, 150 mg/mL
Proposed Indication	For the treatment of the Cryopyrin-Associated Periodic Syndromes (CAPS)
Recommendation for action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Carolyn L. Yancey, M.D.
Statistical Review	David Petullo, M.S.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Kathleen Young, Ph.D.; R. Adam M. Wasserman, Ph.D.; Paul C. Brown, Ph.D.
OBP Quality Review	Ruth Cordoba-Rodriguez, Ph.D.; Lixin Xu, M.D.,Ph.D.; Chana Fuchs, Ph.D.; Patrick Swann, Ph.D.; Kathleen A. Clouse, Ph.D.
Office of Compliance/DMPQ	Partricia F. Hughes, Ph.D.; Anastasia Lolas, M.S.
Microbiology Review	N/A
Clinical Pharmacology Review	Srikanth C. Nallani, Ph.D.; Michael A. Pacanowski, Ph.D.; Issam Zinah, Pharm. D., M.P.H.; Hao Zhu, Ph.D.; Yaning Wang, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Mathilda Fienkeng; Kendra Jones; Andrew Haffer; Sam Skariah
DSI	Roy Blay, Ph.D.; Constance Lewin, M.D., M.P.H.
CDTL Review	Jeffrey Siegel, M.D.
OSE/DMEPA	L. Shenee' Toombs, Pharm.D.; Carlos M. Mena-Grillasca, R.Ph.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DAEA	N/A
OSE/DRISK	Mary Dempsey; Christopher Wheeler, Pharm.D.; Kathy O'Connell, M.D.; Kendra Worthy, Pharm.D.; Claudia Karwoski, Pharm.D.
OSE/DEPI	N/A

OBP=Office of Biotechnology Products
DMPQ=Division of Manufacturing and Product Quality
OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology

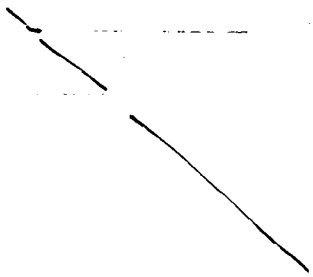
1. Introduction

Canakinumab is a recombinant human monoclonal anti-human interleukin-1β (IL-1β) antibody of the IgG1κ isotype. The drug product, Ilaris, antagonizes the activity of human IL-1β by binding with it and thus interfering with the ability of the cytokine to interact with its receptor. Cryopyrin-Associated Periodic Syndrome (CAPS) comprises three distinct autoinflammatory diseases all characterized by mutations in the gene for the protein cryopyrin. Cryopyrin

responds to infection and other triggers by activating caspase-1 which results in a release of IL-1β. Uncontrolled overproduction of IL-1 is thought to be the pathogenetic mechanism for the resulting inflammation seen in CAPS patients. The three CAPS diseases are Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Neonatal Onset Multisystem Inflammatory Disorder (NOMID). Patients with each of these three disorders suffer from chronic inflammation with rash, fever, conjunctivitis, arthralgias, fatigue and polymorphonulear leukocytosis with organ infiltration. FCAS patients are specifically characterized by urticarial rash, swollen and painful joints, conjunctivitis and fevers following exposure to cold. MWS patients are characterized by sensorineural deafness and an increased risk of amyloidosis. NOMID patients present early in life with severe dermatologic, rheumatologic and neurologic manifestations. There are approximately 200 to 300 CAPS patients in the U.S. Therefore, Novartis was granted orphan product status for Ilaris for the treatment of CAPS. However, they are also developing Ilaris for rheumatoid arthritis, systemic juvenile idiopathic arthritis and gout. The first drug product approved for a CAPS indication was Arcalyst, also an IL-1 blocker. Arcalyst is approved for the treatment of FCAS and MWS patients over 12 years of age. Anakinra is used off-label for the treatment of CAPS, as well. As Novartis submitted this application for the treatment of CAPS in children as young as 4 years of age, the Agency granted the application a priority review based on inclusion of the 4 to 12 year old pediatric CAPS population for which there are no approved products.

2. Background

Agreement with the sponsor regarding the development plan for Ilaris resulted in a submission sufficient for filing and review. The sponsor has submitted the results from a single, adequate and well-controlled study in patients with MWS. As CAPS is a continuum of disorders, the Agency review team felt that successful demonstration of a treatment effect in MWS could be extrapolated to FCAS;



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3. CMC

In her Quality Team Leader review, Dr. Fuchs states on page 1:

> The data submitted in this Biologics License Application support the conclusion that the manufacture of Ilaris® (canakinumab) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. The Division of Monoclonal Antibodies recommends that Ilaris® (canakinumab) be approved for human use (under conditions specified in the package insert) based on the review of the Quality information submitted with the package (Module 3).

The drug quality review team has recommended a Post-Marketing Requirement for the development of a protocol to establish a new Working Cell Bank (WCB) that uses human serum albumin (HSA) obtained from a US-licensed source. The protocol should include acceptance criteria for cell culture metrics and canakinumab quality attributes, and provide limits which assure that validated cell generation time from the Master Cell Bank (MCB) will be maintained. Canakinumab is currently obtained from a MCB and WCB ——— b(4)
——— which is not an approved source of HSA for domestic use. This raises concern regarding the risk of transmissible spongiform encephalopathy (TSE) in the use of non-approved sources of HSA. During the IND phase, a thorough risk assessment by FDA experts on TSE was conducted and it was felt that using the MCB with ——— would have negligible risk for TSE transmission due to the fact that this step was very far "upstream" with many purifications and dilutions of the ultimate product. This decision is consistent with that made for other products such as vaccines. The sponsor was required, for subsequent steps in the cell growth and fermentation process, to use HSA from approved sources. New MCB and WCB were introduced during clinical development. At that time it was believed that these were manufactured using HSA from US approved sources, as the sponsor was told of this requirement during a pre-IND meeting with the FDA. Although the WCB ultimately used for manufacture of canakinumab material under IND was not generated using appropriately sourced HSA, the risk is identical to that initially determined for the original MCB. However, to further reduce the very low risk that currently exists and ensure compliance with the previous safety recommendation, the review team has recommended that a new WCB should be generated using approved has.

In addition the drug quality review team has recommended six Post-Marketing Commitments. (See Section 13 below) I concur with all of these recommendations and the applicant has agreed to implement both the PMR and the PMCs.

All facility inspections have been completed and there are no outstanding concerns.

4. Nonclinical Pharmacology/Toxicology

Drs. Young and Wasserman have determined that the nonclinical data, which included studies of juvenile animal development, submitted by the sponsor support the approval of this application. They found no clinically relevant concerns related to the toxicology of the product. Carcinogenicity studies were not requested based on Agency precedent, feasibility and scientific rationale.

The review team did note some skeletal variations and delays in the reproductive toxicology studies performed with canakinumab in marmosets and with a surrogate IL-1β antibody in the mouse. However, they did not consider these findings to be of great toxicologic significance as the delays in ossification in the marmoset were not as pronounced in the mouse studies and the findings in the mouse were likely to represent a worst case scenario because monoclonal antibodies pass the placenta early in development when major organ systems are developing in the mouse, but they do not in the human. The pharmacology/toxicology review team has recommended that these findings be included in the product labeling and recommends a

Pregnancy Category C classification

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5. Clinical Pharmacology/Biopharmaceutics

The following is reproduced from Page 7 of Dr. Siegel's review:

> In studies in adult patients with CAPS receiving 150 mg canakinumab sc peak serum levels were observed by day 7. The apparent half-life was approximately 26 days. Pharmacokinetics were linear in healthy volunteers, patients with CAPS, and patients with rheumatoid arthritis receiving 0.3-10 mg/kg intravenously. Pharmacokinetic parameters increased in a dose-proportional manner in patients receiving 150 mg and 300 mg sc.
>
> The clinical pharmacology review team examined weight-based dosing in detail because the Applicant is recommending canakinumab at a dose of 150 mg for patients over 40 kg and at 2 mg/kg for children weighing between 15 and 40 kg. They conclude that weight-based dosing is acceptable. However, children weighing less than 40 kg had lower exposure (37% less) than adults. Therefore, they recommend that for children who do not respond to 2 mg/kg that the dose should be increased to 3 mg/kg, a dose that would provide similar exposure as the 150 mg sc dose in adults.
>
> Clearance varied according to body weight. There was no indication of accelerated clearance or changes in pharmacokinetic properties of canakinumab with repeated administration.

Dr. Siegel was in agreement with the additional pediatric dosing recommendations to allow dosing of 3 mg/kg for children 15-40 kg who do not respond initially, but he recommended further study since in clinical trials it was higher doses that led to clinical responses in patients who did not respond initially, i.e., treatment with 4 mg/kg in children 15-40 kg or 300 mg for children over 40 kg or adults. On page 17 of his review he notes the following:

> The Applicant should conduct a study, or trial, investigating the safety of higher doses of canakinumab in patients who do not respond to the recommended doses. The Applicant recommends a dose of 150 mg sc in adults and children over 40 kg and a dose of 2 mg/kg in children 15-40 kg. There is some limited evidence from the clinical trials that increasing the dose in patients with an inadequate response is beneficial; however, the evidence derives from only 5 patients, most given only 1 or 2 doses at the higher dose level. If Ilaris is approved it is likely that some patients will be given the higher doses but the safety of these higher doses used chronically is not adequately characterized. There is adequate information regarding the proposed doses for approval now, but the Applicant should obtain additional information on higher doses postmarketing.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The sponsor conducted an initial dose-finding study, Study A2102. The data from this study in CAPS patients indicated that Ilaris 10 mg/kg iv provided a longer time to relapse (median time approximately 22 weeks) than Ilaris 1 mg/kg iv (median time approximately 10 weeks). A 150 mg sc dose had a time to relapse midway between the two iv doses. As sc dosing would

clearly provide a more acceptable regimen for patients, the 150 mg sc dose given every 8 weeks was chosen for clinical development. In this study, the shortest time to relapse (median time approximately 7 weeks) occurred in the pediatric patients treated with 2 mg/kg sc. Consistent with the analysis performed by the Clinical Pharmacology team, this finding suggests that an increase in dose to 3 mg/kg may be needed in children who do not respond to the lower dose.

Study D2304 began with an 8-week, open-label phase which was followed by a randomized withdrawal phase. Patients ages 9 to 75 with a documented diagnosis of MWS received a single dose of Ilaris 150 mg sc or, for children weighing from 15 to 40 kg, 2 mg/kg sc. Patients who achieved a complete response were then randomized into the withdrawal phase. Complete response was defined as:

- No more than 2 on a 5-point scale on a physician global assessment
- No more than minimal findings on a physician assessment of skin manifestations; and
- Normalization of (less than 10 mg/L) of C-reactive protein (CRP) and serum amyloid A (SAA)

In the second phase, the patients received up to 3 injections of drug or placebo at 8-week intervals. Patients who flared during this phase were then again treated in an open-label third phase with two additional doses. (Drug treated subjects who did not flare during the 24-week controlled phase were then also treated with an additional two doses.) The primary endpoint for the randomized withdrawal phase was disease relapse defined as:

- CRP/SAA above 30 mg/L; and
- Either:
  - A physician global score of greater than 2; or
  - A physician global score of 2, plus a score of greater than minimal for skin manifestations

Of the 35 subjects enrolled in phase one, 89% completed the phase with the remaining 4 subjects failing to achieve a complete response. Fifteen subjects were randomized to Ilaris treatment in phase two and all completed that phase without a flare. Thirteen of the 16 subjects randomized to placebo flared and discontinued phase two early. The 5 pediatric patients enrolled experienced a complete response in phase one and were randomized to treatment. The 2 pediatric patients examined in the placebo group were 14 and 16 years old, while the 3 examined in the Ilaris group were 9, 15, and 17 years old. While there was an imbalance in males and females in phase two (1 female in the drug arm and 7 in the placebo arm), there is no clinical rationale that would raise concerns regarding a disparity in disease manifestation or response to treatment based on sex. The following table reproduced from page 13 of Dr. Siegel's review summarizes the results of the primary outcome analysis:

Primary Efficacy Analyses - Study D2304							
Proportion of Patients with Disease Flare: Comparison between Treatment Groups at the End of Part 2 - (ITT population)							
	ACZ885		Placebo		Differences in Response rates		
	N = 15		N = 16		ACZ885 vs Placebo		
	n / N (%)	95% CI	n / N (%)	95% CI	Difference	95% CI	p-value*
Pts with disease flare	0 /15 (0.0)	(0, 0.22)	13/16 (81%)	(0.54, 0.96)	- 0.81	(-1.00, -0.62)	<0.001 **
n = total number of pts having disease flare; N = total number of pts in treatment group; * p-value from Fisher's exact test; ** statistical significance (two sided) at 5% level.							

Two open-label studies provide some additional support for the efficacy of Ilaris in FCAS patients. In particular, two FCAS patients were enrolled in the dose-finding Study A2102 and eight FCAS patients were enrolled in the open-label Study D2306 and all experienced a complete response. Five pediatric subjects in Study A2102 received weight-based dosing of 2 mg/kg and each experienced a complete response.

Mr. Petullo concluded that there was sufficient evidence demonstrating efficacy in the treatment of MWS only as this was the population studied in the controlled phase of Study D2304. Dr. Yancey concluded that efficacy had been established in both MWS and FCAS, based on the supportive open-label studies and the fact that FCAS is the milder disorder in the spectrum of CAPS disease. Mr. Petullo does note on page 5 of his review:

> ...the pivotal efficacy study only evaluated patients 9 years and older diagnosed with MWS...The Applicant claims the results from the two open-label studies provide sufficient evidence of effectiveness in patients 4 years and older and those diagnosed with FCAS — It needs to be noted that these claims are not supported by statistical evidence; the clinical validity of these claims will be assessed by the medical review team.

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From Dr. Siegel's addendum to his review:

> The clinical reviewer, Dr. Carolyn Yancey, concluded that canakinumab should be approved for the MWS and the FCAS forms of CAPS, — and that approval should be for children aged 4 years old and older. I agree with Dr. Yancey's conclusions. The three different presentations of CAPS represent syndromes with overlapping signs and symptoms all of which are characterized by a common genetic mutation in the gene for cryopyrin. All three syndromes are characterized by chronic inflammation, rash, fever, conjunctivitis, arthralgias, fatigue and polymorphonuclear leukocytosis with organ infiltration as well as by increases in the acute phase reactants C-reactive protein (CRP) and serum amyloid A (SAA). Therefore, efficacy data for the syndrome of middle severity, MWS, can be generalized to the milder form, FCAS. In addition, limited data on treatment of FCAS are available for the open-label trials D2306 and A2102. In these trials, 10 patients with FCAS were enrolled and all experienced a complete response.
>
> With respect to the age for the indication of canakinumab in CAPS, I agree with Dr. Yancey that the data provided by the Applicant support approval for children aged 4 and older. FCAS and MWS present similarly in children and adults. Therefore efficacy data in adults may be extrapolated to children and only safety and dosing information are necessary. The Applicant submitted data on 15 children aged 4, 5, 6, 6, 7, 8, 9, 13, 14, 14, 15, 16, 16, 17 and 17 years of age.

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Safety in children was similar to adults. The Clinical Pharmacology review team reviewed the pharmacokinetic data and concluded that the proposed dosing for children was acceptable, including weight-based dosing of 2 mg/kg in children 15-40 kg.

I agree with Drs. Yancey and Siegel's conclusions and recommendations regarding this issue.

8. Safety

Seventy-eight patients with CAPS received at least one dose of Ilaris in the database submitted to this application. Of these, 56 have been treated for at least 6 months and 31 for a year or longer. Additional support for the safety of Ilaris is based on 622 patients with RA, psoriasis and other conditions who have also been treated with Ilaris. There are no true randomized, controlled safety data in the CAPS population as all subjects were treated with Ilaris prior to the randomized withdrawal phase in the single placebo-controlled study.

There were no deaths in the CAPS subjects. One elderly female subject in an age-related macular degeneration study died of heart failure after a prolonged hospital stay due to a fall at home. This occurred 5 months after receiving a single iv dose of Ilaris. The only other death in the safety data base occurred in an elderly male subject in a COPD study. He died due to pneumonia as a complication of his underlying disease after a single dose of Ilaris or placebo. This study remains blinded. I agree with the review team that these deaths are not likely to be related to treatment with Ilaris. There were 7 serious adverse events reported in the Ilaris studies. These events included: 2 cases of vertigo, 1 case of lower respiratory infection with resolution, and 1 case each of pyrexia associated with a recurrent urinary tract infection, MWS flare, Fibromyalgia and a synovial cyst. These events and the serious adverse events that occurred in the RA studies were typical of the patient populations being studied. There were no unusual events resulting in subject discontinuation.

The most common adverse events in the CAPS studies were infections which occurred in approximately three-quarters of all of the subjects in Study D2304. These infections were of the types typically seen in this population. Seven percent of subjects experienced injection site reactions. There were no concerning laboratory or vital sign abnormalities. No subjects developed antibodies to canakinumab.

9. Advisory Committee Meeting

Ilaris is the third IL-1 blocking agent approved and the second approved for CAPS. This in addition to the fact that the review team found no surprising product safety signals or efficacy concerns, and that the efficacy of the product was clearly established in the clinical trials, led to a decision that discussion at advisory committee was not necessary.

10. Pediatrics

There are no required pediatric studies. As CAPS has been designated an orphan indication, PREA does not apply to this BLA.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

The Agency and the sponsor have concurred on appropriate language for the product labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action

  Approval

- Risk Benefit Assessment

The applicant has provided sufficient evidence to support the safety and efficacy of Ilaris for the treatment of FCAS and MWS in subjects 4 years of age and older. The safety profile of this product is similar to other approved IL-1 blocking agents and no new or concerning safety signals were apparent in the clinical studies. While the data is somewhat limited, given the extremely small population of patients in the FCAS and MWS populations, the data are acceptable to provide substantial evidence of efficacy. I concur with Drs. Yancey and Siegel regarding the extrapolation of adult information on the efficacy and safety of Ilaris to the pediatric population. I also concur with the Clinical Pharmacology review team that additional data supporting the use of a higher dose in some pediatric patients is needed and with Dr. Siegel that that data should be obtained in a post-marketing study.

- Recommendation for other Postmarketing Study Requirements

  - Complete and report on the ongoing open-label clinical trial D2306 investigating the safety of higher doses of Ilaris. Patients in trial D2306, who are non-responders to 2 mg/kg subcutaneously for patients weighing 15-40 kg or 150 mg subcutaneously for patients weighing >40 kg, should receive escalating doses to 4 mg/kg subcutaneously for patients weighing 15-40 kg or 300 mg subcutaneously for patients weighing >40 kg.

    This trial should be conducted according to the following timetable:

Trial Completion Date:	by June, 2010
Final Report Submission:	by September, 2010

- Complete and report on the ongoing multicenter, open-label, 6-month clinical trial D2201 investigating the safety of higher doses of Ilaris. Patients in trial D2201 should receive a dose of 4mg/kg subcutaneously for patients weighing less than 15-40 kg.

  The trial should be conducted according to the following timetable:

Trial Completion Date:	by November, 2010
Final Report Submission:	by January, 2011

- Develop a study protocol for establishing a new Working Cell Bank that uses human serum albumin obtained from a US-licensed source. The protocol should include acceptance criteria for cell culture metrics and canakinumab quality attributes, and provide limits which assure that the validated cell generation time from the Master Cell Bank will be maintained.

Final Protocol Submission:	by February, 2010
New WCB Established:	by July, 2010
Final Report Submission:	by July, 2010

- Recommendation for Postmarketing Study Commitments

  - Provide an evaluation, summary, and data that confirm the adequacy of the proposed equilibration time required for thawed bulk drug substance to prevent excursions of drug product turbidity.
  - Perform validation studies on a [redacted] for canakinumab drug substance. b(4)
  - Monitor Ilaris drug product for the appearance of new bands when compared to reference standard during the [redacted] assessment of registration stability testing, and to set an appropriate [redacted] specifications relative to reference standard upon availability of 24 months of registration stability data for Ilaris drug product.
  - Perform stability testing on at least one marketed drug product lot and one drug substance lot; annually, for each year in which drug substance and/or drug product is manufactured, using the post-approval stability protocol specified in the BLA.
  - Assess release and shelf-life specifications for canakinumab drug substance and Ilaris drug product after manufacture of 15 lots.
  - Qualify the additional biochemical characterization assays that will be used in support of establishing a new canakinumab reference standard.