CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319

CHEMISTRY REVIEW(S)

The Quality Team Leader's Executive Summary

From:	**Chana Fuchs, Ph.D., Team Leader, Division of Monoclonal Antibodies (DMA)**
Through:	**Patrick Swann, Ph.D. Deputy Division Director, DMA**
Through:	**Kathleen A. Clouse, Ph.D., Director, DMA**
To:	**Jeffrey Siegel, M.D. CDTL, DAARP, ODEII**
BLA Number:	**125319**
Product:	**Ilaris® (canakinumab)**
Sponsor :	**Novartis**
Date of Review:	**May 26, 2009**

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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).

B. Recommendation on Phase 4 (Post-Marketing) Commitments (PMC), Agreements (PMA), Requirements (PMR) and/or Risk Management Steps, if Approvable.

PMR:

- To develop a protocol for establishing new Working Cell Banks 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 validated cell generation time from the Master Cell Bank will be maintained. The protocol will be submitted as a Prior-Approval Supplement by **(Novartis, provide date of Submission)**. A new Working Cell Bank will be developed by **(Novartis, provide date)**.

PMCs:

- To 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 (**Novartis - provide date of study completion and date of submission).**

- To perform validation studies on a —— assay for canakinumab drug substance. The protocol, final report, and the proposed specification will be submitted as a CBE-0 by [**Novartis, provide date of submission]** b(4)
- To monitor canakinumab drug product for the appearance of new bands when compared to reference standard during the —— assessment of registration stability testing, and to set an appropriate —— specifications relative to reference standard upon availability of 24 months of registration stability data for canakinumab drug product. The proposed specifications and stability data will be provided as a CBE-0 by [**Novartis, provide date].** b(4)
- To 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. The first update will be included in an annual report to be submitted by [**Novartis, provide date**]
- To assess release and shelf-life specifications for canakinumab drug substance and drug product after manufacture of 15 lots. Specifications assessment and supporting data will be provided by [**Novartis, provide date**]
- To qualify the additional biochemical characterization assays that will be used in support of establishing a new canakinumab reference standard. Qualification of currently used assays will be submitted on [**Novartis, provide date**].

II. Summary of Quality Assessments

A. Description of the Drug Product(s) and Drug Substance

- Ilaris® (canakinumab) Drug Product is supplied as a sterile, preservative free, lyophilized powder, to be reconstituted with 1.0 ml preservative free water for injection (WFI). When reconstituted, the final formulation contains 150 mg/ml canakinumab, — — histidine HCl, —— sucrose, and —— polysorbate 80. b(4)
- Canakinumab drug product is filled in 6 ml —— glass vials sealed with a —— stopper coated —— and sealed with an aluminum cap —— flip-off component.
- Each vial of Ilaris®/canakinumab is a single use vial and is packaged in an individual carton. WFI used for reconstitution of Ilaris, syringe and needles are to be procured separately through the physician.
- Expiration dating of Ilaris® drug product is set as 15 months from time of production when stored at 2-8°C. This is set based on 9 months data at 2-8°C for the to-be-marketed process. Novartis had requested a shelf life of —— for drug product when stored at 2-8°C based on the 12 months supporting stability data at 2-8°C for the process C lots. Drug product expiration dating may be extended in real time based on a stability protocol included in the BLA. b(4)

- Ilaris® (canakinumab) drug product is to be stored refrigerated (2°-8°C) inside the original carton to protect it from light. Photostability studies on the reconstituted product have shown increased dimers and sulfoxidation when exposed to light under the conditions tested.

- After reconstitution, Ilaris® may be stored at 2-8°C for up to 4 hours. The package insert states that it should be used within ; however, this product contains no preservatives so, per recommendation from Dr. Lolas, a 4 hour limit should be set to assure microbiological safety. This should be modified in the PI. Given that Ilaris® does not contain preservatives, any unused portion must be discarded. b(4)

- Concerns were identified during the review regarding the presence of in drug substance samples, with levels of up to . This originated from the preservative used in the , and is not removed in subsequent manufacturing steps. Based on analysis from Drs. Young and Wasserman, the concern is mainly for its impact on neonates, as it may cause toxic and/or allergic reactions in infants. Therefore, FDA required that a statement on this should be included in the label. Novartis has committed to change to a preservative and to implement a concurrent validation study for re-use and carryover. Once the change has been implemented, the label should be modified accordingly. After original review was completed and during labeling discussions, Novartis committed to not marketing any lot that has above the limit of detection of their assay, which is and below the recommended safety limit of The threshold is defined by PQRI Leachables and Extractables Working Group. Based on feedback from Adam Wasserman, this exposure is not significant and therefore the comment does not have to be included in the label. b(4) b(4) b(4)

- A excess volume is used as overfill. Novartis states that the volume used for reconstitution ranged between and that when reconstituting the lyophilized product with 1 mL Sterile WFI using a 1 mL disposable syringe, the volume of the reconstituted solution is which allows reliable withdrawal of 1.0 ml of canakinumab solution for injection (150 mg/ml). This type of dosing is expected to result in a volume range of , which would equal of the declared content of canakinumab. b(4)

- Dosing for patients between 15 and 40 kg is currently stated at 2mg/kg; however, the clinical reviewer would like to increase this level to 3mg/kg. We reviewed acceptance criteria that would be impacted by increasing the dose, and found that the current acceptance criteria would support such an increase. This includes endotoxin levels of drug product and DNA levels in drug substance. Limit for drug product is currently set at b(4)

- Ilaris® (canakinumab) is expressed in a SP2/0-AG14 murine cell line. The cell bank system consists of a Master Cell Bank , and a Working Cell Bank . The only animal or human derived materials used in the manufacture of canakinumab were used for manufacturing the Master and Working Cell Banks. The cell banks were produced using human transferrin sourced from human plasma of USA origin, and There is an b(4)

issue with regard to the HSA as it is not from US approved sources and therefore can pose a potential risk for transmissible spongiform encephalopathy (TSE). During the pre-IND meeting for canakinumab, Novartis was informed that they would need to switch to U.S. approved HSA for manufacturing ACZ885 in order to be able to use the product under IND. Novartis initiated their IND studies in the USA using drug substance manufactured with USA licensed HSA in the production process. New MCB and WCB were introduced during clinical development. At that time it was believed that these were manufactured using HSA from U.S. approved sources. During review of the BLA, it was noted that both the current Working Cell Bank and Master Cell Bank were manufactured using HSA sourced from ——— . A risk assessment was provided, as well as reviewer consultation with FDA experts on TSE. It was assessed that the risk for TSE transmission was extremely low and that this should not prevent approval of the BLA. However, to further reduce the very low risk that currently exists and to ensure compliance with our previous safety recommendation, establishment of a new Working Cell Bank using US-licensed human serum albumin should be included as a post-marketing requirement. It was determined that the potential risk of changes in the product resulting from the generation of a new Master Cell Bank using US-approved HSA would be greater than the risk for TSE transmission, so establishment of a new MCB would not be requested. b(4)

- Ilaris® (canakinumab) Drug Substance is produced by ——— b(4)

  The manufacturing process includes steps validated to remove impurities, retroviruses and model viruses. Measures such as testing of cell banks and raw materials, lot traceability, and acceptance criteria have been implemented to prevent product contamination from potential viral and non-viral adventitious agents.

- The Ilaris® (canakinumab) Drug Substance and Drug Product manufacturing processes have been modified a number of times during clinical development. Biochemical comparability study results between successive processes were reviewed. Based on biochemical, biophysical and biological data submitted, products produced by the different Drug Substance and Drug Product processes appear comparable.

- The process-related impurities validated to be effectively cleared during manufacturing include the following: ——— ——— Testing for these will no longer be performed for Ilaris® (canakinumab) Drug Substance. b(4)

- The expiration dating of canakinumab Drug Substance is set at 18 months when stored at ≤ -60° C. This is based on 9 months data for drug substance lots manufactured by the commercial process (process D) under real storage conditions of ≤ -60°C and 3 months data at accelerated storage conditions of 2-8°C, and on 18 months of supporting data for drug substance lots manufactured by clinical process C stored at both real time storage conditions of ≤ -60°C and at accelerated conditions. Drug substance manufactured by processes D and C has been shown to be comparable. Novartis had

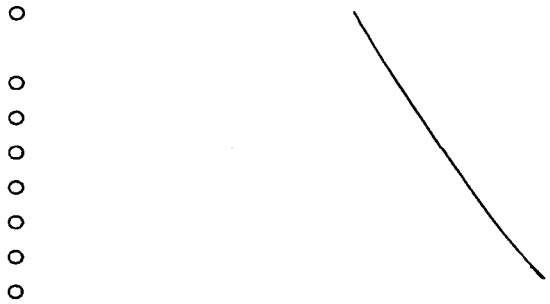
requested a shelf life for drug substance of — when stored at ≤ -60°C. Drug substance expiration dating may be extended in real time based on a stability protocol included in the BLA. b(4)

- The specifications proposed by Novartis for Drug Substance and Drug Product were modified. Final specifications will be included in the review prior to its completion. Stability-indicating assays have been identified and are included among the lot release and stability tests.
- The Potency assay is a — assay — b(4) Acceptance criterion is 80-125% relative biological activity compared to the reference substance.
- Immunogenicity was assessed using — based assays. No anti-drug-antibody positive samples were identified. The assay sensitivity is somewhat low when compared to other non-SPR based assays, and even some other — immunogenicity assays. Although ELISA assays are generally more sensitive, — assays are able to also detect low affinity antibodies that have rapid dissociation rates and which would be washed off on an ELISA. Early immune responses in patients are low affinity responses that typically are IgM as well as IgG. This early immune response is very difficult to detect by ELISA because of the rapid dissociation. While assay sensitivity is the aim, it can be a bit misleading. The — assay definitely will detect both high and low affinity antibodies, but the samples it might miss would be high affinity antibodies that are present in low concentrations. The detection of anti-drug antibody populations by — is driven by the association rate of the antibodies. The assay was used to assess immunogenicity of 192 subjects treated with canakinumab. The sponsor indicated that none of the adult and pediatric subjects showed a canakinumab-induced immune response, and concluded that canakinumab has a low immunogenicity potential. b(4)

B. Physical and Biological Properties

- Canakinumab is a fully humanized anti-human IL-1 β monoclonal antibody of the IgG1/ κ isotype subclass with a molecular formula $C_{6452}H_{9958}N_{1722}O_{2010}S_{42}$, a MW of 145,157 Daltons (deglycosylated), two 447- (or 448-) residue heavy chains, two 214-residue light chains, and at least — N-glycosylation at Asn298. — b(4)
- Characterization identified the following:
  - o
  - o
  - o
  - o
  - o

b(4)



b(4)

- The mechanism of action for canakinumab consists of high affinity binding to human IL-1β, thereby preventing binding of endogenous IL-1β to its cognate receptor, IL-1R Type I. ACZ885 activity is measured as the ability to inhibit IL-1β-dependent expression of the reporter gene luciferase, and comparing it to an internal reference standard.

- Canakinumab was demonstrated throug[redacted] analysis to have [redacted]

b(4)

[redacted]. This is different from the licensed product, rilonacept, which binds IL-1β, IL-1α and IL-1Ra.

C. Description of How the Drug Product is Intended to be Used

- Ilaris® (canakinumab) is indicated for the treatment of adults and children aged 4 years and older with Cryopyrin-Associated Periodic Syndromes (CAPS).

- Dosage is 150 mg for >40 kg of body weight and 2 mg/kg for body weights ranging between ≥15 kg and ≤40 kg delivered subcutaneously every 8 weeks.

- Ilaris® (canakinumab) Drug Product is provided in single-use vials as a sterile preservative-free lyophilate. The single-use vials are 6 ml [redacted] glass vials sealed with a [redacted] stopper coated [redacted] e and sealed with aluminum cap [redacted] lip-off component.

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- Each vial of Ilaris® /canakinumab is a single use vial and is packaged in an individual carton.
- Ilaris® (canakinumab) drug product is to be stored refrigerated (2°-8° C) inside the original carton to protect it from light. Photostability studies on the reconstituted product have shown increased dimers and sulfoxidation when exposed to light under the conditions tested.
- The reconstituted Ilaris® solution may be stored at 2-8°C for up to 4 hours. The package insert states that it should be used within [redacted], however this product contains no preservatives so a 4 hour limit should be set to ensure microbiological

b(4)

safety. This should be modified in the PI. Given that Ilaris® does not contain preservatives any unused portion must be discarded.

- Ilaris® is to be administered by a physician. WFI used for reconstitution, needles and syringe will be provided through the physician.

D. Basis for Approvability or Not-Approval Recommendation

Canakinumab is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Canakinumab is manufactured consistently, leads to a safe and effective product, and approval is recommended for the proposed indication.

Quality unit Assessment

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The review of module 3.2 is provided as a separate document. A review of the product immunogenicity assays is included at the end of the primary review document.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

Novartis claims categorical exclusion from the requirements of environmental assessment based on 21 CFR 25.31(c). Given that canakinumab is composed of a protein, Novartis contends that it meets the criteria for compounds that may be exempted from testing because of their chemical structure and constituents (amino acids and proteins), which should either degrade into their amino acid or constitutive elements in the environment.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

There are no CMC-related deficiencies precluding approval of this BLA.

IV. ADMINISTRATIVE

A. Reviewer's Signature

Product Quality Reviewer: Ruth Cordoba-Rodriguez, Ph.D. 6-03-09

Product Quality Reviewer: Lixin Xu, M.D., Ph.D. 6/3/09

B. Endorsement Block

Product Division Team Leader: Chana Fuchs, Ph.D. 6/4/09

Product Division Deputy Director: Patrick Swann, Ph.D. 6-4-09

Product Division Director: Kathleen A. Clouse, Ph.D. 06/12/09

C. CC Block

OBP Office Director: Steven Kozlowski, M.D.
Clinical Deputy Division Director: Rigoberto Roca, M.D.
Clinical Division Director: Bob Rappaport, M.D.
Division of Monoclonal Antibodies File: BLA STN 125319

Review Cover Sheet

BLA STN 125319/0

ILARIS (Canakinumab)

Sponsor: Novartis

Ruth Cordoba Rodriguez, Ph.D.
Lixin Xu, M.D., Ph.D.
Division of Monoclonal Antibodies; HFD-123

Product Quality Review Data Sheet

1. **BLA#** STN 125319/0

2. **REVIEW #:** 1

3. **REVIEW DATE:** 1 June 2009

4. **REVIEWERS:** Ruth Cordoba, Ph.D
Lixin Xu, M.D., Ph.D.
Chana Fuchs, Ph.D. – Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

Communication/Document	Date
Clinical Pre-BLA Meeting	21-OCT-2008
Drug Product facility Inspection Waiver	15-MAY-2009
Filing Review memo (45 days).	12-FEB-2009
Novartis 483 (Basel Inspection)	03-JUN-2009
Information Request	29/JAN/2009
Information Request	13/MAR3/2009
Information Request	07/APR/2009
Information Request	28/APR/2009
Information Request	21/MAY/2009

6. **SUBMISSION(S) REVIEWED:**

Submission(s) Reviewed	Document Date
STN 125319/0/1 Original Submission–CMC RU	17-DEC-2008
STN 125319/0/3	3-FEB-2009
STN 125319/0/7	9 Feb - 2009
STN 125319/0/17	13-MAR-2009
STN 125319/0/20	20-Mar_2009
STN 125319/0/22	1-APR-2009
STN 125319/0/25	8 APR-2009
STN 125319/0/27	17-APR-2009
STN 125319/0/30	29-APR-2009
STN 125319/0/31	1-MAY-2009
STN 125319/0/34	15-MAY-2009
Response to 483	15-MAY-2009
Labeling	
Package insert	

7. **NAME & ADDRESS OF APPLICANT:**

Name: Novartis Pharmaceuticals Corporation.
Address: One Health Plaza
East Hanover, NJ 07936-1080
USA

Representative: Frederick DeBrito, Ph.D. Assoc Director, Regulatory Affairs
Telephone: 862-778-1274

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name: Ilaris
   b) Non-Proprietary/USAN: canakinumab
   c) Code name: Immunoglobulin G1, anti-(human interleukin 1β) (human clone ACZ885 heavy chain V region) Immunoglobulin G1, anti-(human interleukin-1 beta (Il-1β)) human monoclonal ACZ885; (1Glu>Glp)-γ1 heavy chain (221-214')-disulfide with kappa light chain, dimer (227-227":230-230")-bisdisulfide
   d) Common names: ACZ885, ACZ885-NXA,
   e) Drug Review Status: Accelerated
   f) Chemical Type: recombinant humanized monoclonal antibody

9. **PHARMACOL. CATEGORY:** Therapeutic recombinant humanized monoclonal Antibody to IL-1β

10. **DOSAGE FORM:** Sterile Lyophillisate

11. **STRENGTH/POTENCY:**
   a) The concentration of Ilaris (canakinumab) Drug Product is 150 mg/ml when reconstituted with 1 mL WFI
   b) Potency is defined as percent value relative to the reference standard, using a proprietary chemiluminescent cell-based assay dependent on the ability of canakinumab to inhibit IL-1β binding to a reporter construct transfected HEK293 cell line.
   c) Potency specification : ——— b(4)
   d) Dating period for vialed drug product is 15 months when stored at 2°C -8°C and protected from light.
   e) Canakinumab is filled into 6 mL glass vials containing 150 mg of canakinumab.

12. **ROUTE OF ADMINISTRATION:** Subcutaneous injection.

13. **ACID (Animal Component Information Database)**
Section 3.2.A.2. lists starting materials of biological origin. No animal derived raw materials are used in the current canakinumab manufacturing process. The animal derived raw materials listed below were used to manufacture the canakinumab Master Cell Bank and Working Cell Bank.

b(4)

16. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Pending		
Environmental Assessment	Approve	6/1/09	Ruth Cordoba
BMT – memo for Drug Substance facilities review	Approve	5/21/09	Anastasia Lolas
BMT – memo for Drug Product facilities review	Approve	5/21/09	Anastasia Lolas
DMEPA Carton and vial labeling	Revisions suggested	5/28/09	L. Shenee' Toombs
DMA Carton and vial labeling	Revision suggested	5/20/09	Kimberly Rains
DMEPA tradename review	Approve	3/13/09	L. Shenee' Toombs
EIR for Novartis-Basel	VAI		Lolas/Hughes/Cordoba
Inspection Waiver for DP site (Stein)	Waive PAI	5/15/2009	Lolas/Cordoba

17. **Inspectional Activities**

A pre-licensed inspection for canakinumab bulk drug substance at the Novartis Pharma S.A.S.-Huningue facility and at the Novartis Pharma AG-Basel facility (FEI 3002807772) was conducted on May 4-12, 2009 by BMT inspectors Patricia Hughes and Anastasia Lolas, and by product reviewer Ruth Cordoba-Rodriguez. Novartis-Huningue is responsible for manufacturing and release of canakinumab bulk drug substance, QC testing (except for bioassay testing), and final QA review and approval. Novartis-Basel is responsible for bioassay testing of all canakinumab releasable and in-process material.
Novartis-Huningue inspection did not have any observations. A discussion with management highlighted that there are still some gaps between the electronic database system (SAP) implemented in 2008 and the paper system that was still in use. In addition, several procedures used for testing had insufficient detail to allow for consistent method execution. Novartis-Basel inspection was recommended as VAI by the BMT inspectors and had two observations regarding insufficient detail of laboratory records to ensure consistent method execution and deficiencies in the timelines of closing deviations. The inspection at the DP facility Novartis,-Stein (FEI 3002653483) was waived (waiver memo 5/15/09) based on the compliance history, current GMP status, and previous inspections of manufacturing processes similar to the canakinumab manufacturing process. Novartis-Stein is responsible for manufacturing of canakinumab drug product, packaging and some release and stability testing. Novartis-Stein is an approved multi-product facility. The last inspection on September 9-13/2007 was NAI with no significant deficiencies and no observations.
All other facilities listed in the BLA, including contract facilities for mycoplasma, viral, sterility and stability testing, and facilities responsible for packaging of Ilaris, were not inspected. Inspections were not conducted as the activities in these sites are either low risk and/or these sites are in compliance as per 21 CFR 210,211 and 600. A compliance check did not identify pending actions that could prevent approval at this time..

18. **Recommendations on Approvability**

The data submitted in this 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 or adventitious infectious agents in a way that meets the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.

IV. ADMINISTRATIVE

A. Reviewer's Signature

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189 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process