

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125319Orig1s085, 086, 087**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION <sup>1</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NDA #<br>BLA # 125319                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | NDA Supplement #<br>BLA Supplement # 085, 086, 087 | If NDA, Efficacy Supplement Type:<br><i>(an action package is not required for SE8 or SE9 supplements)</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Proprietary Name: Ilaris<br>Established/Proper Name: Canakinumab<br>Dosage Form: lyophilized powder for reconstitution                                                                                                                                                                                                                                                                                                                                                                         |                                                    | Applicant: Novartis<br>Agent for Applicant (if applicable):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| RPM: Brandi Wheeler                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                    | Division: DPARP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)<br><br>BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)<br>Efficacy Supplement: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a)                                                                                                      |                                                    | <b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <div style="margin-left: 20px;"> <input type="checkbox"/> No changes<br/> <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i><br/>           Date of check:         </div> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p> |
| ❖ Actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is September 23, 28, and 29, 2016</li> </ul>                                                                                                                                                                                                                                                                                                                                                                |                                                    | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>                                                                                                                                                                                                                                                                                                                                                                        |                                                    | <input checked="" type="checkbox"/> None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____ |                                                    | <input type="checkbox"/> Received                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| ❖ Application Characteristics <sup>3</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority  
Chemical classification (new NDAs only):  
(confirm chemical classification at time of approval)

- |                                                                      |                                                   |
|----------------------------------------------------------------------|---------------------------------------------------|
| <input type="checkbox"/> Fast Track                                  | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                              | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation |                                                   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)  
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR  
☐ Submitted in response to a PMC  
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)  
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide  
☐ Communication Plan  
☐ ETASU  
☐ MedGuide w/o REMS  
☐ REMS not required

Comments:

|                                                                                                                                                        |                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)                                                      | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No                                                                                                                                       |
| ❖ Public communications (approvals only)                                                                                                               |                                                                                                                                                                                                           |
| • Office of Executive Programs (OEP) liaison has been notified of action                                                                               | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No                                                                                                                                       |
| • Indicate what types (if any) of information were issued                                                                                              | <input type="checkbox"/> None<br><input checked="" type="checkbox"/> FDA Press Release<br><input type="checkbox"/> FDA Talk Paper<br><input type="checkbox"/> CDER Q&As<br><input type="checkbox"/> Other |
| ❖ Exclusivity                                                                                                                                          |                                                                                                                                                                                                           |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?                              | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes                                                                                                                                       |
| • If so, specify the type                                                                                                                              |                                                                                                                                                                                                           |
| ❖ Patent Information (NDAs only)                                                                                                                       |                                                                                                                                                                                                           |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.                        | <input type="checkbox"/> Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.                                                                                           |
| <b>CONTENTS OF ACTION PACKAGE</b>                                                                                                                      |                                                                                                                                                                                                           |
| <b>Officer/Employee List</b>                                                                                                                           |                                                                                                                                                                                                           |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only) | <input checked="" type="checkbox"/> Included                                                                                                                                                              |
| Documentation of consent/non-consent by officers/employees                                                                                             | <input checked="" type="checkbox"/> Included                                                                                                                                                              |

| Action Letters                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ❖ Copies of all action letters <i>(including approval letter with final labeling)</i>                                                                                                                                                                    | Action(s) and date(s) Approval<br>09/23/16                                                                                                                                                                                                                                                                                                                                                                          |
| Labeling                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| ❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>                                                                                          | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>                                                                                                                                                                   | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                                                                                                                        |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>                                                                                   | <input checked="" type="checkbox"/> Medication Guide<br><input type="checkbox"/> Patient Package Insert<br><input type="checkbox"/> Instructions for Use<br><input type="checkbox"/> Device Labeling<br><input type="checkbox"/> None                                                                                                                                                                               |
| <ul style="list-style-type: none"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>                                                                                          | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                                                                                                                        |
| <ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>                                                                                                                                                                   | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                                                                                                                        |
| ❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>                                                                                                                                                                             | <input checked="" type="checkbox"/> Included                                                                                                                                                                                                                                                                                                                                                                        |
| ❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>Review(s) <i>(indicate date(s))</i></li> </ul>                                                                    | No Proprietary Name review required                                                                                                                                                                                                                                                                                                                                                                                 |
| ❖ Labeling reviews <i>(indicate dates of reviews)</i>                                                                                                                                                                                                    | RPM: <input type="checkbox"/> None 08/26/16<br>DMEPA: <input type="checkbox"/> None 09/14/16<br>DMPP/PLT (DRISK):<br><input type="checkbox"/> None 08/31/16<br>OPDP: <input type="checkbox"/> None 09/12/16<br>SEALD: <input checked="" type="checkbox"/> None<br>CSS: <input checked="" type="checkbox"/> None<br>Product Quality <input checked="" type="checkbox"/> None<br>Other: <input type="checkbox"/> None |
| Administrative / Regulatory Documents                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| ❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>                                                                                                                                                           | 05/19/16                                                                                                                                                                                                                                                                                                                                                                                                            |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee                                                                                                                                                                   | <input checked="" type="checkbox"/> Not a (b)(2)                                                                                                                                                                                                                                                                                                                                                                    |
| ❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>                                                                                                                                                                    | <input type="checkbox"/> Included                                                                                                                                                                                                                                                                                                                                                                                   |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> |                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>                                                                                                                                                                                | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No                                                                                                                                                                                                                                                                                                                                                 |

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo <i>(indicate date)</i></li> <li>If yes, OC clearance for approval <i>(indicate date of clearance communication)</i></li> </ul> </li> </ul>                                                                                                                                                                           | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action |
| ❖ Pediatrics <i>(approvals only)</i> <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____<br/>If PeRC review not necessary, explain: This product has orphan designation.</li> </ul>                                                                                                                                                                                                                                                                                    |                                                                                                                      |
| ❖ Breakthrough Therapy Designation                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/> N/A                                                                                         |
| <ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>                                                                                                                                                                                                                                                                                                                                                       | 04/21/16                                                                                                             |
| <ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i></li> </ul>                                                                                                                                                                                                                                                           | 04/19/16                                                                                                             |
| <ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i></li> </ul> <p><i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a>)</i></p>                                                                                                      |                                                                                                                      |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) <i>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</i> | 09/20/16, 09/07/16, 08/30/16, 07/18/16 07/14/16, 05/31/16, 05/19/16, 05/12/16, 04/08/16                              |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)                                                                                                                                                                                                                                             |                                                                                                                      |
| ❖ Minutes of Meetings                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                      |
| <ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="checkbox"/> N/A or no mtg                                                                    |
| <ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/> No mtg    06/02/15                                                                          |
| <ul style="list-style-type: none"> <li>EOP2 meeting <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> No mtg    05/13/13                                                                          |
| <ul style="list-style-type: none"> <li>Mid-cycle Communication <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                                                                                                                                                                                               | <input checked="" type="checkbox"/> N/A                                                                              |
| <ul style="list-style-type: none"> <li>Late-cycle Meeting <i>(indicate date of mtg)</i></li> </ul>                                                                                                                                                                                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> N/A                                                                              |
| <ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i></li> </ul>                                                                                                                                                                                                                                                                                                                              | WRO issued on 2/12/16                                                                                                |
| ❖ Advisory Committee Meeting(s)                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <input checked="" type="checkbox"/> No AC meeting                                                                    |
| <ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                      |
| <b>Decisional and Summary Memos</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                      |
| ❖ Office Director Decisional Memo <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> None                                                                                        |
| Division Director Summary Review <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                                                                               | <input type="checkbox"/> None    09/23/26                                                                            |
| Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                                                                            | <input type="checkbox"/> None    9/8/16                                                                              |
| PMR/PMC Development Templates <i>(indicate total number)</i>                                                                                                                                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> None                                                                                        |
| <b>Clinical</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                      |

|                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--------------------------------------------------------|
| ❖ Clinical Reviews                                                                                                                                                                                                                                                                                                                                                                                                    |  |                                                        |
| • Clinical Team Leader Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                               |  | <input checked="" type="checkbox"/> No separate review |
| • Clinical review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                           |  | 05/09/16, 08/30/16                                     |
| • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                     |  | <input type="checkbox"/> None                          |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>                                                                                                                                                |  | Clinical Review 08/30/16                               |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> <sup>5</sup>                                                                                                                                                                                                                                                                                      |  | <input checked="" type="checkbox"/> None               |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>                                                                                                                                                                                                                                                                                                            |  | <input checked="" type="checkbox"/> N/A                |
| ❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i></li> <li>REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul> |  | <input checked="" type="checkbox"/> None               |
| ❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>                                                                                                                                                                                                                                                                                                                 |  | <input checked="" type="checkbox"/> None requested     |
| <b>Clinical Microbiology</b>                                                                                                                                                                                                                                                                                                                                                                                          |  | <input checked="" type="checkbox"/> None               |
| ❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                  |  | <input type="checkbox"/> No separate review            |
| Clinical Microbiology Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                |  | <input type="checkbox"/> None                          |
| <b>Biostatistics</b>                                                                                                                                                                                                                                                                                                                                                                                                  |  | <input type="checkbox"/> None                          |
| ❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                      |  | <input checked="" type="checkbox"/> No separate review |
| Statistical Team Leader Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                              |  | <input checked="" type="checkbox"/> No separate review |
| Statistical Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                          |  | <input type="checkbox"/> None 06/06/16, 08/17/16       |
| <b>Clinical Pharmacology</b>                                                                                                                                                                                                                                                                                                                                                                                          |  | <input type="checkbox"/> None                          |
| ❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                            |  | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                    |  | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology review(s) <i>(indicate date for each review)</i>                                                                                                                                                                                                                                                                                                                                                |  | <input type="checkbox"/> None 05/17/16, 08/29/16       |
| ❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>                                                                                                                                                                                                                                                                                                                          |  | <input checked="" type="checkbox"/> None requested     |

<sup>5</sup> For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

| Nonclinical <input type="checkbox"/> None                                                                                                                                                                                                                                                                |                                                                                                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ❖ Pharmacology/Toxicology Discipline Reviews                                                                                                                                                                                                                                                             |                                                                                                                                                                      |
| • ADP/T Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                               | <input type="checkbox"/> No separate review                                                                                                                          |
| • Supervisory Review(s) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> No separate review                                                                                                               |
| • Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )                                                                                                                                                                                                         | <input type="checkbox"/> None 05/13/16, 09/06/16                                                                                                                     |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )                                                                                                                                                                                    | <input checked="" type="checkbox"/> None                                                                                                                             |
| ❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )                                                                                                                                                                                                              | <input checked="" type="checkbox"/> No carc                                                                                                                          |
| ❖ ECAC/CAC report/memo of meeting                                                                                                                                                                                                                                                                        | <input checked="" type="checkbox"/> None<br>Included in P/T review, page                                                                                             |
| ❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )                                                                                                                                                                                                                     | <input checked="" type="checkbox"/> None requested                                                                                                                   |
| Product Quality <input type="checkbox"/> None                                                                                                                                                                                                                                                            |                                                                                                                                                                      |
| ❖ Product Quality Discipline Reviews <sup>6</sup>                                                                                                                                                                                                                                                        |                                                                                                                                                                      |
| • Tertiary review ( <i>indicate date for each review</i> )                                                                                                                                                                                                                                               | <input type="checkbox"/> None                                                                                                                                        |
| • Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )                                                                                                                                                                                                                         | <input type="checkbox"/> None                                                                                                                                        |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )                                                                                                                            | <input type="checkbox"/> None 09/21/16                                                                                                                               |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )                                                                                                                                                                        | <input type="checkbox"/> None                                                                                                                                        |
| ❖ Environmental Assessment (check one) (original and supplemental applications)                                                                                                                                                                                                                          |                                                                                                                                                                      |
| <input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )(all original applications and all efficacy supplements that could increase the patient population)                                                                                                             | 09/21/16                                                                                                                                                             |
| <input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )                                                                                                                                                                                                                               |                                                                                                                                                                      |
| <input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )                                                                                                                                                                                                 |                                                                                                                                                                      |
| ❖ Facilities Review/Inspection                                                                                                                                                                                                                                                                           |                                                                                                                                                                      |
| <input type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> ) | <input checked="" type="checkbox"/> Acceptable<br>Re-evaluation date:<br><input type="checkbox"/> Withhold recommendation<br><input type="checkbox"/> Not applicable |

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

| Day of Approval Activities                                                                                                                                                                                                      |                                                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>                                             | <input type="checkbox"/> No changes<br><input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> ) |
| <ul style="list-style-type: none"> <li>Finalize 505(b)(2) assessment</li> </ul>                                                                                                                                                 | <input type="checkbox"/> Done                                                                                        |
| ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>Notify the CDER BT Program Manager</li> </ul>                                                                                          | <input type="checkbox"/> Done<br>( <i>Send email to CDER OND IO</i> )                                                |
| ❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>Notify the Division of Online Communications, Office of Communications</li> </ul> | <input type="checkbox"/> Done                                                                                        |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email                                                                                                                               | <input type="checkbox"/> Done                                                                                        |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter                                                                          | <input type="checkbox"/> Done                                                                                        |
| ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name                          | <input type="checkbox"/> Done                                                                                        |
| ❖ Ensure Pediatric Record is accurate                                                                                                                                                                                           | <input type="checkbox"/> Done                                                                                        |
| ❖ Send approval email within one business day to CDER-APPROVALS                                                                                                                                                                 | <input type="checkbox"/> Done                                                                                        |

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/s/  
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BRANDI E WHEELER  
09/23/2016



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 20, 2016

|                                                              |                                                                   |
|--------------------------------------------------------------|-------------------------------------------------------------------|
| <b>To:</b> Jennifer Evans, PharmD<br>Drug Regulatory Affairs | <b>From:</b> Brandi Wheeler, PharmD<br>Regulatory Project Manager |
| <b>Company:</b> Novartis Pharmaceutical Corp                 | Division of Pulmonary, Allergy, and<br>Rheumatology Products      |
| <b>Fax number:</b>                                           | <b>Fax number:</b> 301-796-9728                                   |
| <b>Phone number:</b> 862-881-9502                            | <b>Phone number:</b> 301-796-4495                                 |
| <b>Subject:</b> sBLA125319/85, 86, 87 Ilaris PMC Comments    |                                                                   |

**Total Number of Pages Including Cover:** 3

**Comments:** Please respond by Wednesday, September 21, 2016

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**Document to be mailed:** ☐ YES ☒ NO

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other action based on the content of this communication is not authorized. If you have  
received this document in error, please notify us immediately by telephone at (301) 796-  
2300. Thank you.**

We refer to BLA 125319 supplements 85, 86, and 87 for Ilaris Injection (canakinumab). We request that you provide your agreement to the postmarketing commitment outlined below.

Submit data from the randomized withdrawal period (Epoch 3) of the ongoing phase 3 study, CACZ885N2301 (N2301). Include an assessment of the maintenance of efficacy of canakinumab at a reduced dosing frequency in the study report.

Final Report Submission: 10/2016

Provide a response to the request by email (Brandi.Wheeler@fda.hhs.gov) or facsimile (301-796-9728), by noon on Wednesday, September 21, 2016. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

sBLA125319 / 85, 86, 87

Drafted by: B Wheeler 09/19/16

Cleared by: L Jafari 09/19/16

J Maynard 09/20/16

S Seymour 09/20/16

Finalized by: B Wheeler 09/20/16

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/s/  
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BRANDI E WHEELER  
09/20/2016



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 20, 2016

|                                                                |                                                                   |
|----------------------------------------------------------------|-------------------------------------------------------------------|
| <b>To:</b> Jennifer Evans, PharmD<br>Drug Regulatory Affairs   | <b>From:</b> Brandi Wheeler, PharmD<br>Regulatory Project Manager |
| <b>Company:</b> Novartis Pharmaceutical Corp                   | Division of Pulmonary, Allergy, and<br>Rheumatology Products      |
| <b>Fax number:</b>                                             | <b>Fax number:</b> 301-796-9728                                   |
| <b>Phone number:</b> 862-881-9502                              | <b>Phone number:</b> 301-796-4495                                 |
| <b>Subject:</b> sBLA125319/85, 86, 87 Ilaris Labeling Comments |                                                                   |

**Total Number of Pages Including Cover:** 28

**Comments:** Please respond by Wednesday, September 21, 2016

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**Document to be mailed:** ☐ YES ☒ NO

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We refer to BLA 125319 supplements 85, 86, and 87 for Ilaris Injection (canakinumab) and to your proposed revised labeling submission dated September 19, 2016. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. Please be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling comments may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email ([brandi.wheeler@fda.hhs.gov](mailto:brandi.wheeler@fda.hhs.gov)) to Brandi Wheeler by 4 pm on Wednesday, September 21, 2016, followed by an official submission to the BLA. If there are any questions, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

sBLA125319/85, 86, 87

Drafted by: J Maynard 09/20/16  
B Wheeler 09/20/16

Cleared by: L Jafari 09/20/16

Finalized by: B Wheeler 09/20/16

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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BRANDI E WHEELER  
09/20/2016



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 7, 2016

|                                                              |                                                                   |
|--------------------------------------------------------------|-------------------------------------------------------------------|
| <b>To:</b> Jennifer Evans, PharmD<br>Drug Regulatory Affairs | <b>From:</b> Brandi Wheeler, PharmD<br>Regulatory Project Manager |
| <b>Company:</b> Novartis Pharmaceutical Corp                 | Division of Pulmonary, Allergy, and<br>Rheumatology Products      |
| <b>Fax number:</b>                                           | <b>Fax number:</b> 301-796-9728                                   |
| <b>Phone number:</b> 862-881-9502                            | <b>Phone number:</b> 301-796-4495                                 |
| <b>Subject:</b> sBLA125319/85, 86, 87 Ilaris; FDA Comments   |                                                                   |

**Total Number of Pages Including Cover:** 3

**Comments:** Please respond by September 9, 2016

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sBLA125319/85, 86, 87

We refer to BLA 125319 supplements 85, 86, and 87 for Ilaris Injection (canakinumab). We request that you provide your agreement to the postmarketing commitment outlined below and provide the applicable milestones.

Submit data from the randomized withdrawal period (Epoch 3) of the ongoing phase 3 study, CACZ885N2301 (N2301).

|                            |           |
|----------------------------|-----------|
| Final Protocol Submission: | Completed |
|----------------------------|-----------|

|                   |            |
|-------------------|------------|
| Study Completion: | Month/Year |
|-------------------|------------|

|                          |            |
|--------------------------|------------|
| Final Report Submission: | Month/Year |
|--------------------------|------------|

Submit your responses via email to [Brandi.Wheeler@fda.hhs.gov](mailto:Brandi.Wheeler@fda.hhs.gov) by noon, September 9, 2016, followed by an official submission to the BLA. If there are any questions, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

Drafted by: SNabavian/9.7.2016

Cleared by: LJafari/ 9.7.2016

MBorigini/JMaynard/9.7.2016

CHill/SSeymour/9.7.2016

Finalized by: SNabavina (for BWheeler)/9.7.2016

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/s/  
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SADAF NABAVIAN  
09/07/2016



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** August 30, 2016

|                                                                |                                                                   |
|----------------------------------------------------------------|-------------------------------------------------------------------|
| <b>To:</b> Jennifer Evans, PharmD<br>Drug Regulatory Affairs   | <b>From:</b> Brandi Wheeler, PharmD<br>Regulatory Project Manager |
| <b>Company:</b> Novartis Pharmaceutical Corp                   | Division of Pulmonary, Allergy, and<br>Rheumatology Products      |
| <b>Fax number:</b>                                             | <b>Fax number:</b> 301-796-9728                                   |
| <b>Phone number:</b> 862-881-9502                              | <b>Phone number:</b> 301-796-4495                                 |
| <b>Subject:</b> sBLA125319/85, 86, 87 Ilaris Labeling Comments |                                                                   |

**Total Number of Pages Including Cover:** 35

**Comments:** Please respond by Tuesday, September 6, 2016

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We refer to BLA 125319 supplements 85, 86, and 87 for Ilaris Injection (canakinumab) and to your proposed revised labeling submission dated August 3, 2015. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined and deletions are in strike-out. Please be advised that these labeling comments are not necessarily the Agency's final recommendations and that additional labeling comments may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up label via email ([brandi.wheeler@fda.hhs.gov](mailto:brandi.wheeler@fda.hhs.gov)) to Brandi Wheeler by Tuesday, September 6, 2016, followed by an official submission to the BLA. If there are any questions, contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

sBLA125319/85, 86, 87

Drafted by: J Maynard 08/29/16 / G Levin 08/29/16 / J Chen 08/29/16 / A Marathe 08/29/16  
B Wheeler 08/29/16

Cleared by: L Jafari 08/29/16

Finalized by: B Wheeler 08/30/16

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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BRANDI E WHEELER  
08/30/2016



**Food and Drug Administration  
Center for Drug Evaluation and Research  
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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 18, 2016

|                                                              |                                                                   |
|--------------------------------------------------------------|-------------------------------------------------------------------|
| <b>To:</b> Jennifer Evans, PharmD<br>Drug Regulatory Affairs | <b>From:</b> Brandi Wheeler, PharmD<br>Regulatory Project Manager |
| <b>Company:</b> Novartis Pharmaceutical Corp                 | Division of Pulmonary, Allergy, and<br>Rheumatology Products      |
| <b>Fax number:</b>                                           | <b>Fax number:</b> 301-796-9728                                   |
| <b>Phone number:</b> 862-881-9502                            | <b>Phone number:</b> 301-796-4495                                 |

**Subject:** sBLA125319/85, 86, 87 Clinical IR

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**Total Number of Pages Including Cover:** 3

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**Comments:** Please respond by Wednesday, July 20, 2016

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**Document to be mailed:** ☐ YES ☒ NO

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other action based on the content of this communication is not authorized. If you have  
received this document in error, please notify us immediately by telephone at (301) 796-  
2300. Thank you.**

We are currently reviewing your Supplemental Biological License applications dated March 23, 28, and 29, 2016, and have the following request for information.

Regarding Patient N2301-2504-002, provide additional information regarding this SAE, such as, the final pathology report for the liver biopsy, additional information on the patient's baseline liver function, and any additional information that provides clarity on this SAE.

Provide a response to the request by email (Brandi.Wheeler@fda.hhs.gov) or facsimile (301-796-9728), by 4 pm, Wednesday, July 20, 2016. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

sBLA125319/85, 86, 87

Drafted by: M Borigini 07/18/16 / J Maynard 07/18/16  
B Wheeler 07/18/16

Cleared by: L Jafari 07/18/16

Finalized by: B Wheeler 07/18/16

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BRANDI E WHEELER  
07/18/2016



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** July 14, 2016

|                                                              |                                                                   |
|--------------------------------------------------------------|-------------------------------------------------------------------|
| <b>To:</b> Jennifer Evans, PharmD<br>Drug Regulatory Affairs | <b>From:</b> Brandi Wheeler, PharmD<br>Regulatory Project Manager |
| <b>Company:</b> Novartis Pharmaceutical Corp                 | Division of Pulmonary, Allergy, and<br>Rheumatology Products      |
| <b>Fax number:</b>                                           | <b>Fax number:</b> 301-796-9728                                   |
| <b>Phone number:</b> 862-881-9502                            | <b>Phone number:</b> 301-796-4495                                 |
| <b>Subject:</b> sBLA125319/85, 86, 87 Clinical IR            |                                                                   |

**Total Number of Pages Including Cover:** 3

**Comments:** Please respond by Monday, July 18, 2016

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**Document to be mailed:** ☐ YES ☒ NO

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other action based on the content of this communication is not authorized. If you have  
received this document in error, please notify us immediately by telephone at (301) 796-  
2300. Thank you.**

We are currently reviewing your Supplemental Biological License applications dated March 23, 28, and 29, 2016, and have the following request for information.

You describe four non-randomized patients in your summary of the Epoch 2 study population, two of whom were HIDS/MKD patients under two years of age. Submit the safety data on these two subjects.

Provide a response to the request by email (Brandi.Wheeler@fda.hhs.gov) or facsimile (301-796-9728), by 4 pm, Monday, July 18, 2016. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

sBLA125319/85, 86, 87

Drafted by: M Borigini 07/12/16 / J Maynard 07/12/16  
B Wheeler 07/12/16

Cleared by: L Jafari 07/14/16

Finalized by: B Wheeler 07/14/16

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BRANDI E WHEELER  
07/14/2016



BLA 125319/S-085, 086, 087

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

Attention: Jennifer Evans, PharmD  
Global Program Regulatory Director, Drug Regulatory Affairs

Dear Dr. Evans:

Please refer to your supplemental Biologics License Applications (sBLAs) dated March 23, 28, and 29, 2016, received March 23, 28, and 29, 2016, submitted under section 351(a) of the Public Health Service Act for Ilaris (canakinumab) Injection 150mg/mL.

During our filing review of your application, we identified the following potential review issues:

**Clinical**

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.
2. 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, under IND 100040, 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.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Brandi Wheeler, Regulatory Project Manager, at (301) 796-4495.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
05/31/2016



BLA 125319/S-085, 086, 087

**PRIORITY REVIEW DESIGNATION**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

Attention: Jennifer Evans, PharmD  
Global Program Regulatory Director, Drug Regulatory Affairs

Dear Dr. Evans:

Please refer to your supplemental Biologics License Applications (sBLAs) dated March 23, 28, and 29, 2016, received March 23, 28, and 29, 2016, submitted under section 351(a) of the Public Health Service Act for Ilaris (canakinumab) Injection 150mg/mL.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 601.2(a). The review classification for this application is **Priority**. Therefore, the user fee goal dates are September 23, 28, and 29, 2016, respectively for supplements 85, 86, and 87.

We are reviewing your applications according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 2, 7, and 8, 2016, respectively for supplements 85, 86, and 87.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before June 5, 10, and 11, 2016, respectively for supplements 85, 86, and 87.

If you have any questions, call Brandi Wheeler, Regulatory Project Manager, at (301) 796-4495.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
05/19/2016



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODE II**

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** May 11, 2016

|                                                              |                                                                   |
|--------------------------------------------------------------|-------------------------------------------------------------------|
| <b>To:</b> Jennifer Evans, PharmD<br>Drug Regulatory Affairs | <b>From:</b> Brandi Wheeler, PharmD<br>Regulatory Project Manager |
| <b>Company:</b> Novartis Pharmaceutical Corp                 | Division of Pulmonary, Allergy, and<br>Rheumatology Products      |
| <b>Fax number:</b>                                           | <b>Fax number:</b> 301-796-9728                                   |
| <b>Phone number:</b> 862-881-9502                            | <b>Phone number:</b> 301-796-4495                                 |

**Subject:** sBLA125319/85, 86, 87 Stats IR

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**Total Number of Pages Including Cover:** 3

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**Comments:** Please respond by Friday, May 20, 2016

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**Document to be mailed:** ☐ YES ☒ NO

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other action based on the content of this communication is not authorized. If you have  
received this document in error, please notify us immediately by telephone at (301) 796-  
2300. Thank you.**

We are currently reviewing your Supplemental Biological License applications dated March 23, 28, and 29, 2016, and have the following requests for information.

1. Summarize the proportion of patients that received add on canakinumab 150mg between Day 8 and Day 28, or switched from placebo to canakinumab 150mg during the 16-week Epoch 2, or had up titration during the 16-week Epoch 2. Provide descriptive tables and/or graphs to illustrate the proportion of patients who remained on initial randomized treatment in each cohort over time.
2. Submit an analysis dataset which contains each patient's actual treatment received and efficacy measurement at each visit. There should be one record per subject per visit and include the following variables:

Cohort, subject ID, visit (baseline, weeks 3, 5, 9, 13, 17, or unscheduled if applicable), initial randomized treatment (Placebo or 150mg), actual treatment received at each visit (Placebo, 150mg, or 300mg), indicator for patients changing from initial randomized treatment, indicator for the visit when patients changed treatments, PGA score, CRP score, SAA score, resolution of index disease flare (Yes or No), new disease flare (Yes or No), AIDAI score, PPGA score, CHQ-PF50 physical component summary score, SF-12 physical-component summary score, SDS score.

3. Submit analysis datasets and programs that were used to generate the tables and figures in Section 11.4.1.3 exploratory efficacy results.

Provide a response to the request by email (Brandi.Wheeler@fda.hhs.gov) or facsimile (301-796-9728), by Friday, May 20, 2016. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Brandi Wheeler, Regulatory Project Manager, at 301-796-4495.

sBLA125319/85, 86, 87

Drafted by: L Zeng / G Levin 05/11/16  
B Wheeler 05/11/16

Cleared by: L Jafari 05/12/16

Finalized by: B Wheeler 05/12/16

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/s/  
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BRANDI E WHEELER  
05/12/2016

## **DOCUMENT INFORMATION PAGE**

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**Application #(s):** IND 100040

|                             |                                        |
|-----------------------------|----------------------------------------|
| <b>Communication Type:</b>  | Correspondence                         |
| <b>Communication Group:</b> | Breakthrough Therapy                   |
| <b>Communication Name:</b>  | Grant Breakthrough Therapy Designation |
| <b>Communication ID:</b>    | COR-BREAK-02                           |

|                           |                                                                                                                      |
|---------------------------|----------------------------------------------------------------------------------------------------------------------|
| <b>Drafted by:</b>        | L. Brodhead, 4/12/16                                                                                                 |
| <b>Clearance History:</b> | L. Jafari, 4/14/16<br>K. Hull/N. Nikolov, 4/13/2016<br>B. Chowdhury, 4/18/16<br>Miranda Raggio/IO Clearance, 4/18/16 |
| <b>Finalized:</b>         | L. Brodhead, 4/21/16                                                                                                 |
| <b>Filename:</b>          |                                                                                                                      |

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|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>GOAL IMPACT</b>          | Closes the 60-day statutory goal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Signatory Authority:</b> | Division Director or Deputy. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Use Statement:</b>       | Use to GRANT sponsor's request for Breakthrough Therapy designation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Notes:</b>               | <ul style="list-style-type: none"><li>• <b>ALL REQUESTS FOR BREAKTHROUGH THERAPY DESIGNATION SHOULD BE SENT TO THE OND IO (via email to CDER OND IO (no hyphens) and Miranda Raggio. The OND IO will coordinate review of these requests by the Medical Policy Council.</b></li><li>• <b>THIS LETTER MUST BE CLEARED BY OND IO BEFORE DIVISION DIRECTOR SIGN-OFF AND ISSUANCE. FOR OND IO CLEARANCE, SEND DRAFT LETTER, CLEARED BY THE DIVISION DIRECTOR AND ODE DIRECTOR, TO MIRANDA RAGGIO AT LEAST 3 DAYS PRIOR TO GOAL DATE.</b></li><li>• <b>If you choose option B from the letter template, please code the meeting in DARRTS as one of the following:</b><ul style="list-style-type: none"><li>○ <b>End of Phase 1/Breakthrough Therapy-Initial Comprehensive</b></li><li>○ <b>End of Phase 2/Pre-Phase 3/Breakthrough Therapy-Initial Comprehensive</b></li><li>○ <b>Pre-NDA/Supplement/Breakthrough Therapy-Initial Comprehensive</b></li><li>○ <b>Pre-BLA/Supplement/Breakthrough Therapy-Initial Comprehensive</b></li></ul></li></ul> |

Version: 07/30/2015

## **END OF DOCUMENT INFORMATION PAGE**

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IND 100040

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Novartis  
One Health Plaza  
East Hanover, NJ 07936

Attention: Jennifer Evans, PharmD  
Global Program Regulatory Director

Dear Dr. Evans:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for canakinumab.

We also refer to your February 26, 2016, request for Breakthrough Therapy designation. We have reviewed your request and have determined that canakinumab for Familial Mediterranean Fever (FMF) in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of canakinumab for FMF in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for

<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>2</sup>

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProce>

discussion at this initial breakthrough therapy meeting<sup>2</sup>.

We note your recent Pre- Biologic Licensing Agreement meeting held on June 2, 2015. At this point in your drug development program, holding this initial breakthrough therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for canakinumab for in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response is rescinded, submission of portions of the sBLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact LeAnn Brodhead, Regulatory Project Manager, at (240) 402-2605.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
04/21/2016

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| <b>Communication Type:</b>  | Correspondence                         |
| <b>Communication Group:</b> | Breakthrough Therapy                   |
| <b>Communication Name:</b>  | Grant Breakthrough Therapy Designation |
| <b>Communication ID:</b>    | COR-BREAK-02                           |

|                           |                                                                                                                        |
|---------------------------|------------------------------------------------------------------------------------------------------------------------|
| <b>Drafted by:</b>        | L. Brodhead, 4/12/16                                                                                                   |
| <b>Clearance History:</b> | L. Jafari, 04/14/16<br>K. Hull/N. Nikolov, 04/13/2016<br>B. Chowdhury, 4/18/16<br>Miranda Raggio/IO Clearance, 4/18/16 |
| <b>Finalized:</b>         | L. Brodhead, 4/21/16                                                                                                   |
| <b>Filename:</b>          |                                                                                                                        |

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| <b>GOAL IMPACT</b>          | Closes the 60-day statutory goal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Use Statement:</b>       | Use to GRANT sponsor's request for Breakthrough Therapy designation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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Version: 07/30/2015

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IND 100040

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Novartis  
One Health Plaza  
East Hanover, NJ 07936

Attention: Jennifer Evans, PharmD  
Global Program Regulatory Director

Dear Dr. Evans:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for canakinumab.

We also refer to your February 26, 2016, request for Breakthrough Therapy designation. We have reviewed your request and have determined that canakinumab for Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of canakinumab for HIDS/MKD to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting<sup>2</sup>.

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<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

We note your recent Pre- Biologic Licensing Agreement meeting held on June 2, 2015. At this point in your drug development program, holding this initial breakthrough therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for canakinumab for HIDS/MKD is rescinded, submission of portions of the sBLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact LeAnn Brodhead, Regulatory Project Manager, at (240) 402-2605.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
04/21/2016

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**Application #(s):** IND 100040

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|-----------------------------|----------------------------------------|
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| <b>Communication Group:</b> | Breakthrough Therapy                   |
| <b>Communication Name:</b>  | Grant Breakthrough Therapy Designation |
| <b>Communication ID:</b>    | COR-BREAK-02                           |

|                           |                                                                                                                    |
|---------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>Drafted by:</b>        | L. Brodhead, 4/12/16                                                                                               |
| <b>Clearance History:</b> | L. Jafari, 4/14/16<br>K. Hull/N. Nikolov, 4/13/16<br>B. Chowdhury, 4/18/16<br>Miranda Raggio/IO Clearance, 4/18/16 |
| <b>Finalized:</b>         | L. Brodhead, 4/21/16                                                                                               |
| <b>Filename:</b>          |                                                                                                                    |

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|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>GOAL IMPACT</b>          | Closes the 60-day statutory goal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Signatory Authority:</b> | Division Director or Deputy. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Use Statement:</b>       | Use to GRANT sponsor's request for Breakthrough Therapy designation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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Version: 07/30/2015

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IND 100040

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Novartis  
One Health Plaza  
East Hanover, NJ 07936

Attention: Jennifer Evans, PharmD  
Global Program Regulatory Director

Dear Dr. Evans:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for canakinumab.

We also refer to your February 26, 2016, request for Breakthrough Therapy designation. We have reviewed your request and have determined that canakinumab for Tumor Necrosis Receptor Associated Periodic Syndrome (TRAPS) meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of canakinumab for TRAPS to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting<sup>2</sup>.

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<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

We note your recent Pre- Biologic Licensing Agreement meeting held on June 2, 2015. At this point in your drug development program, holding this initial breakthrough therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for canakinumab for TRAPS is rescinded, submission of portions of the sBLA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact LeAnn Brodhead, Regulatory Project Manager, at (240) 402-2605.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
04/21/2016

# CDER Breakthrough Therapy Designation Determination Review Template

|                                                                                  |                                                                                                                                     |
|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| <b>IND #</b>                                                                     | 100040                                                                                                                              |
| <b>Request Receipt Date</b>                                                      | February 26, 2016                                                                                                                   |
| <b>Product</b>                                                                   | Canakinumab (ILARIS)                                                                                                                |
| <b>Indication</b>                                                                | Familial Mediterranean Fever (FMF) in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response |
| <b>Drug Class/Mechanism of Action</b>                                            | Human monoclonal antibody targeted at interleukin-1 beta                                                                            |
| <b>Sponsor</b>                                                                   | Novartis                                                                                                                            |
| <b>ODE/Division</b>                                                              | ODE II/Division of Pulmonary, Allergy, and Rheumatology Products                                                                    |
| <b>Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)</b> | April 26, 2016                                                                                                                      |

*Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.*

## **Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.**

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Familial Mediterranean Fever

- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

☐ YES ☒ NO

*If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:*

- Consideration of Breakthrough Therapy Criteria:**

- Is the condition serious/life-threatening<sup>1</sup>?

☒ YES ☐ NO

*If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:*

- Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review

☐ Undetermined

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

- Only animal/nonclinical data submitted as evidence

☐

<sup>1</sup> For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy<sup>2</sup>/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

**4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:**

***If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.***

***If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.***

**5. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}  
 Team Leader Signature: {See appended electronic signature page}  
 Division Director Signature: {See appended electronic signature page}

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Canakinumab (ILARIS) is a human monoclonal IgG1 antibody with high-affinity against IL-1 $\beta$  and acts by binding and neutralizing endogenous IL-1 $\beta$  thereby blocking its effect. Canakinumab was originally approved by the Agency in 2009 for the treatment of cryopyrin-associated syndromes (CAPS), a related group of three autoinflammatory syndromes comprised of familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS), and neonatal-onset multisystem inflammatory syndrome (NOMID). A supplemental BLA was approved in May 2013 extending the claims of canakinumab to treat children with systemic juvenile idiopathic arthritis (SJIA).

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<sup>2</sup> For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Familial Mediterranean fever (FMF) is the archetype of the hereditary autoinflammatory syndromes and is characterized clinically by recurrent febrile episodes associated with localized inflammation of the serosal membranes, joints, and skin. Biopsies from affected tissues reveal an infiltration consisting principally of polymorphonuclear leukocytes (PMN). Attacks typically last less than 72 hours before spontaneously resolving, but subclinical inflammation may persist and predispose susceptible individuals to AA amyloidosis. Although individuals of Turkish, Armenian, Jewish, Italian, and Arab ancestry are most commonly affected, the relatively mild E148Q mutation has recently been found to be very common in the Chinese and Punjabi Indian populations. It is also interesting to note that patients with FMF appear to be at increased risk for developing vasculitis, Behçet's syndrome, and inflammatory bowel disease, suggesting that the underlying etiology of FMF may contribute to a broader spectrum of inflammatory diseases.

The gene responsible for FMF, designated *MEFV* (for Mediterranean fever), was identified in 1997 by positional cloning. *MEFV* encodes a 781 amino acid protein called pyrin that is predominantly expressed in PMNs and cytokine-activated monocytes. Pyrin consists of 4 functional domains: a 92 amino acid N-terminal PYRIN domain (also referred to as PAD, PYD, or DAPIN), a B-box zinc-finger domain, a coiled-coil domain, and a C-terminal B30.2 domain. Although the C-terminal half of pyrin shares homology with several transcription factors, transfected pyrin localizes in the cytoplasm, and interacts with microtubules via its N-terminal half.

One of the most important advances has been the demonstration that the PYRIN-domain is shared by a number of proteins involved in apoptosis and inflammation, and is a member of the six-helix bundle death domain superfamily that includes death domains, death effector domains, and caspase recruitment domains (CARDs). Similar to other members of this superfamily, the PYRIN domain appears to allow for the interaction, or assembly, of macromolecular complexes by PYRIN-PYRIN interactions. Consistent with this, in vitro studies using yeast two-hybrid systems, coimmunoprecipitation, or immunofluorescence have demonstrated pyrin to interact specifically with another PYRIN domain protein termed apoptosis-associated speck-like protein with a CARD (ASC). In addition to its N-terminal PYRIN domain, ASC contains a C-terminal CARD that specifically binds the CARD of procaspase-1 (also referred to as IL-1 $\alpha$  converting enzyme [ICE]) leading to its aggregation and autoactivation. Activated caspase-1 then processes pro-IL-1 $\beta$  to IL-1 $\beta$ , which is secreted and interacts with the IL-1 receptor to mediate inflammation. Data from the scientific literature suggest that pyrin may act as an anti-inflammatory molecule by inhibiting ASC-induced IL-1 processing and by permitting macrophage apoptosis.

## **7. Information related to endpoints used in the available clinical data:**

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary objective of the randomized, placebo-controlled, treatment period was to demonstrate that canakinumab 150 mg (or 2 mg/kg in patient weighing  $\leq 40$  kg) sc 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. Specifically, the primary efficacy endpoint was defined as the proportion of responders within each randomized group. A responder was defined as a patient who had resolution of his/her index disease flare at Day 15 and did not experience a new flare during the 16 weeks from the time of the resolution of the index flare following randomization. Resolution of the index flare was defined at the Day 15 visit as Physician Global

Assessment of Disease Activity (PGA)  $<2$  and C-reactive Protein (CRP) within normal range ( $\leq 10$  mg/L) or reduction of  $\geq 70\%$  from baseline. New flare was defined from the time of the resolution of the index flare as PGA  $\geq 2$ , and CRP  $\geq 30$  mg/L. subjects 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.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
  - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
  - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

The Division considers the proposed primary endpoint sufficient to capture a clinically meaningful benefit of the drug and therefore supporting a traditional approval. Of note, the only other product approved for the treatment of FMF, colchicine, was approved based on evidence derived from the published literature and relied on comparing the incidence of FMF attacks over a three to four month period (Colcris PI).

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

**8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Colchicine, which is approved for the treatment of patients with FMF, is the only known beneficial therapy for the treatment of FMF.

**9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>3</sup>.**

None.

**10. Information related to the preliminary clinical evidence:**

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<sup>3</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design<sup>4</sup>, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Study N2301 is a four part study consisting of:

- Part 1: Screening phase (completed)
- Part 2: 16 week, double-blind, placebo-controlled phase (completed)
- Part 3: Randomized withdrawal phase (ongoing)
- Part 4: long-term treatment phase (ongoing)

The primary efficacy endpoint of the randomized treatment period (Part 2), and for the overall study, was the proportion of responders within each cohort. A responder was defined as a patient who had resolution of his/her index disease flare (i.e., physician global assessment (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 the 16 week treatment period. For the primary analysis, patients who required dose escalation in the canakinumab arms, who crossed over from placebo to canakinumab, or patients who discontinued from the study for any reason prior to evaluating the primary endpoint were considered non-responders.

Major secondary endpoints for Part 2 of the study included the percentage of patients who achieved a PGA < 2 (“minimal” disease activity); the percentage of patients with serologic remission (defined as CRP  $\leq 10$  mg/L); and the percentage of patients with normalized serum amyloid-A (SAA) (defined as  $\leq 10$  mg/L). The primary endpoint and the 3 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.

The trial was designed and powered to demonstrate that canakinumab treatment at a dose of 150 mg (or 2 mg/kg in patient weighing  $\leq 40$  kg) administered subcutaneously every 4 weeks was superior to placebo in achieving reduction of disease activity defined as resolution of the index flare on Day 15 and no new disease flares over 16 weeks of treatment.

The study population consisted of male and female patients with confirmed FMF who were at least 2 years of age at the time of the screening visit. Patients who experienced persistent “mild”, “moderate” or “severe” disease activity (i.e., PGA  $\geq 2$ ) or CRP persistent  $> 10$  mg/L with less than 40% reduction from baseline from Day 8 to Day 14 received an additional dose of 150 mg (or 2 mg/kg for patients 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 also received an additional dose of 150 mg (or 2 mg/kg for patients less than or equal to 40 kg). If the patient’s condition did not improve after administration of the single add-on canakinumab injection, rescue medication was used until Day 29.

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<sup>4</sup> Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

**Table 8-3 Comparison between treatment groups for patients who responded at Week 16 by cohort (Full analysis set)**

| Cohort | ACZ885 150mg q4w |                | Placebo        |                  | Risk difference<br>(95% CI) | Comparison              |                      |
|--------|------------------|----------------|----------------|------------------|-----------------------------|-------------------------|----------------------|
|        | n/M (%)          | 95% CI         | n/M (%)        | 95% CI           |                             | Odds Ratio<br>(95% CI)  | One-sided<br>p-value |
| crFMF  | 19/31<br>(61.29) | (42.19, 78.15) | 2/32<br>(6.25) | (0.77,<br>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,<br>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,<br>27.00) | 0.37<br>(0.08, 0.61)        | 9.17<br>(1.51, 94.61)   | 0.0050*              |

n=number of patients who responded; M=number of patients evaluated for response; CI=confidence Interval.

\* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.

\* Source: Table 8-3 from Sponsor's Meeting Brochure 03Dec2015

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness*

The submitted data demonstrated clinical evidence of a substantial improvement over placebo in patients who either could not tolerate colchicine or who had an inadequate response to therapeutic doses of colchicine. There are no approved therapies for these patients.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

Overall, the clinical development program was conducted in a manner consistent with the Agency's advice and was adequately conducted.

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

In general, canakinumab was well-tolerated and adverse reactions consistent with what is currently contained in the package insert. No new safety signals have been identified.

#### 11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

The Division recommends that the breakthrough therapy designation request is granted. The Division's considerations include: (1) FMF is a serious condition with unmet need and (2) the preliminary clinical evidence indicates a substantial improvement with canakinumab over available therapies/standard of care for FMF.

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

☐ DENY:

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

**12. Division's next steps and sponsor's plan for future development:**

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor has completed the core Epoch of their phase 3 program and is preparing to submit a sBLA in 2016. Further, based on the information to date, it is likely that the planned sBLA will also meet the criteria for a priority review.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

**13. List references, if any:**

**14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES ☒ NO ☐

**15. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation ☐  
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}  
Team Leader Signature: {See appended electronic signature page}  
Division Director Signature: {See appended electronic signature page}

**Revised 1/15/16/M. Raggio**

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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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KEITH M HULL

04/19/2016

NIKOLAY P NIKOLOV

04/19/2016

I concur. This BTDR was reviewed by Medical Policy Concil who agreed with DPARP's recommendation for granting the request.

BADRUL A CHOWDHURY

04/19/2016

# CDER Breakthrough Therapy Designation Determination Review Template

|                                                                                  |                                                                        |
|----------------------------------------------------------------------------------|------------------------------------------------------------------------|
| <b>IND #</b>                                                                     | 100040                                                                 |
| <b>Request Receipt Date</b>                                                      | February 26, 2016                                                      |
| <b>Product</b>                                                                   | Canakinumab (ILARIS)                                                   |
| <b>Indication</b>                                                                | Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) |
| <b>Drug Class/Mechanism of Action</b>                                            | Human monoclonal antibody targeted at interleukin-1 beta               |
| <b>Sponsor</b>                                                                   | Novartis                                                               |
| <b>ODE/Division</b>                                                              | ODE II/Division of Pulmonary, Allergy, and Rheumatology Products       |
| <b>Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)</b> | April 26, 2016                                                         |

*Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.*

## **Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.**

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency

- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

☐ YES ☒ NO

*If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:*

- Consideration of Breakthrough Therapy Criteria:**

- Is the condition serious/life-threatening<sup>1</sup>?

☒ YES ☐ NO

*If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:*

- Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review

☐ Undetermined

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence

ii. Insufficient clinical data provided to evaluate the BTDR

☐

<sup>1</sup> For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy<sup>2</sup>/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

**4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:**

*If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.*

*If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.*

**5. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

Canakinumab (ILARIS) is a human monoclonal IgG1 antibody with high-affinity against IL-1 $\beta$  and acts by binding and neutralizing endogenous IL-1 $\beta$  thereby blocking its effect. Canakinumab was originally approved by the Agency in 2009 for the treatment of cryopyrin-associated syndromes (CAPS), a related group of three autoinflammatory syndromes comprised of familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS), and neonatal-onset multisystem inflammatory syndrome (NOMID). A supplemental BLA was approved in May 2013 extending the claims of canakinumab to treat children with systemic juvenile idiopathic arthritis (SJIA).

The hyperimmunoglobulinemia-D/Mevalonate Kinase with periodic fever syndrome (HIDS) is a rare, recessively inherited disease caused by mutations in *MVK*, the gene that encodes mevalonate kinase, an

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<sup>2</sup> For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

enzyme that catalyzes the conversion of mevalonic acid to 5-phosphomevalonic acid, involved in both cholesterol synthesis and post-translation prenylation of proteins. Twenty different mutations have been described to date and the majority of patients identified to date have been of Northern European ancestry. The syndrome is clinically characterized by the early onset of systems that include recurrent episodes of fever, abdominal pain, lymphadenopathy, polyarthralgia/polyarthritis, a diffuse maculopapular rash, and in some patients oral or genital ulcerations. As suggested by its name, patients with HIDS usually have elevated serum immunoglobulin D (usually > 100 mg/dL); however, some patient, especially young children, with typical clinical findings and *MVK* mutations, may have normal serum immunoglobulin D levels. Mevalonic acid in the urine is elevated during attacks. There are no approved therapies for HIDS.

## 7. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary objective of the randomized, placebo-controlled, treatment period, was to demonstrate that canakinumab 150 mg (or 2 mg/kg in patient weighing  $\leq 40$  kg) sc 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. Specifically, the primary efficacy endpoint was defined as the proportion of responders within each randomized group. A responder was defined as a patient who had resolution of his/her index disease flare at Day 15 and did not experience a new flare during the 16 weeks from the time of the resolution of the index flare following randomization. Resolution of the index flare was defined at the Day 15 visit as Physician Global Assessment of Disease Activity (PGA)  $< 2$  and C-reactive Protein (CRP) within normal range ( $\leq 10$  mg/L) or reduction of  $\geq 70\%$  from baseline. New flare was defined from the time of the resolution of the index flare as PGA  $\geq 2$ , and CRP  $\geq 30$  mg/L. Subjects 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.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
  - *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
  - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
  - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

While there has not been a regulatory precedent for drug development or approval for HIDS, the Division considers the proposed primary endpoint sufficient to capture a clinically meaningful benefit of the drug and therefore supporting a traditional approval.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

**8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no approved therapies for HIDS. Currently the treatment is aimed at palliation of symptoms with NSAIDs.

**9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>3</sup>.**

None.

**10. Information related to the preliminary clinical evidence:**

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design<sup>4</sup>, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Study N2301 is a four part study consisting of

- Part 1: Screening phase (completed)
- Part 2: 16 week, double-blind, placebo-controlled phase (completed)
- Part 3: Randomized withdrawal phase (ongoing)
- Part 4: long-term treatment phase (ongoing)

The primary efficacy endpoint of the randomized treatment period (Part 2), and for the overall study, was the proportion of responders within each cohort. A responder was defined as a patient who had resolution of his/her index disease flare (i.e., physician global assessment (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 the 16 week treatment period. For the primary analysis, patients who required dose escalation in the canakinumab arms, who crossed over from placebo to canakinumab, or patients who discontinued from the study for any reason prior to evaluating the primary endpoint were considered non-responders.

Major secondary endpoints for Part 2 of the study included the percentage of patients who achieved a PGA < 2 (“minimal” disease activity); the percentage of patients with serologic remission (defined as CRP ≤ 10 mg/L); and the percentage of patients with normalized serum amyloid-A (SAA) (defined as ≤ 10 mg/L). The primary endpoint and the 3 secondary endpoints were assessed in a hierarchical testing strategy designed to protect the family-wise type 1 error rate at α=2.5% (one-sided tests). If the primary objective of the study was met, the

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<sup>3</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

<sup>4</sup> Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

superiority of canakinumab 150 mg q4w over placebo in each secondary endpoint was then assessed in the closed testing procedure.

The trial was designed and powered to demonstrate that canakinumab treatment at a dose of 150 mg (or 2 mg/kg in patient weighing  $\leq 40$  kg) administered subcutaneously every 4 weeks was superior to placebo in achieving reduction of disease activity defined as resolution of the index flare on Day 15 and no new disease flares over 16 weeks of treatment.

The study population consisted of male and female patients with confirmed HIDS who were at least 2 years of age at the time of the screening visit. Patients who experienced persistent “mild”, “moderate” or “severe” disease activity (i.e., PGA  $\geq 2$ ) or CRP persistent  $> 10$  mg/L with less than 40% reduction from baseline from Day 8 to Day 14 received an additional dose of 150 mg (or 2 mg/kg for patients 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 also received an additional dose of 150 mg (or 2 mg/kg for patients less than or equal to 40 kg). If the patient’s condition did not improve after administration of the single add-on canakinumab injection, rescue medication was used until Day 29.

**Table 8-3 Comparison between treatment groups for patients who responded at Week 16 by cohort (Full analysis set)**

| Cohort | ACZ885 150mg q4w |                | Placebo        |                  | Risk difference<br>(95% CI) | Odds Ratio<br>(95% CI)  | One-sided<br>p-value |
|--------|------------------|----------------|----------------|------------------|-----------------------------|-------------------------|----------------------|
|        | n/M (%)          | 95% CI         | n/M (%)        | 95% CI           |                             |                         |                      |
| crFMF  | 19/31<br>(61.29) | (42.19, 78.15) | 2/32<br>(6.25) | (0.77,<br>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,<br>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,<br>27.00) | 0.37<br>(0.08, 0.61)        | 9.17<br>(1.51, 94.61)   | 0.0050*              |

n=number of patients who responded; M=number of patients evaluated for response; CI=confidence Interval.

\* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.

\* Source: Table 8-3 from Sponsor’s Meeting Brochure 03Dec2015

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

The submitted data demonstrated clinical evidence of a substantial improvement over placebo.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

Overall, the clinical development program was conducted in a manner consistent with the Agency’s advice and was adequately conducted.

- *Safety data: Provide a brief explanation of the drug’s safety profile, elaborating if it affects the Division’s recommendation.*

In general, canakinumab was well-tolerated and adverse reactions consistent with what is currently contained in the package insert. No new safety signals have been identified.

**11. Division's recommendation and rationale (pre-MPC review):**

☒ GRANT :

Provide brief summary of rationale for granting:

The Division recommends that the breakthrough therapy designation request is granted. The Division's considerations include: (1) HIDS is a serious condition with unmet need and (2) the preliminary clinical evidence indicates a substantial improvement with canakinumab over available therapies/standard of care for HIDS.

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

☐ DENY:

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

**12. Division's next steps and sponsor's plan for future development:**

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor has completed the core Epoch of their phase 3 program and is preparing to submit a sBLA in 2016. Further, based on the information to date, it is likely that the planned sBLA will also meet the criteria for a priority review.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

**13. List references, if any:** The sponsor's background document supporting the BTDR.

**14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES ☒ NO ☐

**15. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation ☐  
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}  
Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

**Revised 1/15/16/M. Raggio**

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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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KEITH M HULL

04/19/2016

NIKOLAY P NIKOLOV

04/19/2016

I concur. This BTDR was reviewed by Medical Policy Concil who agreed with DPARP's recommendation for granting the request.

BADRUL A CHOWDHURY

04/19/2016

# CDER Breakthrough Therapy Designation Determination Review Template

|                                                                                  |                                                                     |
|----------------------------------------------------------------------------------|---------------------------------------------------------------------|
| <b>IND #</b>                                                                     | 100040                                                              |
| <b>Request Receipt Date</b>                                                      | February 26, 2016                                                   |
| <b>Product</b>                                                                   | Canakinumab (ILARIS)                                                |
| <b>Indication</b>                                                                | Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) |
| <b>Drug Class/Mechanism of Action</b>                                            | Human monoclonal antibody targeted at interleukin-1 beta            |
| <b>Sponsor</b>                                                                   | Novartis                                                            |
| <b>ODE/Division</b>                                                              | ODE II/Division of Pulmonary, Allergy, and Rheumatology Products    |
| <b>Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)</b> | April 26, 2016                                                      |

*Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.*

## **Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.**

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)

- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

☐ YES ☒ NO

*If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:*

- Consideration of Breakthrough Therapy Criteria:**

- Is the condition serious/life-threatening<sup>1</sup>?

☒ YES ☐ NO

*If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:*

- Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review

☐ Undetermined

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐

ii. Insufficient clinical data provided to evaluate the BTDR

<sup>1</sup> For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy<sup>2</sup>/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

**4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:**

*If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.*

*If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.*

**5. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

- *Information regarding the disease and intended population for the proposed indication.  
Disease mechanism (if known) and natural history (if the disease is uncommon).*

Canakinumab (ILARIS) is a human monoclonal IgG1 antibody with high-affinity against IL-1 $\beta$  and acts by binding and neutralizing endogenous IL-1 $\beta$  thereby blocking its effect. Canakinumab was originally approved by the Agency in 2009 for the treatment of cryopyrin-associated syndromes (CAPS), a related group of three autoinflammatory syndromes comprised of familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS), and neonatal-onset multisystem inflammatory syndrome (NOMID). A supplemental BLA was approved in May 2013 extending the claims of canakinumab to treat children with systemic juvenile idiopathic arthritis (SJIA).

The TNF receptor-associated periodic syndrome (TRAPS) is a rare autosomal dominant disorder resulting from mutations in *TNFRSF1A*, the gene that encodes the 55-kDa receptor for TNF

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<sup>2</sup> For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

(TNFRSF1A; also referred to as p55, TNF1, and CD120a). Over 23 mutations have been reported. All of the mutations reported represent missense mutations except for a single splicing mutation, and occur in exons 2-4 and intron 3, respectively. All but the F112I mutation result in changes that affect the first 2 cysteine rich domains (CRD) of the extracellular portion of the receptor. Five of the original mutations were missense changes at cysteine residues: 12 of the 23 currently known mutations are cysteine substitutions. Patients often present with relatively lengthy episodes (>1 week) of fever with abdominal pain, pleurisy, skin rash, myalgia, ocular inflammation, and/or arthritis.

Two *TNFRSF1A* mutations, R92Q and P46L, have been found to occur in greater than 1% of chromosomes among Caucasians and African Americans, respectively. Although this figure clearly overestimates the number of individuals with typical clinical findings of TRAPS in these populations, it is likely to reflect a combination of underdiagnosis and reduced penetrance that in some cases, particularly for the R92Q variant, may manifest as broad spectrum of nondescript inflammatory disorders. Moreover, *TNFRSF1A* mutations may contribute to more complex genetic diseases such as rheumatoid arthritis.

As recognition of TRAPS has grown, both the ethnic distribution and the clinical spectrum of the disease have expanded. Although TRAPS was first described in a large family of Irish ancestry (thus suggesting the term familial Hibernian fever), cases have now been reported among African American, Arab, Ashkenazi and Sephardic Jewish, Belgian, Czech, Dutch, French, Kabyle, German, Italian, Mexican, Polish, Portuguese, and Sardinian/Sicilian patients. While the duration of TRAPS attacks tends to be longer than the other hereditary periodic fevers, genetic testing has confirmed the diagnosis in patients with attacks as short as one day. A recent report strongly suggests that the unique characteristic of the centrifugally migrating myalgia and associated erythematous rash is due to a monocytic fasciitis and not myositis as previously thought. Furthermore, we have found that cysteine mutations tend to confer a higher rate of life-threatening amyloidosis, although occasional cases of amyloidosis have been reported among patients with other mutations.

In the original description of TRAPS, it was shown that patients with mutations in *TNFRSF1A* exhibit lower serum levels of soluble TNFRSF1A as compared with normal controls. It was hypothesized that the mutations in *TNFRSF1A* mediated their effect via decreased shedding of TNFRSF1A, thereby decreasing the amount of soluble receptor available to bind soluble TNF and subsequently quell the inflammatory response. This hypothesis was tested using PMNs and monocytes from patients with the C52F mutation. Experiments demonstrated increased levels of cell surface TNFRSF1A, and decreased PMA-induced shedding of TNFRSF1A, compared with normal controls and patients with rheumatoid arthritis or systemic lupus erythematosus. Simultaneous evaluation of shedding for the 75-kDa TNF receptor, TNFRSF1B, was found to be normal. These data demonstrated a specific defect in TNFRSF1A shedding in patients with the C52F *TNFRSF1A* mutation. Since the initial report, receptor-shedding defects have been identified for H22Y, C30S, C33G, P46L, T50M, and C52F, but not R92Q or the splice mutation, suggesting that defective receptor shedding does not account for the entire pathophysiologic mechanism observed. Some studies have been directed at investigating that some TRAPS mutations in CRD1 may affect homotypic preligand assembly of TNFRSF1A molecules on the cell surface, or that CRD2/3 mutations may affect ligand binding.

## **7. Information related to endpoints used in the available clinical data:**

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary objective of the randomized, placebo-controlled, treatment period was to demonstrate that canakinumab 150 mg (or 2 mg/kg in patient weighing ≤40 kg) sc 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. Specifically, the primary efficacy

endpoint was defined as the proportion of responders within each randomized group. A responder was defined as a patient who had resolution of his/her index disease flare at Day 15 and did not experience a new flare during the 16 weeks from the time of the resolution of the index flare following randomization. Resolution of the index flare was defined at the Day 15 visit as Physician Global Assessment of Disease Activity (PGA) <2 and C-reactive Protein (CRP) within normal range ( $\leq 10$  mg/L) or reduction of  $\geq 70\%$  from baseline. New flare was defined from the time of the resolution of the index flare as PGA  $\geq 2$ , and CRP  $\geq 30$  mg/L. Subjects 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.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
  - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
  - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

While there has not been a regulatory precedent for drug development or approval for TRAPS, the Division considers the proposed primary endpoint sufficient to capture a clinically meaningful benefit of the drug and therefore supporting a traditional approval.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

**8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no approved therapies for TRAPS. Currently there is no consistently effective treatment for TRAPS and treatment is aimed at palliation of symptoms. While the use of TNF-inhibitors have been described in the literature, no formal studies have demonstrated a consistent benefit and TNF inhibitors are not standard of care.

**9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>3</sup>.**

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<sup>3</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

None.

## 10. Information related to the preliminary clinical evidence:

Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design<sup>4</sup>, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Study N2301 is a four part study consisting of

- Part 1: Screening phase (completed)
- Part 2: 16 week, double-blind, placebo-controlled phase (completed)
- Part 3: Randomized withdrawal phase (ongoing)
- Part 4: long-term treatment phase (ongoing)

The primary efficacy endpoint of the randomized treatment period (Part 2), and for the overall study, was the proportion of responders within each cohort. A responder was defined as a patient who had resolution of his/her index disease flare (i.e.,

physician global assessment (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 the 16 week treatment period. For the primary analysis, patients who required dose escalation in the canakinumab arms, who crossed over from placebo to canakinumab, or patients who discontinued from the study for any reason prior to evaluating the primary endpoint were considered non-responders.

Major secondary endpoints for Part 2 of the study included the percentage of patients who achieved a PGA < 2 (“minimal” disease activity); the percentage of patients with serologic remission (defined as CRP  $\leq 10$  mg/L); and the percentage of patients with normalized serum amyloid-A (SAA) (defined as  $\leq 10$  mg/L). The primary endpoint and the 3 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.

The trial was designed and powered to demonstrate that canakinumab treatment at a dose of 150 mg (or 2 mg/kg in patient weighing  $\leq 40$  kg) administered subcutaneously every 4 weeks was superior to placebo in achieving reduction of disease activity defined as resolution of the index flare on Day 15 and no new disease flares over 16 weeks of treatment.

The study population consisted of male and female patients with confirmed TRAPS who were at least 2 years of age at the time of the screening visit. Patients who experienced persistent “mild”, “moderate” or “severe” disease activity (i.e., PGA  $\geq 2$ ) or CRP persistent  $> 10$  mg/L with less than 40% reduction from baseline from Day 8 to Day 14 received an additional dose of 150 mg (or 2 mg/kg for patients 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 also received an additional dose of 150 mg (or 2 mg/kg for patients less than or equal to 40 kg). If the patient’s condition did not improve after administration of the single add-on canakinumab injection, rescue medication was used until Day 29.

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<sup>4</sup> Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

**Table 8-3 Comparison between treatment groups for patients who responded at Week 16 by cohort (Full analysis set)**

| Cohort | ACZ885 150mg q4w |                | Placebo        |                  | Risk difference<br>(95% CI) | Odds Ratio<br>(95% CI)  | One-sided<br>p-value |
|--------|------------------|----------------|----------------|------------------|-----------------------------|-------------------------|----------------------|
|        | n/M (%)          | 95% CI         | n/M (%)        | 95% CI           |                             |                         |                      |
| crFMF  | 19/31<br>(61.29) | (42.19, 78.15) | 2/32<br>(6.25) | (0.77,<br>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,<br>19.16) | 0.29<br>(0.06, 0.50)        | 8.94<br>(1.72, 96.41)   | 0.0020*              |
| TRAPS  | 10/22<br>(45.45) | (24.39, 67.79) | 2/24<br>(8.33) | (1.03,<br>27.00) | 0.37<br>(0.08, 0.61)        | 9.17<br>(1.51, 94.61)   | 0.0050*              |

n=number of patients who responded; M=number of patients evaluated for response; CI=confidence interval.

\* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.

\* Source: Table 8-3 from Sponsor's Meeting Brochure 03Dec2015

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

The submitted data demonstrated clinical evidence of a substantial improvement over placebo.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

Overall, the clinical development program was conducted in a manner consistent with the Agency's advice and was adequately conducted.

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

In general, canakinumab was well-tolerated and adverse reactions consistent with what is currently contained in the package insert. No new safety signals have been identified.

#### 11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

The Division recommends that the breakthrough therapy designation request is granted. The Division's considerations include: (1) TRAPS is a serious condition with unmet need and (2) the preliminary clinical evidence indicates a substantial improvement with canakinumab over available therapies/standard of care for TRAPS.

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

☐ DENY:

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

**12. Division's next steps and sponsor's plan for future development:**

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor has completed the core Epoch of their phase 3 program and is preparing to submit a sBLA in 2016. Further, based on the information to date, it is likely that the planned sBLA will also meet the criteria for a priority review.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

**13. List references, if any:**

**14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES ☒ NO ☐

**15. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation ☐  
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}  
Team Leader Signature: {See appended electronic signature page}  
Division Director Signature: {See appended electronic signature page}

**Revised 1/15/16/M. Raggio**

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/s/  
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KEITH M HULL

04/19/2016

NIKOLAY P NIKOLOV

04/19/2016

I concur. This BTDR was reviewed by Medical Policy Concil who agreed with DPARP's recommendation for granting the request.

BADRUL A CHOWDHURY

04/19/2016



BLA 125319/S-85, 86, 87

**ACKNOWLEDGMENT --  
PRIOR APPROVAL SUPPLEMENT**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

Attention: Jennifer Evans, PharmD  
Global Program Regulatory Director, Drug Regulatory Affairs

Dear Dr. Evans:

We have received your Supplemental Biologics License Applications (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

|                            |                                                                                                       |
|----------------------------|-------------------------------------------------------------------------------------------------------|
| <b>BLA NUMBER:</b>         | 125319                                                                                                |
| <b>SUPPLEMENT NUMBERS:</b> | 085, 086, 087                                                                                         |
| <b>PRODUCT NAME:</b>       | Ilaris (canakinumab) injection                                                                        |
| <b>DATE OF SUBMISSION:</b> | Supplement 085 – March 23, 2016<br>Supplement 086 – March 28, 2016<br>Supplement 087 – March 29, 2016 |
| <b>DATE OF RECEIPT:</b>    | Supplement 085 – March 23, 2016<br>Supplement 086 – March 28, 2016<br>Supplement 087 – March 29, 2016 |

These supplemental applications propose the following change(s) for Ilaris injection: the addition of indications for Tumor Necrosis Factor Receptor Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome / Mevalonate Kinase Deficiency (HIDS/MKD), and Familial Mediterranean Fever (FMF).

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on May 22, 2016 (Supplement 085), May 27, 2016 (Supplement 086), and May 29, 2016 (Supplement 087), in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

### **FDAAA TITLE VIII RESPONSIBILITIES**

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

### **SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me, at (301) 796-4495.

Sincerely,

*{See appended electronic signature page}*

Brandi Wheeler, PharmD  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BRANDI E WHEELER  
04/08/2016



IND 100040

**MEETING REQUEST-  
WRITTEN RESPONSES**

Novartis  
One Health Plaza  
East Hanover, NJ 07936

Attention: Jennifer Evans, PharmD  
Global Program Regulatory Director

Dear Dr. Evans:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACZ885.

We also refer to your submission dated December 3, 2015, containing a Type C meeting request. The purpose of the requested meeting was to discuss the data resulting from your phase 3 pivotal study.

Further reference is made to our Meeting Granted letter dated December 24, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your January 7, 2016 background package.

If you have any questions, call me at (240) 402-2605.

Sincerely,

*{See appended electronic signature page}*

LeAnn Brodhead, PharmD, MPH  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Written Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## WRITTEN RESPONSES

**Meeting Type:** Type C  
**Meeting Category:** IND

**Application Number:** 100040  
**Product Name:** Canakinumab (ACZ885)  
**(Proposed) Indications:** TRAPS, HIDS, and crFMF  
**Applicant Name:** Novartis  
**Regulatory Pathway:** §351 of the Public Health Service Act

### 1.0 BACKGROUND

Ilaris (canakinumab) was originally approved (BLA 125319) on June 17, 2009, for the treatment of CAPS in pediatrics and adults. On May 9, 2013, Ilaris was approved for the treatment of SJIA in patients aged 2 years and older.

A Pre-sBLA meeting was held with the Division of Pulmonary, Allergy, and Rheumatology (DPARP) on June 2, 2015 to discuss Novartis' plan to submit efficacy supplements adding the indications of Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyper Immunoglobulin D Syndrome (HIDS), and colchicine resistant Familial Mediterranean Fever (crFMF) in patients 2 years and older. On December 3, 2015, Novartis requested a meeting with the division to discuss the results of the primary efficacy analysis of pivotal Study CACZ885N2301 and to address the following outstanding concerns related to: including only Epoch 2 data from the primary analysis, evaluation of the broader Familial Mediterranean Fever population, as well as proposed recommended dosing in Periodic Fever Syndromes from the June 2, 2015 discussion.

Novartis submitted a briefing package containing questions to be discussed at this meeting on January 7, 2016. Novartis questions from the briefing package are provided below in *italics* followed by FDA responses in normal font.

### 2.0 QUESTIONS AND RESPONSES

#### **Question 1:**

*The 16-Week data resulting from the double-blind, placebo-controlled part of Study CACZ885N2301 (Epoch 2) are available which demonstrate statistically significant effects for canakinumab vs. placebo in the treatment of patients with crFMF, HIDS/MKD and TRAPS. Given the demonstrated efficacy at the Week 16 primary endpoint in Epoch 2, Novartis is planning to submit a supplemental BLA for each of these three new indications in March 2016. Does the Agency concur?*

**FDA Response:**

The decision to only submit Epoch 2 data to support the proposed sBLAs would be at your discretion. The adequacy of these data will be a review issue. In addition to the issues discussed in previous communications, in your application address the adequacy of the primary endpoint to assess for clinically-meaningful benefit in the intended population, the impact of the cross-over of placebo-treated patients at early timepoints on the interpretation of efficacy, and provide a rationale that the observed short-term benefit could support chronic administration of canakinumab.

For adverse events of special interest, we request that you carry out descriptive (i.e., no hypothesis testing or margin selection) analyses that compare treatment groups with respect to risk (e.g., with a risk difference, relative risk, or rate ratio, along with a confidence interval for the metric used for comparison). Given the substantial proportion of placebo patients who crossed over to canakinumab at Day 15, analyses comparing risk through Week 16 should take into account the follow-up time per patient (e.g., by comparing exposure-adjusted incidence rates or Kaplan-Meier estimates of cumulative incidence proportions).

**Question 2:**

*Novartis is analyzing the data in the FMF population actually enrolled in study CACZ885N2301 in order to characterize the concomitant use of colchicine in these patients. Novartis intends to seek an indication for FMF patients who are inadequate responders or intolerant to effective therapeutic doses of colchicine based on these data. Does the Agency have any comments on this proposal?*

**FDA Response:**

We have no comments on this proposal at this time. The proposed indication will be a review issue.

**Question 3:**

*The results of Study CACZ885N2301 have shown that approximately 16% to 36% of patients (depending on disease cohort) were up-titrated from the canakinumab starting dose of 150mg to 300 mg every 4 weeks.* <sup>(b) (4)</sup>

*Does the Agency have any comments or recommendations on this proposal?*

**FDA Response:**

We have no comments on this proposal at this time. The adequacy of the data to support <sup>(b) (4)</sup> will be a review issue.

### **3.0 OTHER IMPORTANT INFORMATION**

#### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for these indications has an orphan drug designation, you are exempt from these requirements.

#### **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## **Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

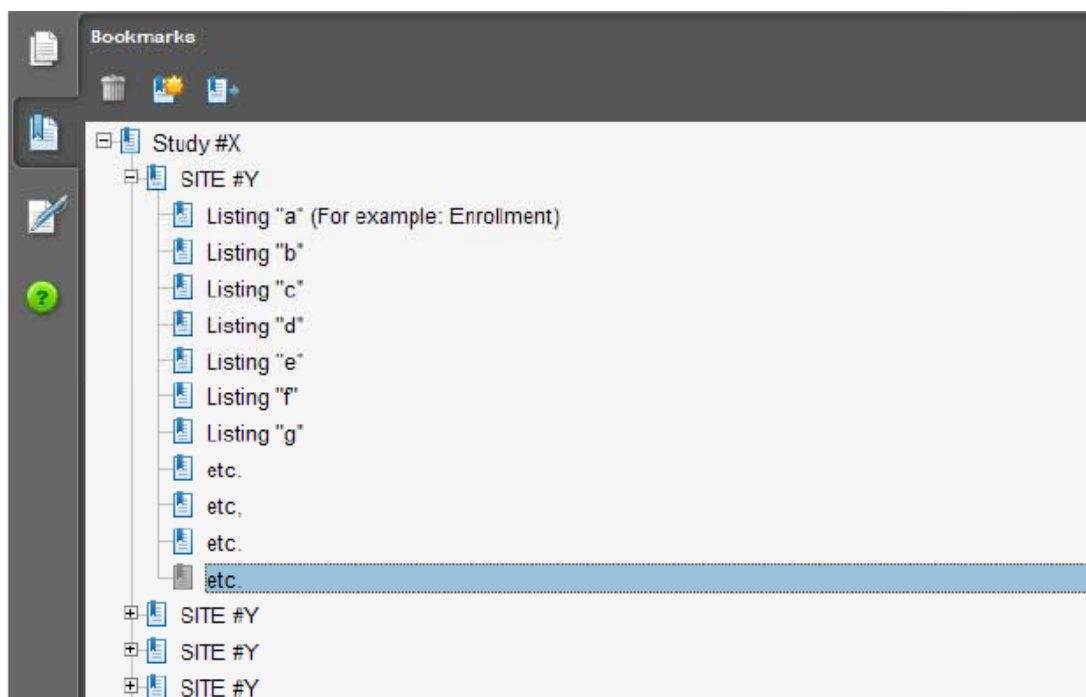
### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is

- the actual physical site(s) where documents are maintained and would be available for inspection
- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
  5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
  - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

**Attachment 1**  
**Technical Instructions:**  
**Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

| <b>DSI Pre-NDA Request Item<sup>1</sup></b> | <b>STF File Tag</b>          | <b>Used For</b>                                     | <b>Allowable File Formats</b> |
|---------------------------------------------|------------------------------|-----------------------------------------------------|-------------------------------|
| I                                           | data-listing-dataset         | Data listings, by study                             | .pdf                          |
| I                                           | annotated-crf                | Sample annotated case report form, by study         | .pdf                          |
| II                                          | data-listing-dataset         | Data listings, by study<br>(Line listings, by site) | .pdf                          |
| III                                         | data-listing-dataset         | Site-level datasets, across studies                 | .xpt                          |
| III                                         | data-listing-data-definition | Define file                                         | .pdf                          |

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

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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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LEANN D BRODHEAD  
02/12/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 100040

**MEETING MINUTES**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

Attention: Donna Vivelo  
Director, Drug Regulatory Affairs

Dear Ms. Vivelo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for canakinumab.

We also refer to the telecon between representatives of your firm and the FDA on June 2, 2015. The purpose of the meeting was to discuss adding the indications of TRAPS, HIDS, and FMF in patients 2 years and older.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4786.

Sincerely,

*{See appended electronic signature page}*

Michelle Jordan Garner, MS, OTR/L  
Senior Regulatory Management Consultant  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** pre-sBLA

**Meeting Date and Time:** June 2, 2015; 9:00 A.M. – 10:00 A.M.  
**Meeting Location:** Teleconference

**Application Number:** IND 100040  
**Product Name:** Ilaris (canakinumab)  
**(Proposed) Indications:** TRAPS, HIDS, and crFMF  
**Sponsor/Applicant Name:** Novartis

**Meeting Chair:** Badrul A. Chowdhury, MD, PhD  
**Meeting Recorder:** Michelle Jordan Garner, MS, OTR/L

**FDA ATTENDEES**

Division of Pulmonary, Allergy, and Rheumatology Products

Badrul A. Chowdhury, MD, PhD, Division Director  
Sarah Yim, MD, Supervisory Associate Director  
Nikolay Nikolov, MD, Clinical Team Leader  
Keith Hull, MD, PhD, Clinical Reviewer  
Michelle Jordan Garner, MS, OTR/L, Senior Regulatory Management Officer

Office of Biotechnology Products

Chikako Torigoe, PhD, Product Quality Reviewer  
Rashmi Rawat, PhD, Product Quality Team Leader

Division of Biometrics II

Yongman Kim, PhD, Biometrics Reviewer  
David Petullo, PhD, Biometrics Team Leader

**SPONSOR ATTENDEES**

Guido Junge, MD (Global Program Head)  
Antonio Speziale, MD (Global Program Medical Director)  
Kathleen Lomax, MD (Lead Medical Director, US Medical)  
Karine Lheritier, PhD (Lead Program Statistician)  
Peter Mesenbrink, PhD (Executive Director, Statistical Scientist)  
Haiying Sun, PhD (Director, Pharmacokinetics/Pharmacodynamics)  
Hans-Joachim Wallny, PhD (Global Program Technical Director)  
Susan Batcha (Regulatory CMC Associate Director)  
Ian Carbarns, MD (Senior Brand Safety Leader)

Yolandi Joubert, MSc (Clinical Scientific Associate Director)  
Rachael Steiner-Swiat, MSc, MBA (Global TA Lead, Drug Regulatory Affairs)  
Donna Vivello, MSc (Global Program Regulatory Director)

## 1.0 BACKGROUND

Ilaris (canakinumab) was originally approved (BLA 125319) on June 17, 2009, for the treatment of CAPS in pediatrics and adults. On May 9, 2013, Ilaris was approved for the treatment of SJIA in patients aged 2 years and older.

On May 13, 2013, a pre-Phase 3 teleconference between Novartis and FDA occurred, to discuss the support needed for the indication of (b) (4)

Subsequently, in response to a request for feedback on new proposed revisions to the clinical development program, on February 10, 2014 FDA provided advice to Novartis regarding dosing regimen selection, defining disease-specific flares, and broadening the FMF population. The Agency also re-iterated its expectation for the assessment of efficacy data from both the placebo-controlled and the randomized withdrawal periods of the study.

The purpose of this telecon, was to discuss Novartis' plan to submit efficacy supplements adding the indications of Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyper Immunoglobulin D Syndrome (HIDS), and colchicine resistant Familial Mediterranean Fever (crFMF) in patients 2 years and older. Novartis is also proposing to submit a supplement for the addition of a new formulation, a solution for injection in a vial, to the already marketed lyophilized powder.

Following receipt of FDA's preliminary comments, Novartis acknowledged the preliminary comments received for Questions 2 -10, and that no additional discussion on those topics was required. The focus of discussion centered around Novartis' request for clarification on FDA's responses to Questions 1 and 3.

## 2.0 DISCUSSION

### Question 1:

*The 150 mg/ 1.0 mL solution for injection in vial presentation has been used in the CACZ885N2301 clinical study. A full comparability package, along with a complete Module 3 for registration, will be submitted to support the approval of the 150 mg/mL solution for injection in vial presentation. This sBLA will be submitted* (b) (4)

*Does the Division agree with Novartis' plan to (b) (4) as well as the new solution for injection in vial market formulation?*

Response:

You propose to submit (b) (4)

You may submit all the relevant information in one of the efficacy supplements and cross-reference this information in the other supplements.

Your proposal to submit a separate supplement for the new formulation is acceptable. Analytical comparability data to support the new solution for injection formulation should include the comparison of release, characterization and stability data between lyophilized powder and liquid in vial presentations. Any statistical approach used to establish acceptance criteria for comparability should be justified in the submission. The comparability assessment of the stability should include the comparison of the rates and pathways of degradation between the liquid and lyophilized presentations under accelerated and stress storage conditions.

Discussion:

**Novartis acknowledged FDA's expectations regarding the CMC data to be included in the sBLA for the new 150 mg/mL liquid in vial formulation. The data package will include analytical release, biological potency assay and extended characterization results comparing three 150 mg/mL liquid in vial to three batches of the currently marketed 150 mg/mL lyophilized powder. As there is a large historical database of the lyophilized formulation, the (b) (4) specifications of the lyophilized formulation are used for comparability acceptance criteria. Chromatograms and gels will be provided for relevant release and stability assays. Stability data for the 150 mg/mL liquid formulation will include data at recommended storage conditions, and at accelerated and stressed storage conditions.**

Novartis clarified that (b) (4)

(b) (4)

Question 2:

Novartis is (b) (4)

Response:

We recommend that (b) (4)

Discussion:

None.

Question 3:

*Does the Agency agree that the efficacy and safety results from the 16-week Epoch 2 part of Study CACZ885N2301 for each disease cohort to support the additional indications of TRAPS, HIDS and crFMF is adequate for filing?*

Response:

We do not agree with your proposal to only submit efficacy data from the 16-week Epoch 2 part of Study CACZ885N2301 to support the additional indications of TRAPS, HIDS and crFMF. The Division's expectation is that, to demonstrate substantial evidence of efficacy within the context of a single clinical study, data from both the randomized placebo-controlled period (Epoch 2) and the randomized withdrawal period (Epoch 3) will be needed to support the submission of your application. Refer to the end-of-phase 2 meeting minutes, dated October 11, 2013, and the additional FDA advice dated February 10, 2014. Further, we have significant concerns with the integrity of the randomized placebo-controlled period due to the protocol provisions to allowing patients to escape and receive open-label active therapy after Day 29 during the Epoch 2. Given the small sample size of each cohort, this may have significant impact on the interpretability of the placebo-controlled data.

Familial Mediterranean Fever (FMF) population: (b) (4)

(b) (4) if effective, canakinumab is expected to work for the broader FMF population and limiting the indication for colchicine resistant FMF is not justified. Further, it may be difficult to adequately describe colchicine resistant FMF to inform labeling. Therefore, prior to submitting a supplemental BLA for that indication, we strongly recommend that you also study the broader population of FMF patients, as advised in the FDA comments dated February 10, 2014.

Discussion:

**FMF population**

FDA inquired about what the intended FMF patient population would entail. Novartis stated that they would determine the patient population based on the enrollment characteristics of the patients, i.e. patients who have failed colchicine treatment, patients with active disease despite therapy with a maximum colchicine dose, or patients who are colchicine intolerant. FDA asked what language Novartis would propose to describe (b) (4) 'intolerant' in the product labeling. Novartis responded that currently they have not established a clinical definition, but the final proposed labeling language would be based on an analysis of the patients enrolled in the study.

FDA reiterated their position that, as canakinumab would be expected to also work in the broader FMF population, it is not justified to limit the population to only those FMF patients who are deemed 'colchicine resistant'. Novartis acknowledged that FDA suggested additional efforts to assess the broader FMF population; (b) (4)

(b) (4)  
Novartis asked for clarification on identifying an acceptable target study population. FDA stated that a response is expected to be observed in any patient diagnosed with FMF; therefore, all FMF patients, as opposed to a subset population, should be studied.

**Amount of clinical data needed to support filing of the BLA(s): Epoch Data**

Novartis proposed a submission based on Epoch 2 data, expecting that these data will be highly robust and sufficient to support the approval of the new indications, and asked if the results, once obtained, would be enough to support filing of a sBLA. FDA stated that no information regarding efficacy or safety from this study has been provided; therefore it would be premature for FDA to agree that the data would be sufficient to support filing of a sBLA. Novartis inquired whether FDA would agree to another meeting to discuss the results of Epoch 2 once available later this year. FDA stated that they would not agree to another meeting to discuss the Epoch 2 results at this time (b) (4)

(b) (4)  
FDA reiterated its expectation that the original BLA(s) would be supported by the clinical efficacy data from Epoch 2 and the final results from Epoch 3 and that any potential disagreement between the efficacy of Epoch 2 and Epoch 3 would be addressed during the review of the original application(s). FDA further stated that the decision to only submit Epoch 2 data would be at Novartis' discretion and risk.

**Integrity of Randomized Placebo to active (unblinding/blinding)**

Novartis requested further clarification of FDA's comment regarding: 'significant concerns with the integrity of the randomized placebo-controlled period due to the protocol provisions allowing patients to escape to open-label active therapy after Day 29'. FDA

**explained that assessment of secondary endpoints in the trial past Day 29 could be impacted by unblinding study subjects or investigators which would raise questions about the reliability of the data. FDA further asked why the blind was not maintained with the escape all the way through Week 16. Novartis clarified that the first up-titration is fully blinded and that there is no unblinding of the assigned treatment at randomization after Day 29. However, after a second up-titration or patients reached the maximum allowed dose of 300 mg every 4 weeks, patients would receive open-label treatment still blinded to the originally randomized treatment. A second blinded up-titration would have required a third injection to all patients of either active or placebo treatment. Novartis understood from previous discussions with FDA that the maximal allowed dose should be restricted to 300 mg every 4 weeks (as studied in SJIA patients). With this dose limitation, a blinded second up-titration is not feasible. FDA stated that Novartis will need to address the limitations of these protocol provisions in the submission, especially as they relate to safety and efficacy. FDA further suggested that, in the application, Novartis should clearly present the efficacy and safety data, taking into account the different pre-defined dose escalation scenarios within study N2301.**

Question 4:

*Does the Agency agree with the proposed submission components for the 120-day safety update?*

Response:

Your proposal is reasonable. We remind you that your application should be complete on submission, meaning that all efficacy and safety data that you consider necessary for approval should be included with the initial submission.

**Discussion:**

**None.**

Question 5:

*Does the Agency agree with the proposed statistical analysis plan for study CACZ885N2301 which will provide the basis for the Clinical Study Report and the main data in the Summary of Clinical Efficacy (SCE; CTD section 2.7.3) and Summary of Clinical Safety (SCS CTD section 2.7.4)?*

Response:

Yes, we agree. However, also refer to the FDA Response to Question 3 for the data needed to support the submission of the efficacy supplement(s).

**Discussion:**

**None.**

Question 6:

*Does the Agency agree with the proposed content and data presentation for the Summary of Clinical Efficacy (SCE; CTD section 2.7.3) and Summary of Clinical Safety (SCS; CTD section 2.7.4)?*

Response:

Your proposal is reasonable.

**Discussion:**

None.

Question 7:

*Does the Agency agree with the proposal for submission of patient narratives and CRFs from study CACZ885N2301 and the phase 2 studies?*

Response:

Your proposal is reasonable.

**Discussion:**

None.

Question 8:

*Does the Agency agree with the proposal to submit SDTM and ADaM data sets for the CACZ885N2301 study and ADaM datasets for the SCS as outlined below?*

- a. *The SDTM data sets will include the trial design model data sets for the phase III CACZ885N2301 study. Is this acceptable to the Agency?*
- b. *Novartis proposes to submit ADaM data sets only in support of the Summary of Clinical Safety for (b) (4) SDTM data sets will not be submitted for the Summary of Clinical Safety. Is this acceptable to the Agency?*
- c. *Novartis proposes to submit only CAPS ADaM datasets included in the safety pooled data sets in the content of CRTs and not to resubmit any individual datasets in the legacy format, is this acceptable to the Agency?*
- d. *Novartis proposes to follow Version 3.1.2 of the SDTM Implementation Guide for all areas except for the Trial Design Model which will use Version 3.1.3 along with Version 1.2 of the SDTM Model. Is this acceptable to the Agency?*

- e. *Novartis proposes to follow Version 1.0 of the Analysis Data Model (ADaM) implementation guide in conjunction with Version 2.1 of the Analysis Data Model. Is this acceptable to the Agency?*
- f. *Novartis proposes to include SAS programs and the supporting documentation to allow all for the confirmation of all primary and secondary efficacy variables from Study CACZ885N2301 submitted as part of the sBLA. Is this acceptable to the Agency?*
- g. *Define.xml Version 1.0 will be used to compile the CRT-DDS. Is this acceptable to the Agency?*

**Response:**

Yes, these are acceptable.

**Discussion:**

**None.**

**Question 9:**

*Does the Agency agree*

(b) (4)

(b) (4)

**Response:**

No, we do not agree.

(b) (4)

the summary portion of the ISE and ISS, respectively, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in section 5.3.5.3. In this case, an explanation should be placed in both Module 2 and Module 5.

**Discussion:**

**None.**

**Question 10:**

*Does the Agency have any comments on Novartis' justification for Priority Review status for canakinumab in the treatment of TRAPS, HIDS and crFMF?*

**Response:**

We have no comments on your justification for Priority Review status. Whether the application meets the criteria for a Priority Review will be determined after the application(s) are submitted.

**Discussion:**

**None.**

**3.0 OTHER IMPORTANT INFORMATION**

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

**PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and PLLR Requirements for Prescribing Information websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **Office of Scientific Investigations (OSI) Requests**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

#### **I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

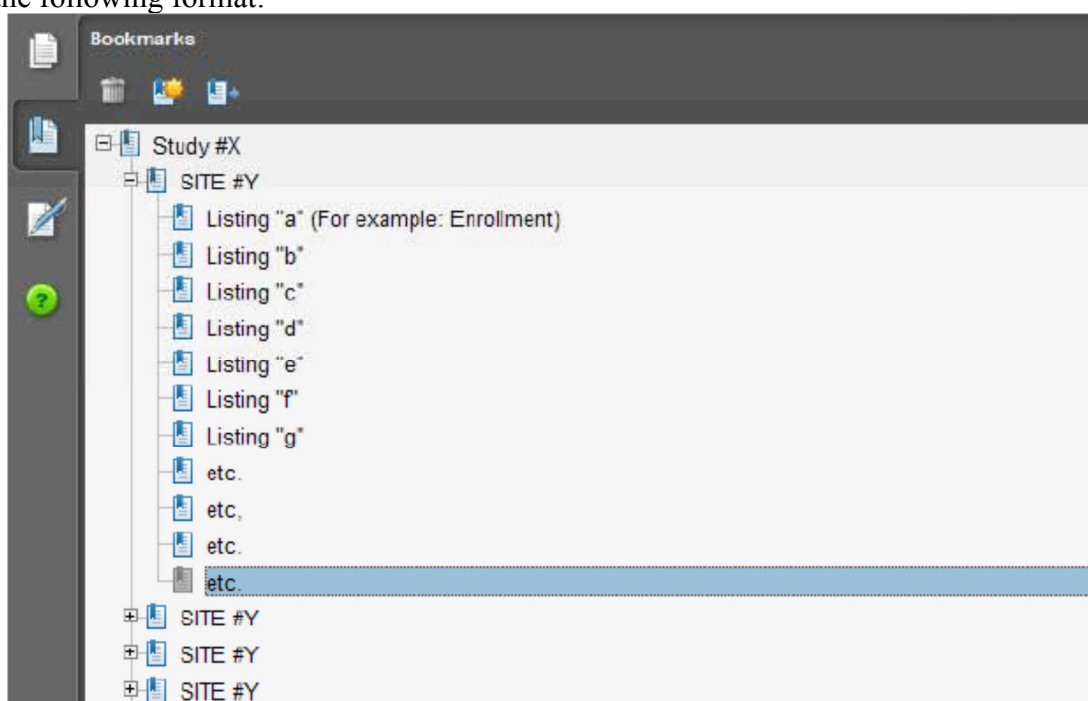
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

- d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
  - a. Number of subjects screened at each site
  - b. Number of subjects randomized at each site
  - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
  - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
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  - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

## **II. Request for Subject Level Data Listings by Site**

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
  - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
  - b. Subject listing for treatment assignment (randomization)
  - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

- d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
  - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - f. By subject listing, of AEs, SAEs, deaths and dates
  - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
  - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



### III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues requiring further discussion.

#### **5.0 ACTION ITEMS**

No action items.

#### **6.0 ATTACHMENTS AND HANDOUTS**

No attachments and handouts.

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/s/  
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MICHELLE Y JORDAN GARNER  
07/01/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 100040

**MEETING MINUTES**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936

Attention: Jiten Rana, Pharm. D.  
Global Program Regulatory Manager

Dear Dr. Rana:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Canakinumab.

We also refer to the telecon between representatives of your firm and the FDA on May 13, 2013. The purpose of the meeting was to discuss the support needed for the indication (b) (4) and PREA requirements for the submission of a Pediatric Study Plan (PSP).

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1226.

Sincerely,

*{See appended electronic signature page}*

Carol F. Hill, M.S.  
Senior Regulatory Health Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-Phase 3

**Meeting Date and Time:** May 13, 2013 at 4:00 pm  
**Meeting Location:** Teleconference

**Application Number:** IND 100040  
**Product Name:** Canakinumab  
**Indication:** (b) (4)  
**Sponsor/Applicant Name:** Novartis Pharmaceuticals Corporation

**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Carol F. Hill, M.S.

**FDA Attendees**

Badrul A. Chowdhury, M.D., Ph.D., Director, DPARP, ODE II  
Sarah K. Yim, M.D., Associate Director  
Nikolov Nikolay, M.D., Acting Clinical Team Leader  
Keith M. Hull, M.D., Clinical Reviewer  
Janet W. Maynard, M.D., Clinical Reviewer  
Carol F. Hill, M.S., Senior Regulatory Health Project Manager  
Laurie Graham, Ph.D., Product Quality Team Leader, DMA.OBP  
Chikako Torigoe, Ph.D., Product Quality Reviewer  
Liang Zhao, Ph.D., Clinical Pharmacology Reviewer, DCPII, OCP  
Joan K. Buenconsejo, Ph.D., Statistical Team Leader, DOBII, OB  
Ruthanna C. Davi, Ph.D., Statistical Reviewer

**Novartis Pharmaceuticals Corporation Attendees**

Mike Perry, Global Program Head  
Ken Abrams, Clinical Program Head  
Viktoria Herman, Brand Safety Leader  
Markus John, Global Program Medical Director  
Penny Giles, Global Regulatory Head, IHC  
Lisa Mauch, Regulatory CMC Manager  
Lynn Mellor, Global TA Lead, Drug Regulatory Affairs  
Jiten Rana, Global Program Regulatory Manager  
Peter Mesenbrink, Director, Statistical Science  
Andrej Skerjanec, Director, Pharmacokinetics/Pharmacodynamics  
Andrea Stancati, Clinical Indication Leader

IND 100040

ODE II  
DPARP

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Gretchen Trout, Director, FDA Liaison Officer  
Donna Vivello, Global Program Regulatory Director

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## 1.0 BACKGROUND

Novartis Pharmaceuticals Corporation submitted a Pre-Phase 3 meeting request on March 4, 2013 to discuss the development program for hereditary Periodic Fever conditions. The meeting request was granted and the meeting was scheduled to occur on May 11, 2013. Briefing packages for the meeting were submitted on April 12 and 17, 2013. The FDA preliminary meeting comments were sent to Novartis on May 9, 2013. In response to the FDA comments, Novartis stated that they would like to continue with the meeting as a teleconference and requested to discuss for clarification the FDA comments regarding questions 2 and 6.

## 2. DISCUSSION

### FDA Introductory Comment:

You propose to <sup>(b) (4)</sup>



### Discussion:

The sponsor accepted FDA's response, no discussion occurred.

### Clinical/Regulatory Development

#### *Question 1*

*We note the Agency's efforts under FDASIA to incentivize the Industry's innovation to develop new medicines for patients with rare, serious or life-threatening diseases. The Hereditary Periodic Fever (HPF) conditions described in this briefing document could qualify for such innovative programs. Considering the rare nature of the HPF conditions as well as the unmet medical need,* <sup>(b) (4)</sup>



*What are the Agency's thoughts for utilizing novel programs such as Breakthrough Therapy Designation to streamline development?*

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FDA Response to Question 1

A. (b) (4)



(b) (4)

it may be possible that the application may meet the criteria for a Priority Review because canakinumab treatment of these disorders, where no satisfactory alternative therapy exists, would fulfill an unmet medical need.

- B. *Breakthrough Therapy Designation: The Breakthrough Therapy Designation is intended to expedite the development and review of drugs for serious or life-threatening conditions and provides sponsors with more intensive FDA guidance regarding an efficient drug development program but does not obviate the need for demonstrating substantial evidence of efficacy. Given that your product is currently licensed in the US and that the development of canakinumab for the treatment of TRAPS, HIDS, and cr-FMF is ready to enter into Phase 3, there is no clear regulatory advantage for you to pursue development of your product via the Breakthrough Therapy Designation pathway.*

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 2

*The proposed clinical program for the Hereditary Periodic Fever conditions (i.e., TRAPS, HIDS, and crFMF) consists of a single, confirmatory clinical study (ACZ885N2301) which allows inclusion of each of the three separate patient populations to evaluate safety and efficacy of canakinumab in each of these rare IL-1 $\beta$ -associated conditions. Does the Agency agree that this study, with independent enrollment for each of the conditions, and supportive data from open label clinical trials, may provide substantial evidence of safety and efficacy*

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***sufficient to support registration of canakinumab in the conditions of crFMF, HIDS and TRAPS?***

***FDA Response to Question 2***

*Whether a single well-controlled trial will be sufficient to provide substantial evidence of safety and efficacy of canakinumab in patients with rare diseases such as TRAPS, HIDS, and cr-FMF, will depend on the review of the data and the robustness of the treatment effect. If the results are not persuasive enough, additional evidence of efficacy may be required to substantiate the treatment benefit. To account for the waxing and waning nature of TRAPS, HIDS, and cr-FMF, and acknowledging the difficulty in recruitment of patients in a separate study, we recommend that you incorporate a randomized withdrawal period following the initial 16-week randomized period where all canakinumab responders will be randomized to either continue canakinumab or placebo withdrawal with assessment of disease flares as an efficacy outcome. This way the primary efficacy would be derived from the controlled period of the study and the randomized withdrawal portion would be used as supportive evidence.*

*As stated in FDA response to Question 1 above, <sup>(b) (4)</sup>*

*As noted above, we consider each of the conditions to be distinct disease entities, therefore, for the purposes of your proposed study, we agree with the use of three separate patient population treatment arms for the assessment of efficacy and safety. It is important to note that assessment of efficacy will be based on the results from each individual treatment arm and not on the pooling of data across patient populations. Therefore, it is possible that canakinumab may demonstrate efficacy in one, two, or all three disorders.*

***Discussion:***

Novartis asked the FDA to confirm that as data becomes available is it acceptable to separately submit each disease entity and dependent upon enrollment to submit three independent submissions on a staggered basis. The FDA stated that this approach is reasonable as long as the efficacy and safety are being assessed for each disease entity as a separate cohort. However, since this is a combined development program within one protocol, the acceptability of separate or staggered submissions would depend on the adequacy of the safety database for the proposed BLA submission. In addition, the protocol should specify procedures for unblinding and analyzing a single stratum at a time without compromising the remaining strata.

The FDA commented that procedures to ascertain the blinding of the study should be specified in the protocol. These should address the risk for unblinding assessors of endpoints by physical exam findings and injections site reactions, and laboratory data such as acute phase reactants ESR, CRP and SAA. In addition, some patients from the same household may participate in the study which may affect the blinding because of injections site reactions for example. Novartis assured that procedures for ascertaining the blinding would be included in the protocol and the blind will be kept until study is complete.

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**Question 3**

***Based on the current clinical experience with canakinumab in these conditions Novartis proposes to use the same dose (starting dose of 2 mg/kg administered every 4 weeks) for these IL-1 $\beta$  related conditions. Does the Agency agree?***

**FDA Response to Question 3**

*While the proposed dosing regimen for study ACZ885N2301 is within the range of clinical doses used in other diseases, your dose selection justification to be used in TRAPS, HIDS, and cr-FMF is not sufficient for us to provide concurrence or advice regarding the proposed dosing regimen. It is at your discretion and risk to proceed with the proposed dosing regimen for study ACZ885N2301. We would encourage you to explore different doses of canakinumab or conduct exposure-response analyses in the target population if the data are available to identify a dose that can provide an acceptable risk:benefit profile to be studied in the Phase 3 program.*

**Discussion:**

The sponsor accepted FDA's response, no discussion occurred.

**Question 4**

***Does the Agency agree with the overall design and concept of proposed study CACZ885N2301, specifically:***

- a. Selection of patient population (i.e. inclusion and exclusion criteria) in each of the qualifying conditions?***
- b. Proposed primary and secondary efficacy parameters and time points for the efficacy analysis?***
- c. Statistical analysis plan for primary and secondary endpoints?***
- d. Proposed safety analysis across the indications?***

**FDA Response to Question 4a**

*The proposed eligibility criteria in each of the qualifying conditions, TRAPS, HIDS, and cr-FMF, in the proposed study CACZ885N2301 seem reasonable.*

**Discussion:**

The sponsor accepted FDA's response, no discussion occurred.

**FDA Response to Question 4b**

*Given the lack of validated endpoints in this group of diseases, your proposed primary endpoint appears to be reasonable and is similar to that used in the CAPS trials. Ideally, use of a patient reported outcome (e.g., Patient/Parent Global Assessment of Disease Activity) for the primary efficacy endpoint would be more advantageous in describing a clinically meaningful effect to the patient than that of the Physician Global Assessment (PGA) endpoint; however, use of the PGA to assess resolution of the index disease flare with no subsequent disease activity over the following 16 weeks can be construed as clinically meaningful as well. Major secondary*

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*endpoints assessing patient outcomes will need to demonstrate support evidence of the primary outcome.*

*With respect to the overall trial design and recommendation for including a randomized withdrawal period and endpoints, see also FDA response to Question 2 above.*

*We recommend that in the protocol you specify procedures to ascertain the blinding of the study. For example, ensure that assessors of efficacy endpoints are not unblinded by injection site reactions or laboratory data.*

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

FDA Response to Question 4c

*Our understanding is that the primary efficacy endpoint, the proportion of responders (defined as a patient who has resolution of their index disease flare and does not experience a new flare during the 16 weeks following resolution, i.e.,  $PGA \leq 1$  and SAA normalized) will be compared between treatment groups using Fisher's exact test and that this analysis will be conducted separately for each disease stratum. We also understand that each disease strata will be appropriately sized to expect demonstration of efficacy within each disease type and that patients who discontinue from the study for any reason or undergo early escape will be considered nonresponders for purposes of the primary efficacy analysis. These proposals are acceptable. We note that demonstration of efficacy in each disease stratum will be necessary for approval of an indication corresponding to that disease type. Results of all disease types, even if negative, may be described in labeling to inform health care providers.*

*Our understanding is that the secondary efficacy endpoints include: PGA disease activity, PPGA disease activity, patient reported disease specific symptoms score (AIDAI items), and serologic remission (across all disease strata) defined as patients with normalized SAA level. We also understand that with the exception of serologic remission, the secondary efficacy endpoints will be assessed independently within each disease stratum. Differences between treatment groups in the PGA disease activity, PPGA disease activity, and patient reported disease specific symptoms score will be analyzed by time point using a Mantel-Haenszel test. Between-treatment differences for the proportion of patients with serologic remission ( $SAA \leq ULN$ , for all disease strata pooled) will be analyzed using Cochran-Mantel-Haenszel test controlling for disease strata. And no multiplicity correction is planned for the secondary endpoints. It appears that details regarding the plans for accounting for missing data in the secondary efficacy endpoints were not provided. Although these plans appear acceptable, it is difficult for us to concur without a more thorough description of the secondary efficacy analyses being proposed. Be aware that if labeling claims based on these secondary endpoints are desired, adjustments to protect the type I error associated with conducting analyses of these multiple endpoints is needed. If our understandings are not correct, please clarify.*

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Discussion:

The sponsor accepted FDA's response, no discussion occurred.

FDA Response to Question 4d

*The proposed safety analyses across the indications appear reasonable.*

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

**Question 5**

(b) (4)

*Do you agree that this may be acceptable?*

FDA Response to Question 5

*No, we do not agree.* (b) (4)

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

**Question 6**

(b) (4)

FDA Response to Question 6

*No, we do not agree. See PREA Requirements in section 3.0 below.*

Discussion:

Novartis asked the FDA to clarify (b) (4)

The FDA stated that the PSP is a requirement

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under law and that the Agency is not authorized to (b) (4). The FDA commented that the PSP template outlines the requirements for the plan and that the template should be submitted along with justification why compliance cannot be met.

### **Technical Development**

#### ***Question 7***

***A liquid in vial formulation which is (b) (4) vs. the currently approved lyophilized formulation, this will be acceptable?***

#### **FDA Response to Question 7**

*No, we do not agree. Insufficient CMC information has been provided on the proposed liquid in vial drug product (DP) to adequately perform a comparability risk assessment. The IND should be updated to contain sufficient CMC information to support clinical use of the vial DP. While you may, at your own risk, decide to use the vial DP under the IND prior to the availability of the comparability assessment, this assessment will be required for approval of the vial DP.*

#### **Discussion:**

The sponsor accepted FDA's response, no discussion occurred.

### **3.0 PREA REQUIREMENTS**

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along

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with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).

#### **4.0 DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

#### **5.0 MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|-----------|--------------|--------------------------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------|
| 1.        |              |                                                                    |                                         |                                                                   |
| 2.        |              |                                                                    |                                         |                                                                   |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|-----------|--------------|--------------------------------|----------------------|---------------|
| 1.        |              |                                |                      |               |
| 2.        |              |                                |                      |               |

**6.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

**7.0 ACTION ITEMS**

There were no action items.

**8.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

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/s/  
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CAROL F HILL  
06/07/2013