CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125319 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DAARP PDUFA Goal Date: 06/18/09 Stamp Date: 12/17/08

Proprietary Name: Ilaris

Established/Generic Name: Canakinumab

Dosage Form: Injection given subcutaneously every eight weeks, 150 mg for patients with body weight greater than 40kg and 2mg/kg for patients with body weight between 15 and 40kg,

Applicant/Sponsor: Novartis Pharmaceuticals

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s) – b(4)
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Cryopyrin Associated Periodic Syndrome

1: Is this application in response to a PREA PMC/PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC/PMR #:_____

Does the division agree that this is a complete response to the PMC/PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

te: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

Ramani Sista, RPM

Ramani Sista 6/17/09

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

STN: BL. 125319, ACZ885, ILARIS (Canakiumab)

Debarment Certification

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Frederick De Brito PhD, Associate Director, IID
Drug Regulatory Affairs

December 8th, 2008
Date

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
10903 NEW HAMPSHIRE AVENUE, BLDG 22, SILVER SPRING, MARYLAND 20993

MEMO TO FILE

DATE: June 10, 2009

RE: Financial Disclosure for Study D2306 in BLA 125319
Ilaris® in Cryopyrin Associated Periodic syndromes (CAPS)

DRUG: Ilaris® (canakinumab), New Molecular Entity

FROM: Carolyn L. Yancey, M.D. Carolyn L. Yancey 06/10/09
Medical Officer, DAARP

THROUGH: Jeffrey N. Siegel, M.D. Jeffrey N. Siegel 6/17/09
Clinical Team Leader, DAARP

TO: Action Package File under BLA 125319

Background
This memo addresses the Financial Disclosure by Clinical Investigators provided to the Agency in response to an Information Request (IR) from the Division of Analgesia, Anesthesia and Rheumatology Products (DAARP) on June 5, 2009. The original biologic license application (BLA) did not include the financial disclosure information by clinical investigators participating in the ongoing Phase 3 Study ACZ885D2306 (Study D2306).

Study D2306 is one of two supportive clinical trials to the pivotal Study D2304 in BLA 125391 Ilaris (canakinumab) for the proposed indication of treatment of CAPS in adults and children aged 4 years and older including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

Summary
The summary of the findings are as follows:

- No clinical investigators in Study D2036 are full or part-time employees of Novartis Pharmaceuticals Corporation.

- The percent of clinical investigators participating in Study D2306 who responded to the applicant's financial disclosure inquiry was 100% of the US clinical investigators (19 out of 19) and 100% of the non-US investigators (61 out of 61).
- Disclosable financial arrangements and arrangements were identified for only one principal investigator. b(4)

  disclosed financial interests of $48,000. Any bias resulting from the principal investigator arrangements is minimized by independent data monitoring by Novartis, multiple investigators used in the studies and double-blind placebo controlled trials. This site was not among those identified by the Agency for site inspection by the Division of Scientific Investigations (DSI).
- The certification and disclosure forms for financial interests and arrangements of clinical investigators b(4) are submitted and signed by the applicant, Novartis.

Conclusions

The financial disclosure information submitted to the Agency by the applicant in response to the IR (June 5, 2009) for Study D2306 is acceptable.

Sista, Ramani V

From: xin.du@novartis.com
Sent: Wednesday, June 17, 2009 9:53 AM
To: Sista, Ramani V
Cc: frederick.debrito@novartis.com
Subject: RE: BLA 125319 - Label Version 2
Attachments: emfinfo.txt

Hi, Ramani:
Here is the revised response to the CMC PMR on new WCB. This revised version includes your request of providing the date for final report, and the request to use the new WCB for future production.

PMR: To develop a protocol for establishing new working cell banks that uses human serum albumin obtained from a US-licensed source. The protocol should include acceptance criteria for cell culture metrics and Canakinumab quality attributes, and provide limits which assure that validated cell generation time from the Master Cell Bank will be maintained. The protocol will be submitted as a Prior-Approval Supplement.
Response:
Novartis accepts this PMR. The protocol will be submitted as a Prior-Approval Supplement to the Agency on February 28, 2010. As requested, we will establish a new Working Cell Bank and will use it to manufacture all future canakinumab drug substance lots once this new WCB is established and approved. The new working cell bank will be developed by July 31, 2010, and the final report including release data and process suitability data on small scale will be submitted by July 31, 2010.

An updated version of this report including process data at commercial scale and end of production testing will be available once the data has been analyzed from a manufacturing campaign using this working cell bank. Because Ilaris is an orphan drug the timing for this campaign is not yet decided. By July 31, 2010 we will confirm with the FDA the timing for the next manufacturing campaign and also the date for submission of the updated report that includes data at commercial scale.

Thanks,

Xin

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
06/16/2009 06:20 PM

Please respond to
Ramani.Sista@fda.hhs.gov

To
frederick.debrito@novartis.com
cc
xin.du@novartis.com
Subject
RE: BLA 125319 - Label Version 2

Hi Fredrick, Xin
We'll be sending you the label and back with revisions later this evening.
Regarding the carton labeling, please move the US license number 1244 to the right to fall under the US address in NJ. Please remove the XXXXX or identify what it is. After making the changes, please send us the revised carton labels.

Xin, please provide us with a date (MM/YY) for submission of the final report for the Working Cell Bank PMR. This can be the same date as the date the WCB was established.

Thanks
Ramani
From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Tuesday, June 16, 2009 1:15 PM
To: Sista, Ramani V
Subject: Re: BLA 125319 - Label Version 2

Hi Ramani - please find attached our response to your label changes which we have largely accepted. Significant changes have been made to Table 1 (see comment) and to Figure 1, the latter providing for a better description of the x-axis. There are a few edits proposed by us. There also some formatting changes that are also present. Any questions please let me know. Thanks

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

<< Images in this email have been removed - please contact the sender to have the images sent as attachments. >>

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
06/15/2009 06:39 PM

Please respond to
ramani.sista@fda.hhs.gov

To
frederick.debrito@novartis.com
cc

Subject
BLA 125319 - Label Version 2

Sista, Ramani V

From: xin.du@novartis.com
Sent: Tuesday, June 16, 2009 2:43 PM
To: Sista, Ramani V
Cc: frederick.debrito@novartis.com
Subject: RE: BLA 125319 CMC PMR and PMCs
Attachments: emfinfo.txt

Hi, Ramani:
We will accept this requirement, and we will like to have this wording for it " This new WCB, once established and approved, must be used for all future canakinumab manufactured lots"

Thanks

Xin

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
06/16/2009 01:36 PM

Please respond to
ramani.sista@fda.hhs.gov

To
xin.du@novartis.com, frederick.debrito@novartis.com
cc

Subject
RE: BLA 125319 CMC PMR and PMCs

Hi Xin,
With regard to the PMR for the new working cell bank, we have a requirement that "this new WCB must be used for all future canakinumab manufactured lots."

Please let us know if this is acceptable by 3:00 pm today.
Thanks,
Ramani

From: xin.du@novartis.com [mailto:xin.du@novartis.com]
Sent: Monday, June 15, 2009 9:52 AM
To: Sista, Ramani V
Cc: frederick.debrito@novartis.com

Sista, Ramani V

From: frederick.debrito@novartis.com
Sent: Monday, June 15, 2009 4:31 PM
To: Sista, Ramani V
Subject: Re: BLA 125319 clarification on PMR
Attachments: ATT271027.gif; emfinfo.txt

Hi Ramani - please see the dates provided in color in your message below. Thanks

Could you let me know when we might have labeling comments back so that we can plan for discussions if needed. Thanks

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

<< Images in this email have been removed - please contact the sender to have the images sent as attachments. >>

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
06/15/2009 01:56 PM

Please respond to
Ramani.Sista@fda.hhs.gov

To
frederick.debrito@novartis.com
cc

Subject
BLA 125319 clarification on PMR

Hi Fredrick,
The PMR we were requiring of you has been split up in two. Please provide the completion and reporting dates for both studies ASAP.
Thanks,
Ramani
1. Complete and report the ongoing open label clinical trial D2306 investigating the safety of higher doses of canakinumab.

The timetable you submitted on June 15 2009 states that you will conduct this trial according to the following timetable:

Study Completion Date: by 06/10
Final Report Submission: by 09/10

2. Complete and report the ongoing multicenter open label 6-month clinical trial D2201 investigating the safety of higher doses of canakinumab.

The timetable you submitted on June 15 2009 states that you will conduct this trial according to the following timetable:

Study Completion Date: by 11/10
Final Report Submission: by 01/11

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Friday, June 12, 2009 4:23 PM
To: Sista, Ramani V
Subject: RE: BLA 125319 Urgent Tcon to get clarification on PMR

Hi Ramani - Once again my sincere apologies for the dealy; please find the PMR attached.

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
06/12/2009 01:32 PM

Please respond to
Ramani.Sista@fda.hhs.gov

To
frederick.debrito@novartis.com
cc

Subject
RE: BLA 125319 Urgent Tcon to get clarification on PMR

From: Stock, Marisa
Sent: Tuesday, June 16, 2009 11:49 AM
To: Lolas, Anastasia
Cc: CDER-TB-EER
Subject: RE: new BLA 125319 (Updated)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the updated status of each facility in red in the original requests below. There are no pending or ongoing compliance actions to prevent approval of new BLA 125319 at this time.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Stock, Marisa
Sent: Thursday, May 21, 2009 3:17 PM
To: Lolas, Anastasia
Cc: CDER-TB-EER
Subject: RE: new BLA 125319 (Updated)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the updated status of each facility in the original requests below. Due to the pending review of some of the facilities, please resubmit this TB-EER at a later time for a final overall compliance evaluation.

Marisa Stock
Consumer Safety Officer
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 4243
Silver Spring, MD 20993
Phone: (301) 796-4753

From: Lolas, Anastasia
Sent: Monday, May 18, 2009 10:25 AM
To: CDER-TB-EER
Subject: FW: new BLA 125319

I forgot to include two additional sites used for mycoplasma and viral testing. They just came in as an amendment. Thanks.

b(4)

Inspected September 5-6, 2005 and classified NAI. The CTL profile was covered and is acceptable. An inspection assignment has been issued for this facility.

b(4)

No inspectional history. An inspection assignment has been issued for this facility.

From: Lolas, Anastasia
Sent: Friday, January 16, 2009 9:18 AM
To: CDER-TB-EER
Cc: Xu, Lixin; Hoyt, Colleen; Hughes, Patricia; Cordoba-Rodriguez, Ruth
Subject: new BLA 125319

Please conduct an establishment evaluation for the sites listed below. BLA 125319 is a new BLA submitted on 15-DEC-2008 for Ilaris (canakinumab) injection, a recombinant monoclonal antibody for the treatment of cryopyrin associated periodic syndrome (CAPS). This is a priority application with orphan drug status and a PDUFA date of 17-JUN-2009.

The sites for the drug substance are:

Novartis Pharma S.A.A. FEI ~~3007198645~~ 3004864869 (**manufacture**, quality control, and stability)
Centre de Biotechnologie
8 rue de l'Industrie
68330 Huningue
France
A pre-license inspection for this BLA was conducted May 4 - 7 and 11 - 12, 2009 and initially classified NAI. A final district decision has not yet been made.

Novartis Pharma AG ~~CFN 117599~~ FEI 3002807772 (quality control and stability)
Lichtstrasse 35
CH-4056 Basel
Switzerland
A pre-license inspection for this BLA was conducted May 8, 2009 and was classified VAI. The CTB profile was covered and is acceptable.

The sites for the drug product are:

Novartis Pharma Stein AG FEI 3002653483 (**manufacture**, quality control, stability, packaging)
Schaffhauserstrasse
4332-Stein
Switzerland
Inspected September 13-21, 2007 and classified NAI. The — — , CTX, SVL, SVS, and — profiles were covered and are acceptable. This site is a Tier 1 inspectional priority for FY '09.

b(4)

b(4)

Inspected September 24-25, 2007 and classified NAI. The CTL profile was covered and is acceptable.

b(4)

b(4)

Inspected February 3-4, 2005 and classified VAI. This facility is a Tier 1 inspection priority for FY '09.

The following sites are only packaging sites:

Novartis Pharmaceuticals Corporation (Suffern) CFN 2416082
25 Old Mill Road
Suffern, New York 10901
Inspected November 17-20, 2008 and classified NAI. Profiles ADM, CHG, CTX, TCM, TCT, TDP, and TTR for packaging operations were covered and are acceptable.

Inspected November 19-21, 2007 and classified NAI. Profiles CHG, CSG, CTR, LIQ, POW, SNI, SUP, SVL, SVS. TCM, TCT, TTR, and TDP for packaging operations were covered and are acceptable.

b(4)

Inspected February 5-6, 2009 and classified NAI. Profiles CHG, CSG, CTR, TCM, TCT, and TTR for packaging operations were covered and are acceptable.

b(4)

Inspected March 12-20, 2009 and classified NAI. Profiles ADM, CHG, CSG, CTR, NEC, POW, TCM, TCT, and TTR for packaging operations were covered and are acceptable.

Thank you,

Anastasia

Anastasia G. Lolas
Microbiologist
Biotech Manufacturing Team/MAPCB/DMPQ
Office of Compliance, CDER
White Oak Bldg 51, Room 4216
301-796-1566

Sista, Ramani V

From: xin.du@novartis.com
Sent: Monday, June 15, 2009 2:56 PM
To: Sista, Ramani V
Cc: frederick.debrito@novartis.com
Subject: RE: BLA 125319 CMC PMR and PMCs
Attachments: emfinfo.txt

Hi, Ramani:
Since teh approval date of our BLA is June 18, 2009, so I need to change the dates below to

for PMC 3.4, I will provide a date of August 18, 2010, since this will be 60 days after the first annual report date.

For PMC 3.5, I will provide August 18, 2014 since this will be 60 days + five years after the BLA approval.

Thanks

Xin

Xin Du/PH/Novartis
06/15/2009 02:46 PM

To
ramani.sista@fda.hhs.gov
cc
frederick.debrito@novartis.com
Subject
RE: BLA 125319 CMC PMR and PMCs

Hi, Ramani:
for PMC 3.4, I will provide a date of August 15, 2010, since this will be 60 days after the first annual report date.

For PMC 3.5, I will provide August 15, 2014 since this will be 60 days + five years after the BLA approval.

Please let me know if these date are acceptable. I will check with my team too.

Thanks

Xin

Sista, Ramani V

From: xin.du@novartis.com
Sent: Monday, June 15, 2009 2:46 PM
To: Sista, Ramani V
Cc: frederick.debrito@novartis.com
Subject: RE: BLA 125319 CMC PMR and PMCs
Attachments: emfinfo.txt

Hi, Ramani:
for PMC 3.4, I will provide a date of August 15, 2010, since this will be 60 days after the first annual report date.

For PMC 3.5, I will provide August 15, 2014 since this will be 60 days + five years after the BLA approval.

Please let me know if these date are acceptable. I will check with my team too.

Thanks

Xin

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
06/15/2009 02:27 PM

Please respond to
ramani.sista@fda.hhs.gov

To
xin.du@novartis.com
cc
frederick.debrito@novartis.com
Subject
RE: BLA 125319 CMC PMR and PMCs

Hi Xin
For PMCs 3.4 and 3.5, please provide us with a date.
Thanks,
Ramani

From: xin.du@novartis.com [mailto:xin.du@novartis.com]
Sent: Monday, June 15, 2009 9:52 AM
To: Sista, Ramani V

Sista, Ramani V

From: Sista, Ramani V
Sent: Monday, June 15, 2009 1:56 PM
To: 'frederick.debrito@novartis.com'
Subject: BLA 125319 clarification on PMR
Importance: High

Hi Fredrick,
The PMR we were requiring of you has been split up in two. Please provide the completion and reporting dates for both studies ASAP.
Thanks,
Ramani

1. Complete and report the ongoing open label clinical trial D2306 investigating the safety of higher doses of canakinumab.

The timetable you submitted on June X 2009 states that you will conduct this trial according to the following timetable:

Study Completion Date: by MM/YY
Final Report Submission: by MM/YY

2. Complete and report the ongoing multicenter open label 6-month clinical trial D2201 investigating the safety of higher doses of canakinumab.

The timetable you submitted on June X 2009 states that you will conduct this trial according to the following timetable:

Study Completion Date: by MM/YY
Final Report Submission: by MM/YY

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Friday, June 12, 2009 4:23 PM
To: Sista, Ramani V
Subject: RE: BLA 125319 Urgent Tcon to get clarification on PMR

Hi Ramani - Once again my sincere apologies for the dealy; please find the PMR attached.

Best regards, Mit freundlichen Grüssen, Meilleures salutations,

Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274

Sista, Ramani V

From: xin.du@novartis.com
Sent: Monday, June 15, 2009 9:52 AM
To: Sista, Ramani V
Cc: frederick.debrito@novartis.com
Subject: RE: BLA 125319 CMC PMR and PMCs
Attachments: 7004942_ANSW_MP_840_12_final.pdf; 7004942_ANSW_MP_840_12_final.doc.zip; emfinfo.txt

Hi, Ramani:
Here is our acceptance of the CMC PMR/PMCs. I am sending you both PFF and word files. I will file the document into our BLA for tracking, if needed.

Thanks

Xin

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
06/12/2009 04:43 PM

Please respond to
ramani.sista@fda.hhs.gov

To
xin.du@novartis.com
cc

Subject
RE: BLA 125319 CMC PMR and PMCs

I would prefer it by 10:00am since it has to be reviewed by many.

From: xin.du@novartis.com [mailto:xin.du@novartis.com]
Sent: Friday, June 12, 2009 4:39 PM
To: Sista, Ramani V
Cc: frederick.debrito@novartis.com
Subject: Re: BLA 125319 CMC PMR and PMCs

Hi, Ramani:
How about Monday Noon? Thanks, Xin

Sista, Ramani V

From: Sista, Ramani V
Sent: Friday, June 12, 2009 1:27 PM
To: 'frederick.debrito@novartis.com'; 'xin.du@novartis.com'
Subject: BLA 125319 Canakinumab - CMC PMRs and PMCs

Hi Fredrick, Xin
Please see below for the CMC PMR and PMCs. Please provide us with your acceptance and the required dates by COB Monday, June 15.

PMR

To develop a protocol for establishing new working cell banks that uses human serum albumin obtained from a US-licensed source. The protocol should include acceptance criteria for cell culture metrics and Canakinumab quality attributes, and provide limits which assure that validated cell generation time from the Master Cell Bank will be maintained. The protocol will be submitted as a Prior-Approval Supplement.

Protocol Submission date: by MM/YY

New Working Cell Bank Developed: by MM/YY

PMCs

1. To provide an evaluation, summary, and data that confirm the adequacy of the proposed equilibration time required for thawed bulk drug substance to prevent excursions of drug product turbidity.

   Study Completion Date: by XXXX
   Final Report Submission: by XXXX

2. To perform validation studies on a for Canakinumab drug substance. The protocol, final report, and the proposed specification will be submitted as a CBE-0.

   Study Completion Date: by XXXX
   Final Report Submission: by XXXX

3. To monitor canakinumab drug product for the appearance of new bands when compared to reference standard during the assessment of registration stability testing, and to set an appropriate specifications relative to reference standard upon availability of 24 months of registration stability data for Canakinumab drug product. The proposed specifications and stability data will be provided as a CBE-0.

   Study Completion Date: by XXXX
   Final Report Submission: by XXXX

4. To perform stability testing on at least one marketed drug product lot and one drug substance lot; annually, for each year in which drug substance and/or drug product is manufactured, using the post-approval stability protocol specified in the BLA. The first update will be included in an annual report to be submitted.

Study Completion Date: by XXXX
Final Report Submission: by XXXX

5. To assess release and shelf-life specifications for canakinumab drug substance and drug product after manufacture of 15 lots. Specifications assessment and supporting data will be provided.

   Study Completion Date: by XXXX
   Final Report Submission: by XXXX

6. To qualify the additional biochemical characterization assays that will be used in support of establishing a new canakinumab reference standard. Qualification of currently used assays will be submitted.

   Study Completion Date: by XXXX
   Final Report Submission: by XXXX

Thanks,
Ramani

Sista, Ramani V

From: Sista, Ramani V
Sent: Thursday, June 11, 2009 1:02 PM
To: 'frederick.debrito@novartis.com'
Cc: 'xin.du@novartis.com'
Subject: BLA 125319 Ilaris - Package Labeling comments and PMRs

Hi Fredrick
As per our discussion yesterday regarding revising the Canakinumab label to read 180mgs, please note the following:

All carton and container labeling should read:

180 mg sterile powder for reconstitution/vial*

* Reconstitute with 1 mL of diluent to obtain a concentration of 150 mg/mL

Also, please make changes to sections 2.3, 3 and 11 of the PI to read:

Section 2.3

[redacted] b(4)

Section 3

ILARIS is supplied as a 180-mg white lyophilized powder for solution for subcutaneous injection. Reconstitution with 1 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted Ilaris is a clear to slightly opalescent, colorless to yellow, essentially free from particulates, 150 mg/mL solution.

Section 11

Ilaris is supplied in a sterile, single-use, colorless, 6-mL glass vial with coated [redacted] b(4) stopper and aluminum flip-off cap. Each vial contains 180 mg of canakinumab as a white, preservative-free, lyophilized powder. Reconstitution with 1 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted solution contains 150 mg/mL. The reconstituted canakinumab is a colorless to yellow 150 mg/mL solution essentially free of particulates, and clear to slightly opalescent. A volume of up to 1 mL can be withdrawn, which is designed to deliver 150 mg canakinumab for subcutaneous administration only. Each vial contains 180 mg canakinumab (150 mg/mL after reconstitution), sucrose, L-histidine, L-histidine HCL monohydrate, polysorbate 80 and Sterile Water for Injection. No preservatives are present.

We are also requiring a PMR for the Clinical section for your application. "Conduct a study, or trial, investigating the safety of higher doses of canakinumab in patients who do not respond to the recommended doses." If the language is acceptable to you, please provide the following:

Protocol Submission date
Study Start Date
Final Report Submission date

Please note that the PMR and PMCs for CMC section of your application will be provided later.
Please provide your acceptance, language and dates for the clinical study by COB today.
Thanks
Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Tuesday, June 09, 2009 6:32 PM
To: Sista, Ramani V
Cc: xin.du@novartis.com
Subject: Re: BLA 125319 Ilaris - Package Labeling comments

Dear Ramani

Thanks for forwarding the DMEPA and OBP comments last week by EM. I have, today also recieved the formal letter with the comments.

You asked for an update on these comments and if I may summarize with the assurance that we will follow up with a written response, I can say that we accept and are looking into implementing the reccomendations that have been made. We would however like to get some clarification on a couple of points and hence our call of this morning with Dr John Cutt. As requested I am providing a little more detail for your consideration.

A1.Revising the drug strength to read "150 mg per vial" or "150 mg/vial" rather than 150 mg/mL. b(4)
Please note that each vial contains 180mg as a — overage to deliver the 150mg/ml dose reccomendation to patients. Consequently, in complying with the regulations to express drug product per vial, this could result in accurately stating the content weight i.e. 180mg. Please could you clarify your reccomendation whether it is based on the delivery of the reccomended dose or on the accuracy of the vial content and how this should be expressed.?

C4. If a Medication Guide is required.....
We do not see the need for a REMS for Ilaris and we have had no discussion with FDA over this. We are therefore not expecting to provide a Medication Guide. Is the reccomendation standard text issued with preliminary notices of this kind?

Concluding paragraph
Since these are preliminary issues, would you be able to indicate when we would receive final packaging labeling comments? This would help us plan the timing of the publications of the new labels.

If you have any questions or if I can be of any help please feel free to contact me

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274

Sista, Ramani V

From: Sista, Ramani V
Sent: Wednesday, June 10, 2009 1:49 PM
To: 'frederick.debrito@novartis.com'; 'xin.du@novartis.com'
Subject: Canakinumab - Clarification requested

Hi Fredrick, Xin

Please address the following by COB today. Please also include Sharon Turner-Rinehardt in your response.

Container Closure integrity (CCI) testing (tightness of containers by dye intrusion) has been included in the latest table for stability specifications for drug product. This is not yet reflected in the testing monograph which is contained in the first of the two sections 3.2.P.5.1 of the BLA. both Table 2-1 "stability testing program for annual batches", and table 3-1 "stability testing program for post-approval changes" refer to the monograph for the tests and specifications to follow. You should update the monograph with all the current parameters.

Additionally, the timelines for stability testing of the commitment batches does not include CCI testing in the test groups identified. As these will be the lots intended to support extension of expiration dating, CCI testing should be added for all additional timepoints remaining, and an updated table 1-2 "test groups for commitment stability" should be submitted.

Should you change any parameters in the monograph as they relate to release or stability testing specifications, you will have to update the BLA.

Thanks,
Ramani

Sista, Ramani V

From: Sista, Ramani V
Sent: Monday, June 08, 2009 10:32 AM
To: frederick.debrito@novartis.com; 'xin.du@novartis.com'
Subject: BLA 125319: Response to IR

Hi Fredrick, Xin

Please provide the following by 2:00pm today.

1. [redacted] Novartis included a comparison to reference standard for release, however, you did not include this criterion for stability testing of DS and DP and retest as per our communication of May 21, 2009. b(4)

2. Updated specifications for qualification of reference standard were not included.

Thanks,
Ramani

Sista, Ramani V

From: Sista, Ramani V
Sent: Friday, June 05, 2009 6:47 AM
To: frederick.debrito@novartis.com; 'xin.du@novartis.com'
Cc: Turner-Rinehardt, Sharon
Subject: BLA 125319

Good Morning Fredrick, Xin

Please provide the following information by noon today. Please include Sharon Turner-Rinehardt in all your communication to me since I will be in office only till 8:00 am.

Based on your June 2, 2009 and May 29, 2009 replies to our information requests, please provide to the BLA updated release and stability specifications tables for drug substance and drug product and for qualification and re-testing of reference standard. This update should include the additional acceptance criteria identified in your responses, for example, addition of 'conforms to Reference Standard' to the specification for [redacted] Include confirmation that all release and stability protocols will be updated accordingly. b(4)

Thanks,
Ramani

Sista, Ramani V

From: Sista, Ramani V
Sent: Tuesday, June 02, 2009 8:59 AM
To: frederick.debrito@novartis.com; 'xin.du@novartis.com'
Subject: BLA 125319 IR

Good morning Fredrick, Xin

We have reviewed your reply to our information request of 5/26/09. Additional clarification is requested for the following items:

2a, For the ——— the request to add a comparison to reference standard as part of the acceptance criteria for ——— for release and stability of drug substance and drug product. b(4)

In your reply you explain that an additional system suitability test will be introduced for ——— to account for variability. Particularly, you have observed a shift in the calibration curve between different gels during ——— investigations. b(4)

Please provide clarification on the following:

- What is the nature and cause of the observed shift in the calibration curve? Please include any information relevant to the stability of the canakinumab reference standard.

- As you do not agree to implement a comparison to reference standard as additional acceptance criteria for release, explain how you will identify and control for potential differences in band pattern that is below LOQ, e.g. for any novel product or process related impurities.

Please provide the requested information by noon this today.
Thanks,
Ramani

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
10903 New Hampshire Avenue
Bld. #22. Rm # 3187
Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD ADN DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 21, 2009

TO: File

FROM: Ramani Sista, Regulatory Project Manager Ramani Sista 6/17/09

SUBJECT: **Pre-Approval Safety Conference**
BLA 125319 Ilaris (Canakinumab)

In lieu of a separate preapproval safety conference with OSE staff, the Division decided to include this as past of the Wrap-Up meeting for BLA 125319 which was held on May 21, 2009. Members of the OSE staff present at the meeting were Chris Wheeler, Peter Diak and Lauren Choi. Also present at the meeting were the following Curtis Rosebraugh, Bob Rappaport, Rigoberto Roca, Jeffery Siegel, Carolyn Yancey, Deborah Seibel, Kathleen Young, Adam Wasserman, Ruth Cordoba-Rodriguez, Chana Fuchs, Lixin Wu, Anastasia Lolas, Patricia Hughes, Srikanth Nallani, Michael Pacnowski, Hao Zhao, David Petullo, Dionne Price and Sharon Turner-Rinehardt.

During the meeting, the clinical reviewer presented a comprehensive overview of the safety profile of canakinumab. OSE asked if the patient population was between ages 4 to 9. The clinical reviewer affirmed and mentioned that the label would reflect a population of ages 4 and older. OSE also inquired about the presence of ——— in the drug substance. The product reviewer clarified that ——— was a ——— . There are ——— that have been manufactured and released at commercial scale. At 3 mg/kg, dosing the potential amount of ——— present would be ——— . Since then, the sponsor has changed the preservative to ——— . Leachable and extractable studies will be conducted using the new preservative. OSE did not have any other questions and was satisfied with the safety information presented for canakinumab.

b(4)

Sista, Ramani V

From: Sista, Ramani V
Sent: Thursday, May 21, 2009 4:12 PM
To: 'frederick.debrito@novartis.com'; 'xin.du@novartis.com'
Subject: BLA 125319 Canakinumab

Hi Fredrick, Xin,

Please provide the following information by COB Tuesday May 26, 2009.

A number of proposed specifications are not supported by information provided in the BLA. The following are our comments regarding revision of Canakinumab specifications.

Address each item and provide updated specifications and justifications accordingly.

1. In reference to appearance of the solution measured by turbidimetry:
   a. Tighten drug product (DP) release and stability acceptance criterion to —— b(4)

2. In reference to color of the solution, set a single color reference specification for drug substance and reconstituted drug product (——) and provide justification for the revised specification.

3. For the ——
   a. Add a comparison to reference standard as part of the acceptance criteria for —— for release and stability of drug substance and drug product. b(4)

   b. Tighten release and stability acceptance criteria for drug product impurities to ——

4. Implement a —— for release and stability of Canakinumab drug substance. Include a limit for monomer band density and comparison to reference standard as part of the acceptance criteria for this assay.

5. In reference to —— Novartis should propose acceptance criteria for drug substance and drug product release and stability that are more detailed than the proposed acceptance criterion of —— for sum of related substances and impurities. The proposed acceptance criteria should include justification based on knowledge of species/peak activity/potency. b(4)

6. In reference to size-exclusion chromatography:
   a. Add a limit for monomer as part of the acceptance criteria for drug substance and drug product release and stability.
   b. Tighten limits for drug product aggregates to —— and drug product degradation products to —— for release and stability. b(4)
   c. Propose a tighter limit for drug substance aggregates and degradation products that would be reflective of your experience based on the submitted drug substance batch data.

7. In reference to host cell protein by ELISA, tighten the limit to better reflect manufacturing and clinical experience. Include any statistical method used to set this limit in your justification.

   Provide updated specifications for the release and re-test of Canakinumab reference standard according to the final commercial specifications set for Canakinumab drug substance release should be provided to the BLA.

Thanks,
Ramani

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
10903 New Hampshire Avenue
Bld. #22. Rm # 3187
Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
Sent: Monday, May 18, 2009 6:08 PM
To: 'frederick.debrito@novartis.com'
Subject: RE: BLA 125319 - Ilaris request for a TCON

Hi Fredrick
A T-con has been arranged for May 20th, 9:00 to 9:30 am. Please provide me with a call in number.
Thanks,
Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Thursday, May 14, 2009 4:15 PM
To: Sista, Ramani V
Subject: Re: BLA 125319 - Ilaris request for a TCON

Hi Ramani - we would like to better understand your request for data [redacted] and whether our response met with the reviewers need for the requested information. We would particularly like to know whether your reviewer has concerns about [redacted] Please could we request a TCON with your reviewer to discuss this? Thanks

b(4)

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

<< Images in this email have been removed - please contact the sender to have the images sent as attachments. >>

Frederick DeBrito/PH/Novartis
05/11/2009 03:54 PM

To
ramani.sista@fda.hhs.gov
cc

Subject
Re: BLA 125319 - Ilaris

Dear Ramani

In response to your request, we confirm that indeed the BLA [redacted] b(4)

CAPS clinical trials were conducted with medical personnel performing the subcutaneous injection in order to ensure compliance with study drug. The accrued safety experience has since demonstrated that no adverse experience [redacted] Specifically, in the absence of i) severe injection site reactions (majority of patients had no injection-site-reactions) ii) immunogenicity iii) anaphylactic or anaphylactoid reactions and iv) no specific adverse event that occurred in close temporal association with drug administration, it is felt safe to recommend [redacted] b(4)

Novartis therefore proposes, for future use of canakinumab in clinical practice, [redacted] which is in line with most other sub-cutaneous treatments available in the market (including anakinra and rilonacept). As with these other products, [redacted] b(4)

[redacted]

[redacted]

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

<< Images in this email have been removed - please contact the sender to have the images sent as attachments. >>

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
05/11/2009 08:39 AM

Please respond to
ramani.sista@fda.hhs.gov

To
frederick.debrito@novartis.com
cc

Subject
BLA 125319 - Ilaris

Good Morning Fredrick
Please provide the requested information:

[redacted]

b(4)

Please provide this information by COB of business today, May 11 2009.
Thanks,
Ramani

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
10903 New Hampshire Avenue
Bld. #22. Rm # 3187
Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 12, 2009

TO: Ramani Sista, Regulatory Project Manager
Carolyn Yancey, M.D., Medical Officer
Division of Anesthesia, Analgesia, and Rheumatology Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

BLA: 125319

APPLICANT: Novartis

DRUG: Ilaris (canakinumab)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of cryopyrin-associated periodic syndrome (CAPS)

CONSULTATION REQUEST DATE: February 2, 2009

DIVISION ACTION GOAL DATE: June 17, 2009

PDUFA DATE: June 17, 2009

I. BACKGROUND:

The conduct of protocol #ACZ885D2304, entitled "A three-part multicenter study, with a randomized, double-blind, placebo controlled, withdrawal design in Part II to assess efficacy, safety, and tolerability of ACZ885 (antiinterleukin-1β monoclonal antibody) in patients with Muckle-Wells Syndrome" was inspected.

The sites below were selected based on total numbers of subjects enrolled; also, at these sites, all subjects in Part II of the study demonstrated no disease flares.

The primary objective of this study was to assess efficacy (percent of patients who relapse) of ACZ885 compared with placebo in Part II as determined by the Physician's Global Assessment of autoinflammatory disease activity, assessment of skin disease and inflammation markers (C-reactive protein (CRP) and/or serum amyloid A (SAA).

II. RESULTS (by Site):

Name of CI, Sponsor Location	**Protocol #/ # of Subjects/**	**Inspection Dates**	**Final Classification**
Isabelle Kone-Paut, M.D. Hopital Kremlin Bicetre Le Kremlin Bicetre 94275 France	D2304/ 5/	4-7 May 2009	Pending. Interim classification NAI.
Dr. Eric Hachulla Hopital Claude Huriez Lille Cedex 59037 France	D2304/ 4	27-30 Apr 2009	Pending. Interim classification VAI.
Dr. Phillip Hawkins National Amyloidosis Centre, Royal Free and University College Medical School London NW3 2PF United Kingdom	D2304/ 9/	20-24 Apr 2009	Pending. Interim classification NAI.
Novartis One Health Plaza, East Hanover, NJ 07936	D2304/	17-24 Apr 2009	Pending. Interim classification VAI.

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Isabelle Kone-Paut, M.D.
   Hopital Kremlin Bicetre
   Le Kremlin Bicetre 94275
   France

   a. **What was inspected:** Ten subjects were screened, five were enrolled in the study, and four completed the study. Study records for five subjects were reviewed.

   b. **General observations/commentary**: There was no documentation of the PPD skin test evaluation for subject 003.

   c. **Assessment of data integrity**: Data appear acceptable in support of the respective application

   Observations noted above are based on the Form FDA 483 and/or communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Dr. Eric Hachulla
   Hopital Claude Huriez
   Lille Cedex 59037
   France

   a. **What was inspected**: Six subjects were screened, and four were enrolled and completed the study. Study records for four subjects were reviewed.

   b. **General observations/commentary**: Dosing visits for two subjects were three to four days outside of the protocol-required timeframe on two occasions. Certain protocol-specified activities were not conducted: for example local tolerability at the injection site was not always indicated, specific biochemistry results were not always obtained, height measurements were not always taken, and there was no documentation of one subject's tuberculosis evaluation.

   c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

   Observations noted above are based on the Form FDA 483 and/or communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. Dr. Phillip Hawkins
National Amyloidosis Centre,
Royal Free and University
College Medical School
London NW3 2PF
United Kingdom

   a. **What was inspected**: 9 subjects were screened, enrolled, and completed the study. The study records for all nine subjects were reviewed.

   b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

   c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

   Observations noted above are based on the Form FDA 483 and/or communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. Novartis
One Health Plaza,
East Hanover, NJ 07936

   a. **What was inspected**: The inspection included review of, but was not limited to, the following: organizational responsibilities, standard operating procedures, records related to the use of contract research organizations, the selection of clinical investigators, monitoring procedures and activities, subject records, quality assurance, adverse event reporting, data collection and handling, record retention, and test article integrity and accountability.

   b. **General observations/commentary**: Periodic Monitoring Visit Reports were not always prepared after each monitoring visit as required by the clinical monitoring plan. Instead, on at least two occasions, the reports were prepared after two or three visits were completed. Routine monitoring visits were not conducted since October 31, 2008, as required for site #30. Also, for site #03, the sponsor did not obtain complete information on the Financial Disclosure Form for the investigator's financial income derived from the sponsor.

   c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

   Observations noted above are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data generated by the clinical sites of Drs. Kone-Paut, Hachulla, and Hawkins and the sponsor appear acceptable in support of the respective application.

Receipt and review of the EIRs for Drs Kone-Paut, Hachulla, and Hawkins, and the sponsor are pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be any observations of clinical and regulatory significance discovered after reviewing the EIRs.

Roy Blay Ph.D. 12 MAY 09

Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin 5/13/09

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

Sista, Ramani V

From: Sista, Ramani V
Sent: Wednesday, April 29, 2009 2:59 PM
To: 'xin.du@novartis.com'
Subject: RE: FW: BLA 125319 - Canakinumab IR

Hi Xin
I already sent you a mail earlier. Your proposal for Question 14 is acceptable.
Thanks,
Ramani

From: xin.du@novartis.com [mailto:xin.du@novartis.com]
Sent: Wednesday, April 29, 2009 2:55 PM
To: Sista, Ramani V
Cc: frederick.debrito@novartis.com; john.cutt@novartis.com
Subject: RE: FW: BLA 125319 - Canakinumab IR

Hi, Ramani:
Here is the response document. This response does not have attachment. However, the external links are not linked.

Will you be able to provide me the response to my email today related to Question 14?

Thanks

Xin

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>

04/29/2009 02:19 PM

Please respond to ramani.sista@fda.hhs.gov

To xin.du@novartis.com, john.cutt@novartis.com
cc frederick.debrito@novartis.com
Subject RE: FW: BLA 125319 - Canakinumab IR

Yes Xin, please email a copy to me.

From: xin.du@novartis.com [mailto:xin.du@novartis.com]
Sent: Wednesday, April 29, 2009 2:13 PM
To: john.cutt@novartis.com
Cc: frederick.debrito@novartis.com; Sista, Ramani V
Subject: Re: FW: BLA 125319 - Canakinumab IR

Yes, Ramani. The submission was out around noon today. Please let me know if you have not received it. Please also let me know if you need me to send the document by email so Ruth can have it quicker.

Thanks

Xin

John Cutt/PH/Novartis

04/29/2009 02:10 PM

To ramani.sista@fda.hhs.gov
cc frederick.debrito@novartis.com, xin.du@novartis.com
Subject Re: FW: BLA 125319 - Canakinumab IR Link

Ramani, Xin will confirm. The submission has been sent today.

Regards

John

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>

04/29/2009 02:07 PM

Please respond to ramani.sista@fda.hhs.gov

To john.cutt@novartis.com, xin.du@novartis.com
cc frederick.debrito@novartis.com
Subject FW: BLA 125319 - Canakinumab IR

Hi John
This IR request was sent last week with a deadline of noon Monday April 27. Could you please send this in by COB today.
Thanks,
Ramani

From: Sista, Ramani V
Sent: Tuesday, April 21, 2009 2:44 PM
To: 'frederick.debrito@novartis.com'

2 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 1

Sista, Ramani V

From: Sista, Ramani V
Sent: Wednesday, April 29, 2009 1:54 PM
To: 'xin.du@novartis.com'
Subject: RE: BLA 125319 - Canakinumab CMC IR

Hi Xin
Your proposal is acceptable.
Ramani

From: xin.du@novartis.com [mailto:xin.du@novartis.com]
Sent: Wednesday, April 29, 2009 11:20 AM
To: Sista, Ramani V
Subject: Re: BLA 125319 - Canakinumab CMC IR

Hi, Ramani:
Regarding question 14, we will accept FDA request to update the description of the manufacturing process. However, this update will take some time, so I will make a commitment in our response to update the relevant sections of the BLA, but submit the updated section to our BLA around May 15. Would you please check with Ruth to see if this is OK?

Thanks

Xin

Sista, Ramani V

From: Sista, Ramani V
nt: Thursday, April 23, 2009 2:38 PM
To: 'frederick.debrito@novartis.com'
Subject: BLA 125319 Canakinumab - IR

Hi Fredrick
Please provide the requested information by COB tomorrow.

Submit any additional information about the reported SAE in Patient # A2102-0001-05106 - SAE - Lower Respiratory Tract Infection. We are specifically seeking information about the etiology of the reported lower respiratory tract infection. The patient narrative is silent about a potential etiology of the reported SAE.

Thanks,
Ramani

Sista, Ramani V

From: Sista, Ramani V
Sent: Monday, April 20, 2009 1:50 PM
To: 'frederick.debrito@novartis.com'
Subject: BLA 125319 - Canakinumab IR

Good afternoon Fredrick,
Hope you are doing well. Please provide the following information by noon Friday, April 24, 2009.

For the gene expression study performed in Study D2304, provide the following:

1. Individual patient gene expression data for all study visits, including normalized Ct values, absolute copy number (if available), and relative change using the $2^{-\Delta\Delta CT}$ method (Livak)
2. Details of statistical analysis plan
3. Study report BMD R0850287

Please contact me if you have questions.
Thanks,
Ramani

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
10903 New Hampshire Avenue
Bld. #22. Rm # 3187
Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

BLA 125319

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

Novartis Pharmaceuticals Corporation
ATTENTION: Frederick DeBrito PhD,
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

APR 10 2009

Dear Dr. DeBrito:

Please refer to your Biologics License Application (BLA) dated December 15, 2008, received December 17, 2008, submitted under section 351 of the Public Health Service Act, for canakinumab injection.

We also refer to your January 13, 2009, correspondence, received January 14, 2009, requesting review of your proposed proprietary name, Ilaris. We have completed our review of the proposed proprietary name, Ilaris and have concluded that it is acceptable.

The proposed proprietary name, Ilaris, will be re-reviewed 90 days prior to the approval of the BLA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 15, 2008, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Chris Wheeler, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0151. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

Jeffrey M. Siegel, acting for Bob Rappaport

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Sista, Ramani V

From: Sista, Ramani V
Sent: Thursday, March 26, 2009 7:09 AM
To: 'frederick.debrito@novartis.com'
Subject: BLA 125319 Canakinumab - Tradename

Good Morning Fredrick
This mail is to inform you that Office of Surveillance and Epidemiology has completed it's review of the tradename "Ilaris" for Canakinumab. Novartis will be allowed to use "Ilaris" for Canakinumab.
Thanks,
Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Tuesday, March 10, 2009 9:29 AM
To: Sista, Ramani V
Subject: RE: BLA 125319 Canakinumab Filing Letter

Hi Ramani
Many thanks for your reply and answers. In recommending that we submit the safety update and CSR in separate submissions, please could you advise whether the CSR should be submitted to the BLA or to the IND. The concern of course is incurring an extension with this submission and so please could you confirm that this will not occur? I also wanted to ask whether you could indicate when DMETS had started its review of our tradename. Will they intend to keep to the FDA guidance of a 90 day review period? Once more very grateful for your consideration of my questions. Thanks

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

<< Images in this email have been removed - please contact the sender to have the images sent as attachments. >>

"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
03/05/2009 07:23 AM

Please respond to
ramani.sista@fda.hhs.gov

To
frederick.debrito@novartis.com

cc

Subject
RE: BLA 125319 Canakinumab Filing Letter

Good Morning Fredrick

Hope you are doing well.

1) The action date for Canakinumab is June 17, 2009. A separate letter will not be issued specifying the action date.
2) The tradename is currently under review. At this time it is not possible to give you a completion date.
3) There will be no separate review of the Drug packaging, this will take place with the BLA.

Additionally, the questions included in the outline of 120 day safety update:

We would recommend, that you submit the safety update and CSR in separate submissions. The CSR will be reviewed only if time permits.
Submission of Safety update on April 13, 2009 is acceptable.

Thanks,
Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Wednesday, March 04, 2009 12:01 PM
To: Sista, Ramani V
Subject: Re: BLA 125319 Canakinumab Filing Letter

Hi Ramani
Just to say that I have as yet recieved the Action Date letter for the BLA and wondered if you were any closer to answering my questions in the email below. Thanks

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

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Frederick DeBrito/PH/Novartis
02/19/2009 06:30 PM

To

ramani.sista@fda.hhs.gov
cc

Subject
Re: BLA 125319 Canakinumab Filing Letter

Hi Ramani
Many thanks for sending me the Filing Communication letter. And once more thanks for your call of last week which made for a good weekend!
I have some questions if I may and would be most grateful for any consideration you give to this, largely around dates.
1. Would I be expecting another letter indicating when the action date is? Are you able to communicate what that date is?
2. For the Tradename review; do you know if this has started and are you able to mention a completion date or roughly by when date?
3. Since we are on a priority review and we need to work hard to meet potential launch times. Are you able to let me know when the drug packaging review will take place since any issues here may impact time lines significantly?
Thanks in advance.

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
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"Sista, Ramani V" <Ramani.Sista@fda.hhs.gov>
02/18/2009 02:36 PM

Please respond to
ramani.sista@fda.hhs.gov

To
frederick.debrito@novartis.com
cc

Subject
BLA 125319 Canakinumab Filing Letter

Hi Fredrick
Please see the attached for a copy of the filing letter. The original has been mailed to you.
Thanks,
Ramani

<<BLA125319_FilingLtr_18Feb09.pdf>>
Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
10903 New Hampshire Avenue
Bld. #22. Rm # 3187
Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
Sent: Friday, March 13, 2009 1:57 PM
To: 'frederick.debrito@novartis.com'
Subject: RE: BLA 125319 Canakinumab Filing Letter

Hi Fredrick,
Sorry I did not get back to you earlier. Please submit the CSR to both the BLA and IND. As mentioned earlier, we will review the CSR only if time permits, so an extension will not be necessary.
As to the tradename, it is under review.
Thanks,
Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Tuesday, March 10, 2009 9:29 AM
To: Sista, Ramani V
Subject: RE: BLA 125319 Canakinumab Filing Letter

Hi Ramani
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03/05/2009 07:23 AM

Please respond to
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Good Morning Fredrick

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One Health Plaza, East Hanover, NJ 07936-1080
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Phone: +1 8627781274
Email : frederick.debrito@novartis.com

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Frederick DeBrito/PH/Novartis
02/19/2009 06:30 PM

To

ramani.sista@fda.hhs.gov
cc

Subject
Re: BLA 125319 Canakinumab Filing Letter

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To
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Subject
BLA 125319 Canakinumab Filing Letter

Hi Fredrick
Please see the attached for a copy of the filing letter. The original has been mailed to you.
Thanks,
Ramani

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Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
10903 New Hampshire Avenue
Bld. #22. Rm # 3187
Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
Sent: Wednesday, March 11, 2009 2:48 PM
To: 'frederick.debrito@novartis.com'
Cc: Turner-Rinehardt, Sharon
Subject: FW: BLA 125319 - Canakinumab IR

Hi Fredrick,
Please note that the following data was not included in the information sent last week in response to our Pharm/Tox IR. Please provide this information by noon tomorrow.

4. Juvenile mouse study in performing laboratory (———) in CD-1 mouse: physical development pre- and post weaning to include day of vaginal opening, sensory development, behavioral performance (motor, auditory startle, passive avoidance), fertility(to include pre and post-implantation loss), necropsy (to include histopathology). b(4)

Please include Sharon Turner-Rinehardt in all your communication to me since I will be in class all day tomorrow.
Ramani

From: Sista, Ramani V
Sent: Monday, March 09, 2009 7:30 AM
To: 'frederick.debrito@novartis.com'
Subject: RE: BLA 125319 - Canakinumab IR

Good Morning Fredrick,
Please see out P/T reviewers comments regarding historical data:

It is always very useful to have entire set of historical data for the performing laboratory and in the specific species tested (mouse, marmoset) for all of the parameters for the Seg I, II, and III reprotox studies. Given a choice, I would also prefer to have entire set of historical data for the performing lab and in the specific mouse species used for the juvenile mouse study.

However, if the Sponsor wants to or must pare the historical control data down to a minimum, these are the parameters that I am most interested in seeing:

b(4)

1. Segment II (embryo-fetal development) study in CD-1 mouse in the performing lab ——— . skeletal examinations

2. Segment II (embryo-fetal development) in marmoset in ——— y (if possible); reproductive performance (including placental weights, numbers of fetuses per litter), external and skeletal examinations (particularly bent/kinked tail, vertebral ossification) b(4)

3. Segment III (pre- and post-natal development) in ——— performing laboratory in CD-1 mouse; necropsy (organ weights, organ/tissue gross and microscopic examinations) data for both Fo and F1 generations, including lymph nodes, b(4)

4. Juvenile mouse study in performing laboratory ———) in CD-1 mouse: physical development pre- and post weaning to include day of vaginal opening, sensory development, behavioral performance (motor, auditory startle, passive avoidance), fertility(to include pre and post-implantation loss), necropsy (to include histopathology). b(4)

Please let me know if you have questions.
Thanks,

Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Friday, March 06, 2009 11:21 AM
To: Sista, Ramani V
Subject: Re: BLA 125319 - Canakinumab IR

Hi Ramani

Further to my VM earlier, thanks for your message and hope you are well too. We have reviewed your request and are making preparations to provide the desired information by the deadline set of Monday 2.00pm. With regard to the historical control data requested, is your reviewer able to be more specific as to what he or she may be specifically interested in as there is a substantial amount of data that we could consider providing.

This data is presently being discussed with ——— who conducted the reprotox studies. There are very few parameters that span all four studies and historical control data would cover a myriad of possible parameters. What parameters would your reviewer consider as pertinent to support your evaluation? Novartis would prefer to provide initially historical controls for the treatment-related effects observed in these studies and provide any additional information at the reviewers request. If your reviewer would like to TC with us to get this clarified we would welcome this and I can arrange. Please let me know. b(4)

I will be in the office all day so feel free to call to discuss. Thanks

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

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03/05/2009 02:19 PM

Please respond to
ramani.sista@fda.hhs.gov

To
frederick.debrito@novartis.com
cc

Subject
BLA 125319 - Canakinumab IR

Good Afternoon Fredrick,
Please provide the following information:
1. Toxicokinetic analyses on exposure (AUC, Cmax, etc) in the Reproductive Toxicity Studies on Fertility, Embryofetal Development and Pre- and Postnatal Development studies (Segments I, II, and III) in mouse using the ACZ885 surrogate 01BSUR, in addition to the serum levels already provided in the study reports.
2. Historical control data for the reproductive toxicity (Segments I, II, and III) and juvenile toxicity studies in mouse, for comparison with the results of these studies.
Please provide the information by 2:00pm Monday, March 9, 2009.
Thanks,
Ramani

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
10903 New Hampshire Avenue
Bld. #22. Rm # 3187
Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
Sent: Monday, March 09, 2009 9:22 AM
To: 'frederick.debrito@novartis.com'
Cc: Turner-Rinehardt, Sharon
Subject: RE: BLA 125319 - Canakinumab IR

Hi Fredrick
Please send the information as soon as possible. Since this is a Priority review, this leaves our reviewers in a time crunch. Please ensure all the requested information is turned in by COB tomorrow.
Also, include Sharon Turner-Rinehardt in all your communication to me, since I will be in training all day tomorrow.
Thanks,
Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Monday, March 09, 2009 9:13 AM
To: Sista, Ramani V
Subject: RE: BLA 125319 - Canakinumab IR

Dear Ramani
Thanks for your reply and for providing the details that we requested from your reviewer. [redacted] have indicated that there is not a substantial amount of historical data for the mouse reprotox models and so perhaps it would be best as your reviewer suggests to provide you with the entire set of historical data available for this performing lab. They are going to let us have the data around 1.30 pm or earlier today and ask that you bear with us in case we just miss the 2.00pm deadline. With regard to the reviewer's request for historical data Segment II (embryo-fetal development) in marmoset in [redacted] (if possible), we have made a request to this laboratory and should be able to provide this data too, except that it is unlikely that we could meet the same deadline. Please let me know if this is acceptable.

b(4)

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
One Health Plaza, East Hanover, NJ 07936-1080
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Phone: +1 8627781274
Email : frederick.debrito@novartis.com

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Please respond to

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To
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Subject
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Ramani

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b(4)

I will be in the office all day so feel free to call to discuss. Thanks

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Novartis Pharmaceuticals Corporation
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One Health Plaza, East Hanover, NJ 07936-1080
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Phone: +1 8627781274
Email : frederick.debrito@novartis.com

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03/05/2009 02:19 PM

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To
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Subject
BLA 125319 - Canakinumab IR

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Please provide the information by 2:00pm Monday, March 9, 2009.
Thanks,
Ramani
Ramani Sista, PhD, RAC
Regulatory Project Manager
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Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
nt: Thursday, February 19, 2009 2:10 PM
: 'frederick.debrito@novartis.com'
Cc: Turner-Rinehardt, Sharon
Subject: BLA 125319 Canakinumab - IR

Hi Fredrick
Please provide the following information:

In Study A2102, provide the summary of physician and patient assessments of disease activity and the summary of physician assessment of skin disease activity by time *(all periods average)*, employing the safety analysis set, across all dose groups.

Provide this information by 2:00 pm February 20, 2009. Also, include Sharon Turner-Rinehardt in all your communication with me since I will not be in office tomorrow.
Thanks,
Ramani

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
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mail: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
nt: Wednesday, February 18, 2009 2:36 PM
: 'frederick.debrito@novartis.com'
Subject: BLA 125319 Canakinumab Filing Letter

Attachments: BLA125319_FilingLtr_18Feb09.pdf

Hi Fredrick
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Thanks,
Ramani

BLA125319_FilingLt
r_18Feb09.pd...

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mail: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
nt: Wednesday, February 18, 2009 8:40 AM
: 'frederick.debrito@novartis.com'
Subject: BLA 125319 Canakinumab

Good Morning Fredrick
Please provide the following information:

See Table 14.2-5.1 (page 1 of 1), page 195 of 10679.
In Study A2102, clarify among 27 adult patients and 7 pediatric patients, how many adult and how many pediatric patients had audiograms performed at baseline. Specify what the baseline results were, n (%), in the following categories:
Normal,
Clinically insignificant abnormalities,
Clinically significant abnormalities'
Not available/ not done.

Please provide this information by noon tomorrow, February 19, 2009.
Thanks,
Ramani

Ramani Sista, PhD, RAC
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email: Ramani.Sista@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

STN: BL 125319/0

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

FEB 13 2009

Attention: Frederick De Brito, PhD
Associate Director, Drug Regulatory Affairs

Dear Dr. De Brito:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated December 15, 2008, received December 17, 2008, for Ilaris® (Canakinumab) to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application on February 15, 2009. The review classification for this application is Priority. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

At this time, we have not identified any potential review issues. Our filing review is only a preliminary review, and deficiencies may be identified during substantive review of your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Ramani Sista, Regulatory Project Manager, at (301) 796-1236.

Sincerely,

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Sista, Ramani V

From: Sista, Ramani V
Sent: Wednesday, February 11, 2009 9:51 AM
To: 'frederick.debrito@novartis.com'
Cc: Turner-Rinehardt, Sharon
Subject: BLA 125319 - Canakinumab - Information Request (3)

Hi Fredrick
Thank you for the information.

We have another request:

In study D2304, your protocol (CACZ885D2304, section 7.4.1) and electronic case report forms indicate that the primary efficacy endpoint is the Physicians global assessment of autoinflammatory disease activity less than or equal to minimal (using a 5-point scale ranging from absent to severe) and the assessment of skin disease less than or equal to minimal (using a 5-point scale ranging from absent to severe). The meta-data you submitted (2304define.pdf) indicate that a 7-point scale was used. Clarify this discrepancy and/or submit data variables consistent with the original protocol.

Please submit the information to BLA 125319 by noon of February 13, 2009.
Thank you.
Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Wednesday, February 11, 2009 9:05 AM
To: Sista, Ramani V
Subject: Re: BLA 125319 - Canakinumab - Information Request (2)

Hi Ramani
Please find attached a document which is Novartis's response to the information required and which you requested in your email below i.e. exposure data for the 10 ongoing additional clinical trials. Let me know if the data provided is exactly what you requested.

Best regards, Mit freundlichen Grüssen, Meilleures salutations,
Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH
USEH
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USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

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Please respond to
ramani.sista@fda.hhs.gov

To
frederick.debrito@novartis.com
cc

Subject
BLA 125319 - Canakinumab - Information Request (2)

Hi Fredrick
Please provide the following information:
In BLA 125319, you report safety data including serious adverse events reported to you as of September 12, 2008 from 10 ongoing studies. You do not provide the exposure data for these 10 ongoing clinical trials (safety reporting cutoff 12Sept08) from which these SAEs were reported. Submit the number of patients exposed and the extent of exposure (days) for each of these 10 ongoing studies employing the safety cutoff 12Sept08.
Please submit the information to BLA 125319 by noon (EST) February 11, 2009. Please confirm that you received this request and the one sent yesterday.
Thanks.
Ramani

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
10903 New Hampshire Avenue
Bld. #22. Rm # 3187
Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
Sent: Monday, February 09, 2009 3:51 PM
To: 'frederick.debrito@novartis.com'
Cc: Turner-Rinehardt, Sharon
Subject: RE: BLA125319 - Canakinumab -Information Request

Hi Fredrick
Thank you for the document. Although this document includes information on line listing, it lacks the summary tables and text summaries that were also requested. This additional information is very critical for adequate review of the application. Your responses need to contain, at minimum, tables with descriptive statistics on each of the parameters at baseline, at the end of part one with a specified imputation technique for any missing data, and during parts 2 and 3. The deadline for submitting this information will still be February 11, 2009.

Additionally we also require the following information:

In Study D2304, special assessments were reported for audiogram testing, neurological and ophthalmological assessments, and MRI of the brain. In the electronic submission, clarify if you defined the terms clinically insignificant abnormality and clinically significant abnormality for the reported special assessments. If not, provide any information about what constituted clinically insignificant abnormality and clinically significant abnormality. Please provide the requested information by noon (EST), February 11,2009.

Also, according to our conversation on February 2, 2009, you mentioned that you will be submitting the data supporting PAR (summaries) sometime today. Are you still on schedule to do that? If not we would recommend that you submit the entire available data as discussed on our call.

Please include Sharon Turner-Rinehardt on all your responses to me since I will be out of office all day tomorrow.

Thank you.

Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Friday, February 06, 2009 5:14 PM
To: Sista, Ramani V
Subject: Re: BLA125319 - Canakinumab -Information Request

Hi Ramani
Please find a document attached to this message that explains where the information requested by your reviewers in the below messagecan be found within the BLA. if the document is lacking in any way with regard to your request or you need more information, please let me know. You may also want to let your reviewers know that the attached document will be submitted via an amendment to the BLA (on Feb 9, 2009). In this submission, the document will contain operable links to the specific information in the BLA which your reviewers may would find easier to use to locate the required information.

Sista, Ramani V

From: Sista, Ramani V
nt: Friday, February 06, 2009 1:05 PM
.o: 'frederick.debrito@novartis.com'
Subject: BLA 125319 - Canakinumab - Information Request (2)

Hi Fredrick

Please provide the following information:

In BLA 125319, you report safety data including serious adverse events reported to you as of September 12, 2008 from 10 ongoing studies. You do not provide the exposure data for these 10 ongoing clinical trials (safety reporting cutoff 12Septo8) from which these SAEs were reported. Submit the number of patients exposed and the extent of exposure (days) for each of these 10 ongoing studies employing the safety cutoff 12Septo8.

Please submit the information to BLA 125319 by noon (EST) February 11, 2009. Please confirm that you received this request and the one sent yesterday.
Thanks.
Ramani

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ver Spring, MD 20993
el # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
nt: Thursday, February 05, 2009 1:44 PM
.o: 'frederick.debrito@novartis.com'
Subject: BLA125319 - Canakinumab -Information Request

Hi Fredrick,

Please provide the following Clinical information to allow for an adequate review of the application:

1. In Study D2304, you employed a 5-point scale for the Physician's global assessment of auto inflammatory disease activity (absent, minimal, mild, moderate and severe), assessment of skin disease and the measured levels of CRP and SAA. In additional, you employed the assessment of the following 8 items: skin disease, arthralgia, myalgias, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and other symptoms not related to autoinflammatory syndrome.

We are unable to identify the datasets for the additional 8 items in Study D2304 or text summaries, tables, or line listings summarizing the results for these parameters. If they are in the submission, please let us know where to find them. If they are not in the submission, please submit the text summaries, summary tables, line listings and datasets that include results for these parameters at baseline, at the end of Part 1, and during Part 2 and Part 3 of Study D2304. Please integrate this additional information into the already existing efficacy dataset, AEFFPAT.

Please submit the information to BLA 125319 by noon (EST) February 11, 2009.

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
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Silver Spring, MD 20993
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
nt: Thursday, January 15, 2009 8:15 AM
To: 'frederick.debrito@novartis.com'
Subject: BLA 125319 Canakinumab

Good Morning Dr. De Brito
Regarding the PK\PD information requested yesterday with tomorrow's deadline, we are willing to give you additional time. Please send in the requested information by 10 am (EST), January 21, 2009. We understand your concerns regarding planning for an AC, our team is working on it and we will let you know as soon as we come to decision.
Thank you.
Have a great day.
Ramani

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
nt: Wednesday, January 14, 2009 12:41 PM
:o: 'frederick.debrito@novartis.com'
Subject: BLA 125319 - Canakinumab - Information Request

Good Afternoon Dr. De Brito

Please provide the following PK and PD information to allow for an adequate review of the application:

Information Request to the Clinical Pharmacology group with regard to PK and PD of ACZ885.

With regard to ACZ885 population PK PD modeling report, provide all datasets used for PK PD model development and validation as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Please provide the requested information by 2 pm (EST) January 16, 2009.
Thank You.

Regards,
Ramani

mani Sista, PhD, RAC
.egulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Tel # (301) 796-1236 or 2280
Fax # (301) 796-9713
email: Ramani.Sista@fda.hhs.gov

Sista, Ramani V

From: Sista, Ramani V
Sent: Tuesday, January 13, 2009 6:34 PM
To: 'frederick.debrito@novartis.com'
Subject: RE: Resending Re: BLA 125319

Dr.De Brito:

In response to your questions:

a) Since the label information was already provided in the submission, this point does not apply to you.

b) Your information will be reviewed as scheduled.

c) Please be reassured that, we will contact you if any additional information is required. The Project Manager is the primary contact for this application, so names of the reviewers are not necessary.

d) We will notify you if an AC meeting is required for this application.

e) Although you have been interacting with Kathleen so far, I will be the main point of contact for this BLA. Please continue to contact Kathleen for questions\information with matters related to the IND.

Please contact me if you have additional questions. Have a good evening.
Thanks!!
Ramani

From: frederick.debrito@novartis.com [mailto:frederick.debrito@novartis.com]
Sent: Tuesday, January 13, 2009 4:08 PM
To: Sista, Ramani V
Subject: Resending Re: BLA 125319

Dear Dr Sista

Thanks you for your emails. I called yesterday and left a VM to introduce myself and ask you a few questions. I will try again today as I would like very much to establish a dialogue with you to provide what you may need to ease the review of the canakinumab BLA and thus avoid delays. Below I have a list of questions that I would be most grateful if you would answer.

a) In response to your communication of Dec 31, 2009 acknowledging receipt of the canakinumab BLA, and requesting submission of the label in the SPL format, please note that this was provided in the BLA submission.
b) The request for proprietary review of Novartis's proposed tradename 'Ilaris' will be submitted today as an amendment to the BLA as directed. Please could you comment whether we have lost any name review time as a result of making the submission together with the BLA?
c) Are there any initial questions or information needs that you or the reviwers may have at this early stage and which I could help with? Novartis would be more than happy to provide a presentation of the format and content of the BLA if this would help orient the reviewers. Please could you provide me with the names of the reviewers assigned to this BLA?
d) Please could you indicate whether a Scientific Advisory Meeting will be required? We have requested Priority Review which if granted will leave us with a limited time to prepare and hence the information is critical for us.
e) Please could you clarify what Kathleen Davies's role will be in this BLA review as I have interacted with Kathleen and continue to do so on IND matters associated with canakinumab e.g. EOP2 meeting for —

b(4)

Thanks and I look forward to speaking to you later today.
Best regards, Mit freundlichen Grüssen, Meilleures salutations,

Frederick DeBrito
Novartis Pharmaceuticals Corporation
PH

USEH
One Health Plaza, East Hanover, NJ 07936-1080
USA
Phone: +1 8627781274
Email : frederick.debrito@novartis.com

Sista, Ramani V

From: Sista, Ramani V
nt: Thursday, January 08, 2009 8:44 AM
: 'frederick.debrito@novartis.com'
Subject: BLA 125319 - Canakinumab: Trade name document request

Attachments: draft guidance for proprietary name submissions.pdf

Good Morning Dr. De Brito

Please refer to BLA 125319 for Canakinumab.

We note that the trade name was included in the original submission. The Agency released a new guidance for review of trade names where the documents for review must be a separate submission from the BLA. I have attached the guidance for your review. Please submit the trade name documents separately from the BLA (i.e., an amendment to the BLA) as per the guidance.
Please let me know if you have questions.

Ramani

draft guidance for proprietary...

Ramani Sista, PhD, RAC
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email: Ramani.Sista@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

STN: BLA 125319/0

BLA ACKNOWLEDGEMENT

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

DEC 30 2008

Attention: Frederick De Brito, PhD
Associate Director, Drug Regulatory Affairs

Dear Dr. De Brito:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Ilaris® (Canakinumab)

Date of Application: December 15, 2008

Date of Receipt: December 17, 2008

Our Submission Tracking Number (STN): BLA 125319/0

Proposed Use: Treatment of Cryopyrin Asssociated Periodic Syndrome (CAPS)

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/oc/datacouncil/spl.html. 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 format and content requirement of revised 21 CFR 201.56-57.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited 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
Therapeutic Biological Products Document Room
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.

If you have any questions, call me at (301) 796-1236.

Sincerely,

Ramani Sista 12/30/08

Ramani Sista, PhD, RAC
Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 21, 2008

TIME: 10:00 AM – 11:00 AM (EST)

LOCATION: Food and Drug Administration, Bldg. 22, Room 1315
10903 New Hampshire Ave., Silver Spring, MD 20993-0002

APPLICATION: IND 100,040

PRODUCT: ACZ 885

INDICATION: Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS)

SPONSOR: Novartis

TYPE OF MEETING: Pre-BLA, type B

MEETING CHAIR: Jeff Siegel, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

MEETING RECORDER: Kathleen Davies, MS, Regulatory Health Project Manager

FDA Attendees	Title
Bob A. Rappaport	Director, Division of Anesthesia, Analgesia and Rheumatology Products
Rigoberto Roca	Deputy Director (Rheumatology Team)
Jeff Siegel	Medical Team Leader
Rosemarie Neuner	Medical Reviewer
Ruth Cordoba-Rodriguez	Product Reviewer, Division of Monoclonal Antibodies
Marjorie Shapiro	Team Leader, Division of Monoclonal Antibodies
Adam Wasserman	Pharmacology/Toxicology Supervisor
Kathy Young	Pharmacology/Toxicology Reviewer
Srikanth Nallani	Clinical Pharmacology Reviewer
Yongman Kim	Biostatistics Reviewer
Jessica Benjamin	Regulatory Health Project Manager
Erin Elwood	Pharmacy Student
Kathleen Davies	Regulatory Health Project Manager

Novartis	Title
Thomas Jung	Global Program Head
Mona Wahba	VP, US Clinical Development and Medical Affairs
Xavier Gitton	Global Program Medical Director
Ralph Preiss	Global Program Medical Director
Chin Koerner	Executive Director, Regulatory Policy
Gerhard Krammer	Clinical Program Section Leader

Lorenz Meinel	Global Program Technical Director
Hermann Gram	Nonclinical Research
Paul Vancutsem	Senior Project Team Representative, Preclinical Safety
Albert Widmer	Program Statistician
Ken Somberg	VP, Global Drug Regulatory Affairs
John R Cutt	VP, US Drug Regulatory Affairs
Haimin Büergin-Liang	Global Program Regulatory Director
Xin Du	CMC, Director Drug Regulatory Affairs
Frederick De Brito	Associate Director, Drug Regulatory Affairs
Miguel Arguinzoniz	Senior Brand Safety Leader, Integrated Medical Safety

BACKGROUND
Novartis submitted a Pre-BLA meeting request for ACZ885 for the treatment of CAPS. Novartis has Orphan Designation and Fast Track Designation for this indication. Novartis intends to submit a BLA by the end of 2008.

Each of the Sponsor's questions is presented below in italics, followed by the Division's response in bold. A record of the discussion that occurred during the meeting is presented in normal font. The Division provided written responses to the firm on October 20, 2008.

CLINICAL

Question 1. *Does the Agency agree with the proposed content of the clinical module of the submission being acceptable for filing for the CAPS indication?*

FDA Response:
You are planning to submit a biological licensing application (BLA) for canakinumab as a treatment for the orphan indication of cryopyrin-associated periodic syndromes (CAPS), which includes Familial Cold-Induced Autoinflammatory Syndrome (FACS), Muckle-Wells Syndrome (MWS) ____ ____ ____ . In support of this broad indication you are proposing to submit clinical data generated from the Phase 1/2 open-label dose-titration study (A2102) in 34 patients with MWS, a pivotal Phase 3 controlled randomized withdrawal study (D2304) in 35 patients with MWS, and the Phase 3 open-label extension study (D2306) in 21 subjects with CAPS that includes patients with FCAS, MWS, or MWS with overlapping symptoms of NOMID. b(4)

As stated in our Pre-IND meeting with you on Jan. 18, 2006, registration of a product for the _ ____ CAPS indication would require data from one pivotal double-blind controlled trial for MWS and FCAS, ____ , as well as clear and robust evidence of a favorable risk/benefit ratio for these indications. Based on our review of the information contained in this meeting package, it appears that you may have clinical data to support the indications of MWS and FCAS ____ ____ Therefore, you can either file your BLA requesting the former two indications ____ ____ b(4)

However, whether the results from these studies will be sufficient to support these claims can only be determined after review of the data.

Discussion:
The Sponsor stated that their intent is to file a biologics license application for CAPS

b(4)

Post-Meeting Note:
We have reviewed your Oct. 24, 2008 submission that contained updated patient exposure data for canakinumab as a treatment for CAPS. According to the synopsis for Protocol ——— , you plan on enrolling a total of 30 patients with a diagnosis ——— into this open label study. We concur that safety and clinical outcome data on approximately 25-30 patients with ———

b(4)

Question 2. *Does the Agency agree that the clinical data provided in this submission supports a Target Product Profile proposal for "the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including FCAS, MWS, ——— is adults and children 4 years and older"?*

b(4)

FDA Response:
We refer you to our response to Question 1 regarding the proposed indication of FCAS, MWS . With respect to the age range, according to page 16 of your meeting package, you have data from 14 children and adolescents ranging in ages 4-17 years who have participated in the ongoing CAPS studies. Four of these pediatric subjects have been exposed to canakinumab for more than one year. However, only 5 patients who participated in the CAPS studies are between 4 and 12 years of age (one 4-year old, two 6-year old, one 7-year old and one 9-year old) as per page 31 of the meeting package. Additionally, you plan to submit the safety data collected from 22 children (age ranging 4-17 years) participating in the ongoing open label study in systemic onset juvenile idiopathic arthritis in support of pediatric dosing to age 4 years and older. Based on the relatively small number of pediatric subjects in the canakinumab database and their age distributions, we are concerned that you do not have adequate numbers of pediatric CAPS patients to support dosing down to age 4 and older for this orphan indication when you file your proposed BLA.

Discussion:
The Sponsor acknowledged that the data presented to the Division does not support a CAPS indication down to 4 years of age. The Sponsor asked for clarification as to whether their data did support an indication down to 12 years of age, similar to the Arcalyst® label. The Division stated that it was likely that the Sponsor's indication would include treatment of children as young as 12 years of age, but a final determination would be made upon review of the BLA. The Division further explained that the metabolism profile of children between the ages of 4 and 12 years is different than adults and therefore this indication cannot be extrapolated from adults to children aged 4 to 12 years. CAPS is also a chronic disease and these children will be exposed to the drug product for their lifetime. It is critical that the Sponsor collect long-term safety data in pediatric age groups. The ideal age groups are 4 to 7 years, 8 to 12 years and 12 to 17 years of age. The Division agreed that the Sponsor's pediatric patient numbers for ages 12 -17 are acceptable; however, the lower age ranges do not have adequate patient numbers to support dosing.

The Division acknowledged that the Sponsor's intent is to treat children as young as 4 years of age to address an unmet medical need and would like to work with the Sponsor to achieve this indication; however, at this time, the data is insufficient to grant this age range for this product. The Division agreed to provide to the Sponsor the number of pediatric patients that would potentially support an indication down to age 4 years as a post-meeting note.

The Division also conveyed to the Sponsor the criticality of having a complete submission at the time of initial submission. The Sponsor's proposal for its BLA in the meeting package included additional data at the 120-day safety update. The Division explained this is unacceptable and the Sponsor should not expect any additional data outside of the new safety data between filing and 120 days to be reviewed during the review cycle. All data that the Sponsor wants for support of its BLA must be submitted at the time of initial submission.

Post-Meeting Note:
Based on our review of your patient exposure spreadsheet from your Oct. 24, 2008 submission, you have a total of five pediatric patients with long-term exposure to canakinumab as follows: four between ages 4-7 and 1 between ages 8-12. In order to support pediatric dosing down to 4 years of age for a CAPS indication, you will need a total of 9-12 children between the ages of 4-12 years old. Although we understand the difficulties involved in recruiting children diagnosed with this rare syndrome, optimally the enrollment should include children representative of the entire age spectrum, including both the younger children (ages 4-7 years old) and the older children (ages 8-12).

Question 3. *Does the Agency agree with the proposed content of the Summary of Clinical Efficacy (SCE; CTD section 2.7.3) being based on the statistical methodology applied of the individual clinical trials?*

FDA Response:
The content of the SCE will include a summary of the efficacy results for each trial, individually. This is acceptable.

Discussion:
There was no further discussion on this point.

Question 4. *A) Does the Agency agree with the proposed content of the Summary of Clinical Safety (SCS; CTD section 2.7.4) being based on the statistical analysis of clinical trials?*

FDA Response:
According to your meeting package, the Summary of Clinical Safety section of your BLA submission will contain safety data generated from the studies A2102 (completed) and D2304 (Parts I and II completed; partial data from ongoing Part III). Due to differences in trial design, we concur that the safety data from these studies should be presented per study and not in pooled format in the SCS section of your application.

In order for us to appropriately assess canakinumab's safety profile for use as a chronically administered product in patients with CAPS, you will need to submit safety data collected from patients who have been treated continuously with canakinumab for a minimum of one year in your BLA application at time of filing. In view of this requirement, you should not file your application until you have collected safety data from Part III of study D2304 when all patients randomized to the canakinumab arm have been treated for one year postrandomization to canakinumab.

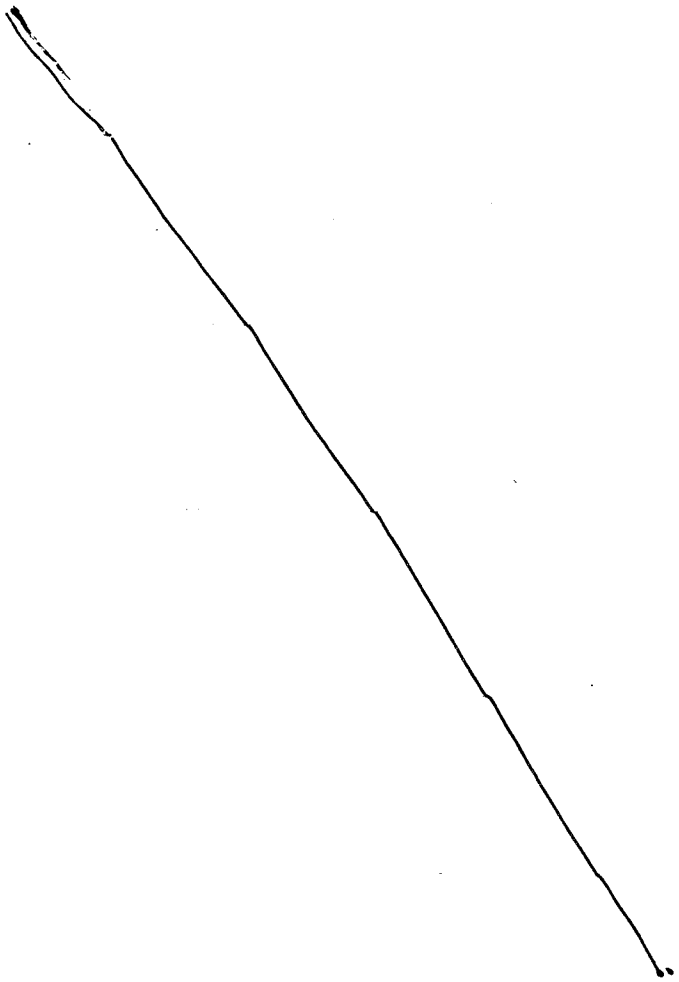
Discussion:
The Sponsor stated that it would have 31 patients exposed for 52 weeks, 6 patients for 2 years and 4 patients for 3 years at the time of the initial submission. At the 120-day update, the Sponsor will have 56 patients exposed for 52 weeks. The Division asked how many patients would be exposed for 52 weeks if the Sponsor were to wait for the conclusion of Part III of Study D2304. The Sponsor stated that there would be an additional 5 to 10 patients at most that would be treated for 52 weeks if the Sponsor were to wait for the conclusion of Part III of Study D2304. The Division clarified that the Sponsor has, in Study D2304, 31 patients currently with 52 weeks of data and could potentially have 36 to 41 patients at the conclusion of Part III. The Sponsor stated that, at the time of the intended December 2008 submission, there will be 15 patients with continuous 48 weeks data the have completed D2304 and 14 patients ongoing in the study who have not been exposed for 48 weeks. The Division explained that it is important to have continuous 1-year exposure data for the safety database versus exposure from various studies to total 1-year exposure. The Division asked the Sponsor to submit the data outlining exposure information for the patients described above for review so that the Division can make a determination as to whether there is adequate safety information to support this BLA.

Post-Meeting Note:
We refer to your patient exposure spreadsheet submitted October 24, 2008. You are proposing to submit a safety dataset containing a total of 31 CAPS patients with an overall exposure of 48 weeks to canakinumab. Approximately 6 of these patients will have been exposed for 96 weeks (2 years) and 4 patients will have been exposed for more than 144 weeks to the product. All things considered, given the rarity of this indication, these numbers appear to represent an acceptable database for assessing of safety of canakinumab in this population.

B) Does FDA have any comments at this time with Novartis's assessment of vertigo/dizziness/syncope events occurring in clinical studies with canakinumab?

FDA Response:
We have reviewed your safety assessment of vertigo/dizziness/syncope events contained in canakinumab's clinical trial safety database and have no comments to share with you at this time.

Discussion:
There was no further discussion on this point.



b(4)

Discussion:
There was no further discussion on this point.

Question 5. Does FDA agree with the proposed provision of case report tabulations?

FDA Response:
We note that you propose to submit datasets to support the population pharmacokinetic analysis. In this regard, to facilitate data review, we provide the following general comments:

1. **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**

2. **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).**

3. **A model development decision tree and/or table which gives an overview of modeling steps.**

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Discussion:
There was no further discussion on this point.

NONCLINICAL

Question 6. Does the agency agree that the preclinical safety package assembled for canakinumab is sufficient to support a BLA filing for an adult population?

FDA Response:
The nonclinical safety package described in the pre-BLA meeting package appears sufficient to support filing for an adult population. Note that the final study reports for the Segment I, II, and III reproductive toxicology studies in mice and marmosets will be needed by the time of the BLA submission. The adequacy of the nonclinical studies to support approval of the BLA will be determined upon review of the final study reports of all the nonclinical studies submitted in the BLA.

Discussion:
There was no further discussion on this point.

Question 7. *Does the Agency concur with Novartis that the additional study in juvenile mice with a surrogate antibody (01BSUR) will provide adequate nonclinical information to support the pediatric indication for canakinumab?*

FDA Response:
The juvenile mouse study with a surrogate antibody (01BSUR) appears to be adequate to support filing for the pediatric indication. Submission of this study report is needed at the time of the BLA. The adequacy of the data to support the safety of administration of ACZ885 in the pediatric population will be determined upon review of the juvenile mouse study results.

Discussion:
There was no further discussion on this point.

PRODUCT

Question 8. *Does FDA agree with the proposal to register a production range from ——— as the commercial production process?* b(4)

FDA Response:
Your proposal to register a production range from approximately ——— units as the commercial production appears appropriate, but it will depend on the thoroughness of your validation studies as well as adequate comparability data. b(4)

The proposed production range is acceptable based on:

1. **All scales use the same process on the identical equipment.**
2. ——— b(4)
3. **Lyophilization cycle and parameter settings are the same for different batch sizes.**

Discussion:
There was no further discussion on this point.

Question 9. *Does FDA agree that the physico-chemical comparability and clinical data package presented for drug product type B and C is sufficient to support the final commercial material (type D)?*

FDA Response:
The information provided in the pre-BLA package is insufficient to address this question. Neither the comparability protocol including pre-specified acceptance criteria nor the data

for the manufacturing change from type C to type D have been provided. The assessment of comparability from type C to type D will be a BLA review issue.

Discussion:
The Sponsor requested clarification as to whether it was acceptable to show comparability between product type C and product type D by demonstrating physico-chemical comparability similarly to the comparability performed for the change between product type B and product type C. The Division stated that the CMC comparability protocol performed in previous manufacturing changes is appropriate, but the specification requirements should reflect the advanced manufacturing and clinical stages (i.e., tighter specifications).

The Division also noted that if CMC assessment of the comparability data between type C and type D is acceptable, no additional nonclinical studies would be required for this manufacturing change. Final determination of the acceptability of comparability between type C and type D product will be determined after review of the data.

Question 10. Provided pre- and post-change products i.e., product C and D respectively are shown to be comparable:

a) Does the Agency agree that the supportive stability data (product C) can be used to set the shelf life (product D)?

b) Doe the Agency agree that Novartis can claim —— shelf life for DS and —— shelf life for DP based on the data in the submission? b(4)

c) Does the agency agree that three months before the action date of the BLA Novartis can still provide the update on registration stability data?

FDA Response:

a) Provided that the results from the physico-chemical comparability study between type C and type D support comparability, we agree that the combination of stability data from process C and D can be submitted, but expiration dating should be supported by real-time stability data of the proposed commercial DS and DP material.

b) A determination of DS and DP shelf life will depend on an assessment of the real time stability data of the proposed commercial DS and DP material submitted with the BLA.

c) We agree that three months before the action date of the BLA you may provide an update on registration stability data.

Discussion:
There was no further discussion on this point.

REGULATORY

Question 11. Does FDA agree with the proposed content and format of the eCTD (TOC provided in Appendix V) is adequate for filing this submission.

Proposed FDA Response:
We encourage you to contact the eCTD review team (esub@fda.hhs.gov) and to utilize the information provided on the FDA website for electronic submissions (http://www.fda.gov/cder/regulatory/ersr/ectd.htm).

From a CMC perspective, the proposed content and format of the eCTD product quality section looks appropriate; however, there is not sufficient granularity to assess the CMC data completeness.

1. **For example, in the case of the data presented in Table 7-15, the BLA should provide appropriate data that supports that the changes to the chromatography unit operations listed are properly validated.**

2. **Please include in your submission all comparability data from type A to type B, type B to type C, and type C to type D changes under the appropriate sections of DS and DP manufacturing development. Also, include comprehensive analytical validation and process validation in section 3.2R.**

3. **For additional information that should be included in the BLA, please see the additional CMC comment #1.**

Discussion:
There was no further discussion on this point.

Question 12. Does FDA agree with the proposed submission components for the 120 day safety update?

FDA Response:
According to your meeting package, you are proposing to include the following in the 120-day safety update:

1. **Final report of pivotal CAPS study D2304;**

2. **Additional interim data from CAPS study D2306;**

3. **First interim data from study** [redacted] **b(4)**

4. **Final reports of two RA studies (A2201 and A2207); and**

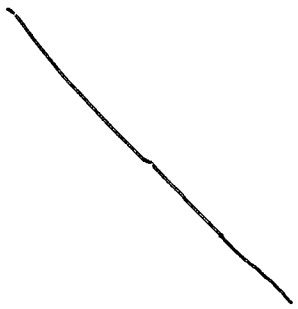
5. **Serious adverse events of other ongoing and completed Phase 1/2 studies or final study reports, if already available.**

The purpose of the 120-day safety update is to submit additional safety data that becomes available during the 120 days following submission of the BLA. The material you propose to include in your 120-day safety update appears to contain considerable extra information that does not meet the intention of the 120-day safety update. More importantly, your BLA should be complete at the time of submission. Therefore, material that is needed for review of the BLA should be included in the initial submission and not in the 120-day safety update. We recommend that your confine your 120-day safety update to additional safety data. Additional efficacy data will not be reviewed during that review cycle.

Discussion:
See Discussion under Question #1.

Question 13. Does the Agency have any comments on the potential risk identification/minimization concerns for canakinumab?

FDA Response:



b(4)

Discussion:
There was no further discussion on this point.

Question 14. Does FDA have any comments at this time on the Novartis's justification for Priority Review status for canakinumab in the treatment of CAPS?

FDA Response:
We have reviewed your justification for priority review status of your proposed BLA for canakinumab. Your rationale for this designation is based on the following:

1. **Difference in canakinumab's biological activity (i.e., it is a selective anti-IL β inhibitor) as compared to Rilonacept® and Anakinra® which inhibit both IL-1α and β activity which may make it less immunosuppressive and safer;**

2. **Improved convenience of administration due to its long half life;**

3. **Improved safety due to its low potential for immunogenicity and low incidence of administration site reactions;**

4. **Exposure data to support dosing in children as young as age 4 based on data collected in 5 patients between 4 and 12 years of age; and**

5. **Evidence of sustained disease control (i.e., approximately 90% response in patients with MWS treated for 1.8 years).**

Determination of priority review status is based on a product's ability to provide a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. We will determine the review status of your application at the time of filing; however, based on our review of your meeting package we are not convinced that you have provided a compelling rationale for priority review. There is no evidence to suggest that canakinumab's selective inhibition of IL-1β but not IL-1α improves its safety profile compared to the approved IL-1 inhibitor (rilonacept) for CAPS. There is no evidence that canakinumab has improved safety due to reduced immunogenicity compared to the approved IL-1 inhibitor (rilonacept) for CAPS. Additionally, there are no data to suggest that there are compliance problems associated with the weekly administration of rilonacept in patients with CAPS that would be ameliorated with canakinumab's less frequent administration schedule. The strongest rationale for eligibility of your proposed BLA as a priority review would be if you have data to support an indication of MWS and FCAS in children aged 4-12 years which represents an unmet medical need population. However, as discussed in our response to Question 2, it does not appear that you will have adequate numbers of children under the age of 12 years to support pediatric dosing, and thus may not qualify for this designation.

Discussion:
There was no further discussion on this point.

ACTION ITEMS:

1. [redacted] b(4)

2. The Sponsor will submit a breakdown of pediatric age groups and the Division will provide feedback as to the required numbers to gain an indication in these age groups.

3. The Sponsor understands that its BLA submission must be complete at the time of initial submission and should not expect any additional data submitted after this date to be reviewed during the review cycle.

4. The Sponsor will submit a breakdown of patients exposed to ACZ885 for one year for the Division's review prior to the BLA submission.

Additional Comments

Division of Manufacturing and Product Quality (DMPQ)

The CMC Drug Product part of the BLA should contain validation summary data to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance of the Submission Documentation for Sterilization Process Validation for Human and Veterinary Drug Products". Methods and validation information and data for the container closure integrity test should be submitted under Section 3.2.P.2.5.

Provide the following summary validation data and information under section 3.2.P.3.5:

1. **sterilizing filter validation;**
2. **sterilization and depyrogenation of sterile product contact equipment and components;**
3. **in-process hold times;**
4. **summaries from three media fill runs, including summary environmental monitoring data obtained during the media fills and a description of the environmental monitoring program; and**
5. **lyophilization process validation, if applicable.**

All facilities should be ready for inspection at the time of the BLA submission. Include a complete list of the manufacturing and testing sites in the BLA. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspection.

Discussion:
The Division reiterated to the Sponsor that all facilities information must be included in the BLA at the time of initial submission.

CMC

1. **The information provided in the pre-meeting package was too general for us to assess the completenesss of the CMC data that will provided in the BLA. As stated in the guidance for industry on IND meetings (http://www.fda.gov/cder/guidance/3683fnl.pdf), the CMC portion of the pre-BLA meeting is a critical interaction between the CMC review team and the sponsor to**

ensure the submission of a well-organized and complete BLA. You may wish to schedule a separate meeting with us if you have additional concerns or questions not addressed at this meeting. An incomplete Module 3 may be a refuse-to-file issue.

2. **The multiple manufacturing changes of the ACZ885 drug substance have shown some changes in the glycosylation distribution of each type of material. Please include in the BLA data that supports that Fc effector function is still irrelevant in the mechanism of action of canakinumab.**

Discussion:
There was no further discussion on the CMC additional comments.

CLINICAL

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the manual of policies and procedures (MAPP) 6010.3 at: http://www.fda.gov/cder/mapp/6010.3.pdf.

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. **Section 2.6 Other Relevant Background Information - important regulatory actions in other countries or important information contained in foreign labeling.**
2. **Section 5.3 Exposure-Response Relationships - important exposure-response assessments.**
3. **Section 7.1.6 - Less common adverse events (between 0.1% and 1%).**
4. **Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.**
5. **Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.**
6. **Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.**
7. **Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.**
8. **Section 7.1.8.3.2 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.**
9. **Section 7.1.8.3.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.**
10. **Section 7.1.9.1 – Overview of ECG testing in the development program, including a brief review of the nonclinical results.**
11. **Section 7.1.9.3. – Standard analyses and explorations of ECG data.**

12. **Section 7.1.16 – Overdose experience.**
13. **Section 7.4.2.1 - Explorations for dose dependency for adverse findings.**
14. **Section 7.4.2.2 - Explorations for time dependency for adverse findings.**
15. **Section 7.4.2.3 - Explorations for drug-demographic interactions.**
16. **Section 7.4.2.4 - Explorations for drug-disease interactions.**
17. **Section 7.4.2.5 - Explorations for drug-drug interactions.**
18. **Section 8.2 - Dosing considerations for important drug-drug interactions.**
19. **Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.**

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, please include a table in the original NDA for each of the completed Phase 3 clinical trials that has the following columns:

1. **Site number**
2. **Principle investigator**
3. **Location: City State, Country**
4. **Number of subjects screened**
5. **Number of subjects randomized**
6. **Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites**
7. **Number of protocol violations (Major, minor, definition)**

Common PLR Labeling Deficiencies

Highlights:

1. **Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]**
2. **The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]**

3. **The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].**
[See 21 CFR 201.57(a)(1)]

4. **The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]**

5. **The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).**

6. **For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].**

7. **The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:**

   "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

8. **Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.**

9. **Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).**

10. **A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].**

11. **Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]**

12. **The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]**

13. **A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.**

14. **A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]**

Contents (Table of Contents):

15. **The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]**

16. **The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]**

17. **Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.**

18. **Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.**

19. **When a subsection is omitted, the numbering does not change.**

20. **[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:**

    8.1 Pregnancy
    8.3 Nursing Mothers (not 8.2)
    8.4 Pediatric Use (not 8.3)
    8.5 Geriatric Use (not 8.4)

21. **When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents:**

    "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):

22. **Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).**

23. **Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.**

24. **Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.**

25. **The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]**

26. **Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]**

27. **Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]**

28. **The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.**

29. **There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.**

30. **The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.**

31. **Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.**

32. **If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.**

33. **Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.**

34. **Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.**

The Division requests the following for the submitted datasets:

1. **Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the Division which studies are most appropriate for integration.**

2. **The integrated safety dataset should include the following fields/variables:**

    a. **A unique patient identifier;**
    b. **Study/protocol number;**
    c. **Patient's treatment assignment;**
    d. **Demographic characteristics, including gender, chronological age (not date of birth), and race;**
    e. **Dosing at time of adverse event;**
    f. **Dosing prior to event (if different);**
    g. **Duration of event (or start and stop dates);**
    h. **Days on study drug at time of event;**
    i. **Outcome of event (e.g. ongoing, resolved, led to discontinuation);**
    j. **Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo);**
    k. **Marker for serious adverse events; and**
    l. **Verbatim term.**

3. **The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the verbatim term taken from the case report form.**

4. **See the attached mock adverse event data set (Page 16) that provides an example of how the MedDRA variables should appear in the data set. This example pertains only to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.**

5. **In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.**

6. **The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.**

7. **Provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.**

8. **Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: (1) Severe cutaneous adverse reactions SMQ; and (2) Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**

9. **The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**

10. **For the concomitant medication dataset, you should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**

11. **For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. The variable for the laboratory result should be in numeric format.**

12. **Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**

13. **In every dataset, all dates should be formatted as ISO date format.**

14. **Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.**

15. **All datasets should contain the following variables/fields (in the same format and coding):**

    a. **Each subject should have one unique ID across the entire BLA;**
    b. **Study number;**
    c. **Treatment assignment; and**
    d. **Demographic characteristics (age, race, gender, etc.).**

16. **A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. A listing should be provided of**

patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The BLA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.

17. **Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.**

18. **For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.**

19. **If you and/or the Division believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with the Division about the nature of the risks and the potential need for Risk Evaluation and Mitigation Strategies (REMS).**

20. **The HLGT and HLT level terms in this table are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.**

CDISC Data Requests to Sponsors
Quantitative Safety and Pharmacoepidemiology Group

The following comments relate specifically to the submission of CDISC Data. This information may be updated prior to your NDA submission date. Refer to http://www.fda.gov/oc/datacouncil/cdisc.html for additional information.

I. Safety Analysis Plan

In conjunction with the Statistical Analysis Plan which generally addresses statistical issues for efficacy, please include a Quantitative Safety Analysis Plan (QSAP). The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are

obtained, analyzed and presented appropriately. The Clinical Data Interchange Standards Consortium (CDISC) Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) outline the principles for data submission and analysis (www.cdisc.org).
At a minimum the Safety Analysis Plan should address the following components:

1. **Study design considerations (See: *FDA Guidance to Industry: Pre-Marketing Risk Assessment, http://www.fda.gov/CDER/guidance/6357fnl.pdf*);**
2. **Safety endpoints for Adverse Events of Special Interest (AERI);**
3. **Definition of Treatment Emergent Adverse Event (TEAE);**
4. **Expert adjudication process (Expert Clinical Committee Charter);**
5. **Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP);**
6. **Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered; and**
7. **When unanticipated safety issues are identified the QSAP may be amended.**

II. Study Data Tabulation Model (SDTM)

1. **The current published SDTM and Implementation Guide (SDTMIG) should be followed carefully; refer to the SDTMIG section on Conformance (3.2.3).**

2. **Domains:**

   a. **The additional domains listed below are not included in the current SDTMIG. Information on these domains may be obtained at www.CDISC.org and are expected to be published in the next versions of SDTM and SDTMIG. If applicable, use these domains:**

      i. **(DV) Protocol deviations;**
      ii. **(DA) Drug Accountability;**
      iii. **(PC, PP) Pharmacokinetics;**
      iv. **(MB, MS) Microbiology; and**
      v. **(CF) Clinical Findings.**

   b. **The following domains are not available with SDTM but may be included if modeled following the principles of existing SDTM domains:**

      i. **Tumor Information;**
      ii. **Imaging Data; and**
      iii. **Complex Inclusion/Exclusion Criteria.**

3. **Variables:**

   a. **All required variables are to be included.**
   b. **Expected variables should be included in all SDTM datasets.**
   c. **Variables (expected or permissible) for which no values will be submitted should be explicitly stated and discussed with the division.**

d. **A list of all Permissible variables that will be included and those that will not be included for each domain should be provided for review and discussed with the Division, if necessary.**
e. **A list and description of all variables that will be included in the Supplemental Qualifier dataset should be provided.**
f. **Do not include any variables in the SDTM datasets that are not specified in the SDTMIG.**

4. **Specific issues of note:**

   a. **SDTM formatted datasets will not provide replication of core variables (such as treatment arm) across all datasets.**
   b. **Only MedDRA preferred term and system organ class variables are allowed in the AE domain; however, all other levels of the MedDRA hierarchy may be placed in the SUPPQUAL dataset or an ADaM dataset.**
   c. **These issues can be addressed through the request for ADaM datasets.**

III. Analysis Data Model (ADaM)

1. **Specify which ADaM datasets you intend to submit.**
2. **Include a list of all variables (including sponsor defined or derived) that will be included in the ADaM datasets.**
3. **Discuss the structure of the datasets with the reviewing Division and specify it in the QSAP.**
4. **Within each adverse event analysis dataset, include all levels of the MedDRA hierarchy as well as verbatim term.**
5. **Indicate which core variables will be replicated across the different datasets, if any.**
6. **SDTM and ADaM datasets should use the same unique subject ID (USUBJID). Each unique subject identifier should be unique across the entire submission.**

IV. General Items

1. **Controlled terminology issues:**
   a. **Use a single version of MedDRA for a submission. It does not have to be the most recent version.**
   b. **We recommend that the WHO drug dictionary be used for concomitant medications.**
   c. **Refer to the CDISC terminology for lab test names.**
   d. **Issues regarding ranges for laboratory measurements should be addressed.**

Discussion:
There was no further discussion on the Clinical additional comments.

Attachment 1: Mock adverse event data set.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HGLT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 2 (SOC3)
01-701-1015	1	701	1015	MedDRA Version 8.0	Redness around application site	10003058	Application Site redness	Application Site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders	

Linked Applications	Sponsor Name	Drug Name
IND 100040	NOVARTIS PHARMACEUTICALS CORP	IND [redacted] ACZ885 b(4)

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/s/

KATHLEEN M DAVIES
12/03/2008