

Point 1a advises to only show mcg (250 mcg or 500 mcg) ~~\_\_\_\_\_~~ However, 1c then references expression of strength and removing it (in the colored dot on the vial label), but restating it differently somehow under the name.

If you have any comments from a CMC perspective and per previous discussions that we've had regarding the fill justifications, it would be helpful.

If you cannot comment and this is strictly a medical team issue, just let me know.

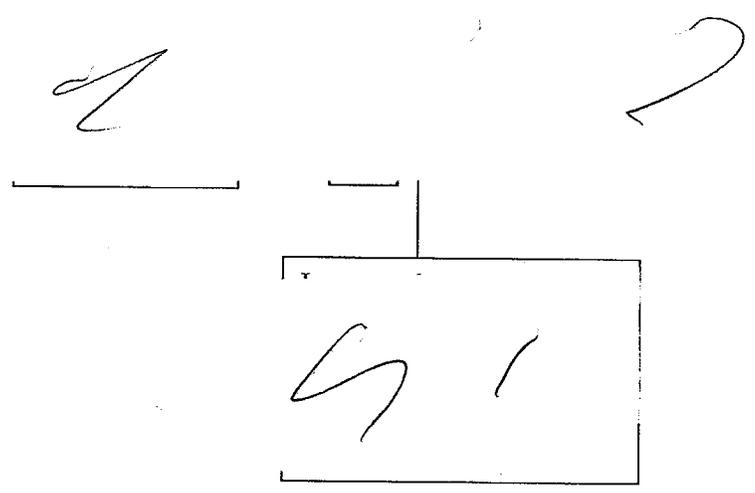
Thanks,  
Lisa

*Appears This Way  
On Original*

Clarification of points 1a and 1c

1. ~~\_\_\_\_\_~~ The strength should be in mcg  
(i.e. 250 mcg and 500 mcg).

2. Delete the dot containing the \_\_\_\_\_ strength, and increase the prominence of the strength below the name. See picture below.



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Amgen Telecon  
BLA 125268  
February 28, 2008  
2:00 p.m. – 2:30 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participant: David Frucht  
Amgen participants: Lisa Erickson, Bill Gargen, Steve Swanson, Vibha Jawa

The following issues were discussed:

1. FDA (DF) requested further information regarding Subject #302221 (Study 20030213). Specifically, FDA (DF) requested whether Amgen had determined whether romiplostim depleted anti-TPO responses.

Amgen: Amgen replied that this had not been performed, because the patient had low-level pre-existing antibodies that did not increase following romiplostim administration.

FDA: This response is acceptable. I (DF) indicated that, at this point in my review, I was inclined to support the position that the raw immunogenicity data supported the written conclusions.

2. FDA requested clarification in the 14 Feb 2008 response to our question concerning leachables/extractables as follows: "testing of the container system was comprised of USP<381>...". This would indicate that extractable testing was performed with the vehicle to be used f \_\_\_\_\_

Amgen: Amgen indicated that the vehicle \_\_\_\_\_

FDA: FDA stated that the vehicle should be been used unless there were technical reasons why it could not be used.

Amgen: Amgen stated that this topic would be discussed at a telecon on March 5<sup>th</sup> when the Amgen experts would be available. In addition, Amgen committed to providing initial non-compendial extractable testing data by the end of next week and perhaps prior to the telecom.

3. FDA requested that Amgen clarify its position on oceanic shipping of DP. Thus far, Amgen has not provided validation for this mode of transport.

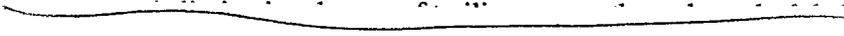
Amgen: Amgen will provide temperature and vibration data for trial runs with the transport configuration packaging to be used for DP. This will not involve actual romiplostim DP, but would be otherwise representative of actual shipments. These data will be discussed in the March 5 telecon with Amgen shipping experts.



- g. Bar codes should be added to both carton and container labels.
- h. Please indicate the purpose of the semi-circular pattern on the carton label, as it partially obscures critical information.
- i. The applicant name, address and license number should match exactly the applicant name on the 356h (Amgen Inc.) on the carton and container labels.

2. Package Insert Labeling:

- a. We recommend expressing the strength of the product consistently throughout the labeling to reduce the potential for confusion between mg and mcg.

- b. 
- c. 

3. The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. FDA believes the risks that have been identified can be addressed and mitigated prior to drug approval, and provides the recommendations above that aim at reducing the risk of medication errors.

4. Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage you to provide the FDA with medication error reports involving your marketed drug products regardless of adverse event severity.

It is requested that you promptly submit a complete response to the items enumerated above. Failure to respond in a timely manner or submission of a partial response may result in a determination that your application is not approvable. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Receipt of a major amendment during the last 90 days of the review period extends the review period by an additional 90 days. Review of the clinical, non-clinical, clinical pharmacology and CMC sections of your application is continuing.

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

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, at (301) 796-2095.

Sincerely,

A handwritten signature in black ink, appearing to read "Rafael Rieves".

Rafael Dwaine Rieves, M.D.  
Acting Director  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

**Moore, Florence O**

---

**From:** Moore, Florence O  
**ent:** Tuesday, February 26, 2008 5:01 PM  
**ro:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: Information Request

**Attachments:** RomiplastimRequests2-26-08.doc

Hi Mei-Ling,

Please disregard the first email and use this version instead. We actually need this information request turned around in 72 hours. Especially the MDS information.



RomiplastimRequest  
s2-26-08.doc...

Thanks,  
Florence

---

**From:** Moore, Florence O  
**Sent:** Tuesday, February 26, 2008 4:55 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** Information Request

Dear Mei Ling,

Please see attached FDA information request. Please provide these information request latest by COB 3/4/08 and if you could provide it earlier than that we would really appreciate it (needed for our presentation).

<< File: RomiplastimRequests2-26-08.doc >>

Thanks,  
Florence

*Florence O. Moore, M.S.  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2381  
Silver Spring MD 20903*

*Tel: 301-796-1423  
Fax: 301-796-9849*

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The requests listed below are priority items to potentially include in slides/we request a response within 72 hours, if possible:

- 1. Of the 271 patients exposed to Romiplostim, how many had thrombotic events reported? What were the preferred terms for events that occurred in more than one patient and how many patients had each event--for example, "DVT(n = 2), MI (n = 2), etc?*
- 2. Of the 271 patients exposed to Romiplostim, how many had "neoplasia" events reported? Exclusive of the two patients who had a neoplasia adverse event reported in the phase 3, pivotal studies, what were the preferred terms for events that occurred in more than one patient and how many patients had each event--for example, "multiple myeloma (n = 2), hepatic neoplasm (n = 2), etc.*
- 3. What are the follow-up platelet counts (if available) for patient number 31701 in Study 20010218 after week 79? This is the patient who developed a neutralizing antibody to Romiplostim.*
- 4. Overall, based upon the information contained within the 120 day safety update, we understand 392 subjects have been exposed to Romiplostim, including 271 patients with chronic ITP. Within the set of phase 3 ITP studies, one Romiplostim patient had an adverse event of "increased reticulin" on a bone marrow examination:*
  - a. Exclusive of the set of phase 3 ITP studies (overall n would exclude the 84 patients in the set of phase 3 studies; ie.  $271 - 84 = 187$ ), how many patients had increased reticulin reported on a bone marrow examination (whether as adverse event or not)?*
  - b. Exclusive of the set of phase 3 ITP studies, how many patients had increased reticulin reported as an adverse event?*
  - c. Our understanding of available follow-up information for patients who had increased reticulin detected on a marrow examination is:  
  
-2 patients had marrows "improved" with Romiplostim discontinuation; 3 others had "stable" reticulin in marrows upon follow-up;  
  
-2 patients remained on Romiplostim or only had the dose interrupted despite the increased reticulin in the marrow;  
  
-1 patient developed reticulin and collagen fibrosis that persisted through 1 year follow-up (based upon a bone marrow examination 1 year after the initial event)*
  - d. Are the preceding statements accurate? If not, please clarify. Do you have additional brief additional follow-up information for any other subjects who had increased reticulin detected in a marrow examination?*

5. *We are especially concerned about two subjects with serious adverse events cited in the 120 day safety update and request that you provide a description of these cases in your planned advisory committee presentation. The subjects are: 901002 (marrow fibrosis with splenomegaly) and 90502 (aplastic anemia). We would like to discuss these cases with you, as well as other presentation plans. Please be aware that we are not using the name "Nplate" at this time; the name is under reconsideration by our advertising/promotion staff.*

6. Please supply all available information regarding MDS/AML status including (but not limited to) dates of AML progression or AML type, treatment, cytogenetics, IPSS score, blast counts, bone marrow evaluations, and survival status regarding the following subjects (from the MDS study of 44 patients):  
1590401, 1591208, 1590116, 1590106, 1590114, 1590407, 1591206, 1591204.

7. Please also supply the information below within one week, if possible:

A. Case# 311131 (study 213):

Case# 311131, thirty seven y/o man who apparently developed myelofibrosis on Romiplastim (trichrome positive for collagen) and bone marrow did not improve months after discontinuation of study drug.

-supply the most recent information regarding the findings from the peripheral blood count and differential (especially blast count) or confirm that the most recent information is contained within the 120 day safety update. Please supply reticulocyte counts in "%" and absolute reticulocyte counts, not "g/dL

-supply the most results of the most recent bone marrow examination or confirm that the information within the 120 day safety update is the most recent information.

-supply the most recent update regarding treatment or confirm no additional information is available (beyond the 120 day safety update).

-what were the immunogenicity tests results for this patient during the treatment and follow-up period?

B. (case # US249761) (study 209): date of AE was October 24, 2007:

A 29 year old woman on study 209 (refractory ITP) with history of receiving Depo provera as an contraceptive developed multiple small pulmonary emboli 5 days after the first dose of Romiplastim ( baseline platelet count:17K increased to 459 on the day of AE: PE).

- Please provide a more recent update on this patient's status--specifically, is this patient currently receiving Romiplostim? Is she receiving other medications? Has

she experienced additional serious adverse events? If all available data are within the safety update, please confirm.

C. case # 90502 (study 209), the patient who developed aplastic anemia:

-what was the triggering event for the bone marrow evaluation that resulted in a diagnosis of aplastic anemia?

-can you identify which specific concomitant medications the patient was receiving at the time of the event that triggered the bone marrow that resulted in a diagnosis of aplastic anemia?

-explain the status of her breast cancer. Was she receiving any medication for this diagnosis, what type of medication and for what duration of time (temporal relationship to aplastic anemia)?

-please provide a summary table of the patient's hemoglobin, hematocrit, white blood cell count (differential) and platelet count (and reticulocyte count, if available) over the course of Romiplostim treatment and following Romiplostim discontinuation.

-if all available data are supplied within the 120 day safety update, please confirm. Specifically, were all available bone marrow results supplied?

8. Within the subset of patients with thrombotic events, what was the distribution of platelet counts at the time of the event?

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**Delasko, Jeanne**

*Jeanne Delasko*

---

**From:** Delasko, Jeanne  
**nt:** Tuesday, February 19, 2008 1:50 PM  
**o:** Moore, Florence O  
**Cc:** Burke, Laurie B; Rieves, Rafel; Araojo, Richardae; Kang, Kyong A  
**Subject:** GRMP Pilot: Comments BLA 125268 (Nplate)  
**Attachments:** JMDelaskoReview.02.19.08.doc

Hi Florence,

Here are SEALD's comments. MHT comments will be sent separately. I spoke to Chardae last week and she is actively working on this label since you consulted MHT when the application was submitted. Let me know if you have questions.

Jeanne



JMDelaskoReview.0  
2.19.08.doc (...)

7 Page(s) Withheld

       Trade Secret / Confidential

X Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative- 10

**Moore, Florence O**

**From:** Moore, Florence O  
**Sent:** Wednesday, February 13, 2008 4:16 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: Information Request

No problem. I will be waiting for it.

Thanks,  
Florence

---

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Wednesday, February 13, 2008 3:48 PM  
**To:** Moore, Florence O  
**Subject:** RE: Information Request

Hello Florence,

We will provide this information to you by COB for sure.  
Thanks for your understanding Florence,

Mei Ling

---

**From:** Moore, Florence O [mailto:florence.moore@fda.hhs.gov]  
**Sent:** Wednesday, February 13, 2008 12:41 PM  
**To:** Chang-Lok, Mei Ling  
**Subject:** RE: Information Request

When do you think we'll be getting this information?

Thanks,  
Florence

---

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Wednesday, February 13, 2008 3:34 PM  
**To:** Moore, Florence O  
**Subject:** RE: Information Request

Dear Florence,

My apologies but we still do not have this request done yet. We will provide it to you as soon as we can.  
Thank you,

Mei Ling

---

**From:** Moore, Florence O [mailto:florence.moore@fda.hhs.gov]  
**Sent:** Tuesday, February 12, 2008 3:45 PM  
**To:** Chang-Lok, Mei Ling

2/19/2008

**Subject:** Information Request  
**Importance:** High

Hi Mei-Ling:

please provide the information below to me by 3: 30 PM tomorrow (Wednesday 2/13/08).

- 1) **Were there any ITP patients who had an adverse event of increased blasts in the peripheral blood?**
- 2) **In the datapool of the two phase 3 studies in ITP, how many patients had a history of receiving only one prior ITP treatment (broken down by treatment group assignment)?**
- 3) **Overall, of the 44 MDS patients in the phase 1/2 study is the following statement a correct description of the data as of February, 2007--"5 patients had increases in blast cells; 2 documented as transient and 3 still being evaluated" ? If not, please accurately rephrase the statement.**
- 4) **Regarding subject 31701 in Study 20010218, is the following statement accurate: "At week 79, the platelet count was 37,000/mcL and no reports of adverse events were recorded between week 79 and the time of the final antibody test (four months after the detection of the neutralizing antibody)." If not, please accurately rephrase the statement.**

Thanks,  
Florence

*Florence O. Moore, M.S.*  
*Regulatory Project Manager*  
*FDA/CDER/ODDP/DMIHP*  
*Phone:301-796-2050*  
*Fax: 301-796-9849*

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**Moore, Florence O**

**From:** Moore, Florence O  
**Sent:** Wednesday, February 13, 2008 4:06 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: Information Request  
**Follow Up Flag:** Follow up  
**Due By:** Wednesday, February 20, 2008 12:30 PM  
**Flag Status:** Flagged

Hi Mei-Ling:

I just got this information request. Please provide a timeline (one week) when you think we can get this information. However the one sent yesterday is of priority. That needs to go into our BD due today.

Please provide the following information requested below:

1. Complete up-to-date subject data listings for all subjects in the 20050159 study, supply in the same format as was listed in Appendix 6 of the 20050159 clinical report.
2. All additional follow up information and patient status, if available, for subjects:

1591210  
1590603  
1591001  
1591102  
1591207  
1590602  
1590103  
1590402  
1590109

---

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Wednesday, February 13, 2008 3:34 PM  
**To:** Moore, Florence O  
**Subject:** RE: Information Request

Dear Florence,

My apologies but we still do not have this request done yet. We will provide it to you as soon as we can. Thank you,

Mei Ling

---

**From:** Moore, Florence O [mailto:florence.moore@fda.hhs.gov]  
**Sent:** Tuesday, February 12, 2008 3:45 PM  
**To:** Chang-Lok, Mei Ling  
**Subject:** Information Request

2/19/2008

**Importance:** High

Hi Mei-Ling:

please provide the information below to me by 3: 30 PM tomorrow (Wednesday 2/13/08).

- 1) **Were there any ITP patients who had an adverse event of increased blasts in the peripheral blood?**
- 2) **In the datapool of the two phase 3 studies in ITP, how many patients had a history of receiving only one prior ITP treatment (broken down by treatment group assignment)?**
- 3) **Overall, of the 44 MDS patients in the phase 1/2 study is the following statement a correct description of the data as of February, 2007--"5 patients had increases in blast cells; 2 documented as transient and 3 still being evaluated" ? If not, please accurately rephrase the statement.**
- 4) **Regarding subject 31701 in Study 20010218, is the following statement accurate: "At week 79, the platelet count was 37,000/mcL and no reports of adverse events were recorded between week 79 and the time of the final antibody test (four months after the detection of the neutralizing antibody)." If not, please accurately rephrase the statement.**

Thanks,  
Florence

*Florence O. Moore, M.S.*  
*Regulatory Project Manager*  
*FDA/CDER/ODDP/DMIHP*  
*Phone:301-796-2050*  
*Fax: 301-796-9849*

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2/19/2008

Amgen Telecon  
BLA 125268  
February 6, 2008  
3:00 p.m. – 3:30 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participant: David Frucht  
Amgen participants: Lisa Erickson, Bill Gargen, Steve Swanson, Vibha Jawa

The following issues were discussed:

1. On page 49 of section 5.3.5.3.1, Amgen states, "As expected, antibodies directed against AMG 531 (romiplostim) were not cross reactive with TPO", however, this was not clearly demonstrated. A clarification will be requested.

Amgen: This will be clarified in the future amendment regarding immunogenicity.

2. FDA requested an update on the timing of future submissions to the BLA:

a. Biacore cross-reactivity studies involving the two patients who developed both anti-TPO and anti-romiplostim responses.

Amgen: This will be formally submitted to the BLA by February 22<sup>nd</sup>.

b. The raw Biacore data for each of the 10 patients that developed anti-TPO responses.

Amgen: This will be formally submitted to the BLA by February 22<sup>nd</sup>.

c. Investigation of the \_\_\_\_\_ during the manufacturing process, as well as more detailed information regarding the preparation of the \_\_\_\_\_

Amgen: This will be formally submitted next week.

d. \_\_\_\_\_  
d. \_\_\_\_\_

Amgen: This will be formally submitted next week.

e. Verification that there are no product quality attributes that would be captured by \_\_\_\_\_ but not be the HPLC methods (e.g., smaller fragments or contaminating proteins).

Amgen: This will be formally submitted next week.

f. Justification for the amount of overfill for each dosage format and should validate that minimal and maximal prescribed doses can be consistently withdrawn from both dosage format vials.

Amgen: This will be formally submitted next week.

g. Justification that leachable studies are not required for the DS container.

Amgen: This will be formally submitted next week.

h. Data regarding the experimental determination of the extinction coefficient of romiplostim.

Amgen: This will be formally submitted next week.

i. Data regarding the source of \_\_\_\_\_

Amgen: This will be formally submitted next week.

Other point: Amgen will amend the BLA to state that they will provide appropriate validation data prior to oceanic shipping of DS or DP.

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10903 New Hampshire Ave. Silver Spring, MD 20993 (All regulatory mail should be addressed to the Central Document Room)

**Food & Drug Administration  
Office of Oncology Drug  
Products  
Division of Medical Imaging &  
Hematology Products**

# Fax

**To:** *Mei-Ling Chang-Lok, Ph.D., RAC*

**From:** Florence Moore, M.S.

**Fax:** 805-499-6296

**Fax:** 301-796-9849

**Phone:** 805-447-6543

**Phone:** 301-796-2050

**Re:** STN 125268/0 Information Request Letter **Pages:** 4

**Urgent**     **For Review**     **Please Comment**     **Please Reply**     **FYI**

• **Comments:** Please call 301-796-2050 to confirm that you have received this fax. Thanks.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

O Our STN: BL 125268/0

Amgen, Inc.  
ATTENTION: Mei-Ling Chang-Lok, Ph.D., RAC  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799

**FEB 05 2008**

Dear Dr. Chang-Lok:

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

We also refer to your January 23, 2008 submission to your application which requested an explanation on FDA's concern pertaining to Nplate and the use of a Medication Guide as a risk management tool for patients. We have the following comments:

We requested in our December 10, 2007, letter that you provide a Medication Guide instead of Patient Package Inserts because our preliminary review has determined that Nplate poses a serious and significant public health concern requiring the distribution of a Medication Guide. Nplate is a product for which patient labeling could help prevent serious adverse effects and inform the patient of serious risks relative to benefit that could affect their decisions to use, or continue to use, the product. Therefore, a Medication Guide is necessary for safe and effective use of this product.

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

If you have any questions, please contact the Regulatory Project Manager, Florence O. Moore, M.S., at (301) 796-2050.

Sincerely,

A handwritten signature in black ink, appearing to read "Rafel Dwaine Rieves". The signature is written in a cursive style with a large initial "R".

Rafel Dwaine Rieves  
Acting Director  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Center for Drug Evaluation and Research

**Moore, Florence O**

---

**From:** Moore, Florence O  
**Sent:** Tuesday, February 05, 2008 5:00 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** Information Request IND 10205/0266

**Follow Up Flag:** Follow up  
**Due By:** Friday, February 08, 2008 3:30 PM  
**Flag Status:** Flagged

Hi Mei Ling,

We have reviewed your amendment 0266 to IND 10205 containing an initial safety report. Please provide the information below for this patient:

- a detail report of the bone marrow exam
- peripheral blood smear
- history of splenectomy (yes or no?)
- patient condition
- have immunogenic responses to romiplostim and/or TPO been checked recently for this patient.

Please add the information requested above to the items being submitted this Friday, 2/8/08. Please call or email me if you have any questions regarding this information request.

Thank you,  
Florence

*Florence O. Moore, M.S.  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2381  
Silver Spring MD 20903*

*Tel: 301-796-1423  
Fax: 301-796-9849*

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## RECORD OF TELEPHONE CONVERSATION

BLA: 125268

Today's date: January 31, 2008

Speakers: Amgen: Susan Boynton  
FDA: Dwaine Rieves

### **FDA Participants:**

Dwaine Rieves, MD, CDTL/Acting Director  
Kathy Robie-Suh, MD, PhD, Clinical Team Leader  
Faranak Jamali, MD, Clinical Reviewer  
Jyoti Zalkikar, PhD, Biometrics Team Leader  
Richard Chen, PhD, Biometrics Reviewer  
Hong Zhao, PhD, Clin Pharm Team Leader  
Angela Men, PhD, Clin Pharm Reviewer  
Tushar Kokate, PhD, Pharm/Tox Reviewer  
Florence Moore, MS, Regulatory Project Manager

### **Sponsor Participants:**

Susan Boynton, Executive Director, Regulatory  
Sean Harper, Sr. Vice President, Clinical Development  
George Dimitrov, Executive Director, Safety  
Mark Rutstein, Director, Clinical  
Steven Cha, Director, Safety  
Reggie Kelly, Director, Clinical  
Christine Dale, Sr. Manager, Medical Writer  
Matthew Guo, Sr. Manager, Biostat  
David Chang, Vice President, Clinical  
Roy Baynes, Vice President, Clinical  
Dietmar Berger, Executive Director, Clinical  
Monica Batra, Director, Regulatory  
Mei Ling Chang-Lok, Sr. Manager, Regulatory  
Yow-Ming Wang, Principal Scientist, PKDM  
Wende Davis, Scientific Director, Toxicology

Amgen requested this telephone conversation (t-con) to discuss their proposed table of contents (TOC) for their briefing document and presentation for the upcoming Oncology Drug Advisory Committee (ODAC) in March. Amgen requested this t-con to address any questions FDA may have regarding their proposed TOC.

The following FDA concerns and recommendations below wear related to Amgen:

1. In addition to discussion of your ~~\_\_\_\_\_~~ and other topics, we would like to give you an update of our major concerns to date, regarding Nplate. These concerns are all tentative and may change but we anticipate they may be especially relevant for the upcoming advisory committee discussion.
2. We are especially concerned about the apparent association of Nplate with reticulin fibrosis and malignancies. Consequently:
  - a. We are considering the need for some form of restricted distribution program that will help ensure the collection of long term follow-up information from all exposed patients and also minimize the potential for unsafe "off label" use. We have conceptualized some form of registry format in which patients and physicians would need to provide consent for long term follow-up before release of the product and all patients would be tracked for several years during use of Nplate and for resolution or stabilization of any complications that cause termination of Nplate therapy. We are generally considering a follow-up program that is not intensive but focuses upon the detection of malignancy/signs of malignancy, immunogenicity and marrow fibrosis. We encourage you to consider this type of need and invite you to comment upon the concept.
  - b. We are also concerned that the proposed recommendation to maintain platelets ~~\_\_\_\_\_~~ 50,000 ~~\_\_\_\_\_~~ may result in excessive risks for patients. We have conceptualized a recommendation that the goal of Nplate therapy should generally be one of maintaining platelets at a sufficient level to avoid bleeding or perhaps a minimal level of 50,000 with dose reductions considered for patients who consistently maintain platelet counts considerably above this level (for example, 100,000/mcL). We invite you to comment upon this consideration; we are especially interested in any analyses you have performed that would address the targeting of solely the lower bound (50,000 /mcL) for the dose titration goal.
  - c. We anticipate that our advisory committee discussion will focus upon the safety aspects of Nplate/the limited knowledge of long term toxicity/the dosing considerations/the risk management plan and potential consideration of some form of program that will ensure collection of long term follow-up for exposed patients and minimize unsafe use of the product.

Other topics:

3. The proposed label does not clearly indicate how often platelets should be assessed during Nplate therapy and following discontinuation of Nplate. What are you recommending? The proposed label seems to indicate that you are recommending to " ~~\_\_\_\_\_~~ "

\_\_\_\_\_

\_\_\_\_\_ Please propose specific recommendations; the label should provide explicit instructions.

4. The proposed label does not seem to clearly indicate how physicians should monitor patients for the development of reticulin fibrosis. The warning text provides minimal information that notes, \_\_\_\_\_  
9 \_\_\_\_\_ ? What laboratory tests are you recommending to monitor for this fibrosis and how often should the tests be performed? The label should provide specific instructions.
5. Provide data including follow ups on the 4 patients who developed marrow fibrosis. FDA would like to know how often and how the these patients were monitored and what happened to the patients after they discontinued treatment with the product.

Amgen indicated they will quickly address these concerns but submitting the information requested during these t-cons and will also provide a revised labeling to address the concerns raised by the FDA regarding the label. Amgen stated they will provide proposals and available data for FDA to consider regarding the restricted distribution proposal and will address these proposals and data in the briefing documents for the March ODAC meeting.

Amgen also informed FDA that they will be submitting the 120 day safety report to the BLA around February 22, 2008 after the briefing documents for the March ODAC meeting are due. However, Amgen will address any new information from the 120 day safety update in their presentation for the AC meeting. Amgen stated that the MDS data will also be provided in the 120 day safety update.

Lastly but not the least, Amgen informed FDA that they have a publication coming out in the Lancet (journal) and will provide this article to the FDA. The publication will include the integrated analysis data for the romiplostim pivotal clinical trials.

**Moore, Florence O**

**From:** Frucht, David  
**Sent:** Wednesday, January 23, 2008 5:39 PM  
**To:** 'Erickson, Lisa'  
**Cc:** Moore, Florence O  
**Subject:** RE: Draft responses for

---

Hi Lisa,

After further thought, although the validation that appropriate amounts of romiplostim can be withdrawn from the vials overlaps with the clinical review, the justification for the levels of the DP overfills is primarily a CMC concern. In advance of any clinical team inquiries, I was wondering if you could provide this justification (i.e., how were the specific fill amounts determined for each of the dosage formats?) .

Thanks,

David

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**From:** Erickson, Lisa [mailto:[lisae@amgen.com](mailto:lisae@amgen.com)]  
**Sent:** Wednesday, January 23, 2008 5:31 PM  
**To:** Frucht, David  
**Subject:** Draft responses for

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David,

As discussed, I'll be sending you DRAFT responses on the above items. Since it is later your time, I'll be sending these via e-mail tonight.

Also, for the stability amendment, I will bring you a paper copy of the update as it will be ready here on Friday. It will get submitted to the e-submission next week.

If you have questions, let me know. Otherwise we will discuss next week in Colorado.

Lisa

Amgen Telecon  
BLA 125268  
January 22, 2008  
2:00 p.m. – 2:50 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participant: David Frucht, Kathleen Clouse  
Amgen participants: Lisa Erickson, Bill Gargen, Steve Swanson, Vibha Jawa

The following issues were discussed:

(1) Amgen clarified that 2/204 patients developed immunogenic responses to both romiplostim and TPO, while 8/204 patients developed immunogenic responses to only TPO. Steve Swanson commented that the responses that have been observed were just above the threshold and represented approximately 1 mcg/mL of specific antibody.

FDA: Dr. Frucht requested the following information: location of the immunogenicity data for individual patients.

Amgen: This can be accessed from section 5.3.5.3.1, p. 42, which has links to the individual study reports. The subjects that developed antibodies to both romiplostim and TPO were in the Phase II extension study.

FDA: Dr. Frucht requested the raw Biacore data for each of the 10 patients that developed anti-TPO responses. All time points should be submitted.

Amgen: This will be submitted in 1-2 weeks.

FDA: Dr. Clouse asked whether patients that had developed anti-TPO responses were still receiving romiplostim

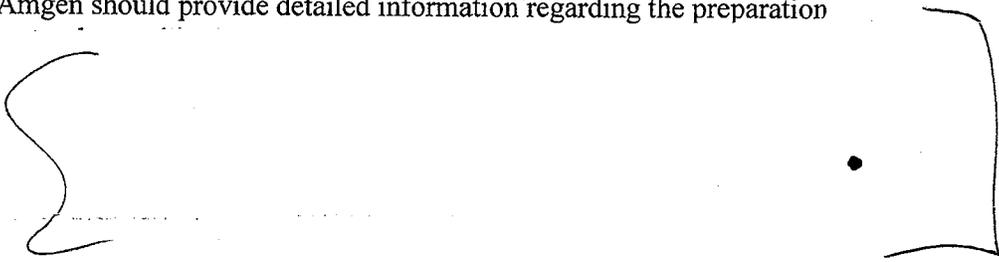
Amgen: Amgen indicated that the low levels of anti-TPO antibodies would not indicate that romiplostim should be stopped.

FDA: Dr. Frucht inquired when the Biacore cross-reactivity studies involving the two patients with both TPO and romiplostim responses would be completed. These should be completed by mid-February.

Amgen: Amgen will attempt to have these data submitted by mid-February.

FDA: Dr. Frucht then discussed the table sent by Amgen regarding outstanding questions that had been introduced during the past meetings. Dr. Frucht detailed the outstanding issues as follows:

1. Amgen should provide detailed information regarding the preparation



Amgen: A draft report will be submitted by the end of the week covering issues 1 to 3. They propose that the need for #4 will be abrogated by these data.

2. Strict reject limits should be adopted for

Amgen: A draft response will be submitted by the end of the week.

3. Confirmed stability update will be submitted in late January.

4. Amgen is proposing to drop the assay as a DS release test, stating the HPLC methods are redundant with this assay. Amgen should indicate if there are any product quality attributes that could be captured by , but not be the HPLC methods (e.g., smaller fragments or contaminating proteins).

Amgen: A draft response will be submitted in 1-2 weeks.

5. Amgen should provide a justification for the amount of overfill for each dosage format and should validate that minimal and maximal prescribed doses can be consistently withdrawn from both dosage format vials.

Amgen: Amgen will await the inquiry from the clinical team. They have CMC information gathered, but are awaiting the clinical inquiry before submitting the data.

FDA: Dr. Frucht commented that he will be in contact with the clinical team regarding this point.

Additional questions:

FDA: Dr. Frucht asked whether leachable testing had been done for final DP in the proposed container.

Amgen: These data are not in the submission. Amgen will check into this.

FDA: Dr. Frucht asked for more information regarding DP shipping. Amgen states in the submission that they will not be performing shipping validation.

Amgen: Amgen clarified, as stated in the text, "The bottles are packaged for shipping on dry ice per qualified transport packaging configurations (TPC)". Qualification of the TPC involved demonstration that DS can be shipped under specified shipping conditions. This can be examined during the inspection, along with the allowable shipping parameters.

FDA: Regarding DP shipping validation, the allowable shipping parameters (duration, allowable temperature range, etc.) are not indicated. In addition, no data is provided demonstrating that oceanic shipment will meet these requirements. Finally, it is not indicated what will be done when there is an excursion.

Amgen: Amgen will provide these data within 1-2 weeks.

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**Memorandum**

**From:** Florence O. Moore, M.S.   
**To:** File: STN 125268/0  
**Subject:** Mid-Cycle Meeting Summary  
**Sponsor:** Amgen, Inc.  
**Product:** Nplate™ (romiplostim)  
**Date, Location, & Time of Meeting:** January 17, 2008  
WO Rm 1419  
1:00 p.m. – 2:30 p.m.

**Purpose:**

Midcycle meeting for BLA to support the use of romiplostim which has been the subject of IND 10205 for the treatment of thrombocytopenia in adult patients with chronic Immune (idiopathic) Thrombocytopenic Purpura (ITP)

**Summary:**

The review team presented their review status and discussions followed.

**Administrative**

- Introduction of primary reviewers and team leaders
- Timeline/Relevant Milestones
  - Stamp Date: October 23 2007
  - Filing Date/ Day 74 Letter: December 10, 2007
  - ODAC Meeting: March 12, 2008
  - Review Completion Goal Date: March 23, 2007
  - PDUFA Goal Date: April 23, 2007

- **CMC**
  - DMA
  - DMPQ/TFRB
- **Non-Clinical**
- **Clinical Pharmacology-**
- **Biostatistics**
- **Clinical**
- **Oncology**

**Conclusion:**

The meeting concluded with the following items related to risks that need to be followed upon:

- Data on withdrawal/discontinuation of product, lower dose
- Restriction on use
- Dosing and long term use of the product

**Review Committee:**

Clinical –Faranak Jamali  
Clinical –John Lee  
CMC – David Frucht  
P/T – Tushar Kokate  
PK – Angela Men  
DMPQ- Patricia Hughes  
DMPQ- Susan Laska  
Stats – Richard Chen  
RPM – Florence Moore

OSE/DDRE- Betsy Scroggs  
DSI- Karen Storms  
DDMAC- Sean Bradley  
OSE/DMETS- Richard Abate  
OSE/DSRCS- Sharon Mills  
OSE/RisKMAP- Suzanne Berkman  
IO/SEALD- Richardae Arajo

Team Leaders

CDTL- Dwaine Rieves  
Clinical – Kathy Robie Suh  
CMC – Katherine Clouse  
DMPQ- Gilbert Salud  
P/T – Adebayo Lanionu  
PK – Hong Zhao  
Stats – Jyoti Zalkikar  
RPMTL –Alice Kacuba  
OSE/DMETS- Kelly Taylor  
OSE/DDRE- Susan Lu

Division Heads

DMIHP- Dwaine Rieves  
DMA – Kathleen Clouse

**Other FDA Representatives:**

See attached Meeting Attendance List

STN 125268/0 Midcycle Meeting

Sponsor: Amgen

Product: Nplate (romiplostim)

**Mid-cycle Meeting AGENDA**

**Product:** Nplate™ (romiplostim)

**Indication:** Treatment of thrombocytopenia in adult patients with chronic Immune (idiopathic) Thrombocytopenic Purpura (ITP)

**Review Status**

**Administrative**

5 minutes

- Introduction of primary reviewers and team leaders
- Timeline/Relevant Milestones
  - Stamp Date: October 23 2007
  - Filing Date/ Day 74 Letter: December 10, 2007
  - ODAC Meeting: March 12, 2008
  - Review Completion Goal Date: March 23, 2007
  - PDUFA Goal Date: April 23, 2007

• **CMC**

- DMA David Frucht 10 minutes
- DMPQ/TFRB Patricia Hughes/Susan Laska 10 minutes

- **Non-Clinical** Tushar Kokate 10 minutes

- **Clinical Pharmacology-** Angela Men 10 minutes

- **Biostatistics** Richard Chen 10 minutes

- **Clinical** Dwaine Rieves 10 minutes

- **Oncology** Steven Lemenary 10 minutes

- Questions and Discussions** All 15 minutes

# MEETING ATTENDANCE LIST

Internal Mid-Cycle Meeting (STN 125268/0)

Date: 1/17/08

Time: 1-2:30 PM

Room 1419

NAME- Please Print	Office/Division
Xuan Who Chen	OB/DBV
Florence Moore	DOOP/DMIHP
Chardae An	MHT
Leyla Sahin	MHT
David Frucht	DMA/OBP/OPS/CDER
Palma F. Hughes	OC/DMPA/BHCT
Sharon Miller	OSE
Angela Men	ODP/OTS
Hong Zhao	ODP/OTS
Bill Pascoe	DBOP
NAM RANNAN	ODP, OTS, CDER
Jeorge Shasha by	
Andrew Smyth by	DMFHP
Farvank Samant	DMIHP
Bayo Lanyore	DMIHP
Aloka Chakravarty	OB/DBV
Luzanne Beckman	OSE/RMP
(L. O. S.)	
Stacy Lany	OBOP
Karen Ross	DOOP
Kathy Robin-Suh	DMIHP
Betsy Soroga	OSE/DDRE
Pete O'Neill-Nella-tram	OSE/DDRE
Kathleen Wong	OBP/DMA
Elekta Papadimitriou	OND/SEAD
Kathryn Gaines	DOOP/CO
Rick Pascher	

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Amgen Telecon  
BLA 125268  
January 16, 2008  
2:00 p.m. – 2:30 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participant: David Frucht  
Amgen participants: Lisa Erickson, Bill Gargen

The following issues were discussed:

(1) As was discussed in the last telecon, \_\_\_\_\_  
Amgen was asked to provide an update on the status of the assessment \_\_\_\_\_

Amgen: Amgen stated that they have received more detailed information regarding the manufacture of \_\_\_\_\_ (the manufacturer). They are using these data to prepare a risk assessment regarding the potential for \_\_\_\_\_ contaminants that should be completed by the time of the facility inspection in late January. They also stated that this risk assessment will involve quantitative assessments.

(2) Amgen was requested to provide the rationale for not adopting in-process \_\_\_\_\_ testing. Amgen was informed in the December 12<sup>th</sup> telecon that it is DMA's general practice to require strict reject limits for in-process \_\_\_\_\_ testing. At this time, Amgen stated that this will be discussed further internally at Amgen. FDA asked for an update on the progress of these deliberations

Amgen: Amgen stated that there is inconsistency across its products regarding this issue. Embryl, for example, has a "contact FDA" specification for \_\_\_\_\_. They report that panitumumab has no strict reject limits for \_\_\_\_\_. Also, if \_\_\_\_\_ reject limits were to be adopted, Amgen requested to know if all FDA will require if all unit operations will require these limits.

FDA: Dr. Frucht stated that he will discuss these points internally and respond later.

(3) Please indicate the method through which the extinction coefficient for romiplostim was calculated.

Amgen: We have provided a paper referencing how the theoretical calculation was made.

FDA: FDA requests that the extinction coefficient be determined experimentally.

Amgen: Amgen stated that these data may exist already and, if so, will be submitted. If it has not been performed, Amgen will perform these studies.

(4) Amgen should provide more data regarding the \_\_\_\_\_ source used to produce the \_\_\_\_\_ and used in the DS manufacturing process.

Amgen: This \_\_\_\_\_ For this reason, Amgen believes the product is at low risk. In addition, Amgen will provide data detailing the rigorous processing of this component, which meets \_\_\_\_\_ standards.

FDA: This response is appropriate

(5) Amgen is proposing to drop the \_\_\_\_\_ assay as a DS release test, stating the HPLC methods are redundant with this assay. Amgen should indicate if there are any product quality attributes that could be captured by \_\_\_\_\_ but not be the HPLC methods (e.g., smaller fragments or contaminating proteins).

Amgen: Amgen is still collecting this information and will respond at a later date.

(6) Amgen should provide a justification for the amount of overfill for each dosage format and should validate that minimal and maximal prescribed doses can be consistently withdrawn from both dosage format vials.

Amgen: Amgen will provide a response to this request at a later date.

Other discussion points:

(7) Amgen requested FDA meeting notes from the January 15<sup>th</sup> telecon regarding mechanism of action and immunogenicity.

FDA: The distribution of these notes will be coordinated by the RPM, Florence Moore.

Amgen Telecon  
BLA 125268  
January 15, 2008  
2:00 p.m. – 2:30 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participants: David Frucht (Product Quality Reviewer), Dwaine Rieves (Acting Clinical Division Director), Tushar Kokate (Pharmacologist), Faranak Jamali (Clinical Reviewer), Adebayo Lanionu (Supervisory Pharmacologist), Kathy Robie Suh (Medical Team Leader)

Amgen participants: Lisa Erickson (Regulatory Affairs, CMC), Francesco Galimi (Hematology Research), Dietmar Berger (Global Clinical Development), Vibha Jawa (Clinical Immunology), Naren Chirmule (Clinical Immunology), Susan Boynton (Regulatory Affairs), Monica Batra (Regulatory Affairs), Wende Davis (Toxicology)

The following issues were discussed:

Introduction (David Frucht, FDA)

This meeting was organized to address CMC questions regarding the mechanism of action of romiplostim. Since the mechanism of action and immunogenicity are cross-disciplinary issues, other members of the FDA romiplostim review team were invited to participate. The specific questions are as follows: (1) does romiplostim binds to the same site on the TPO receptor as does TPO, and (2) has Amgen identified the epitope where it binds?

In addition, Amgen requested to discuss immunogenicity, as this topic relates the questions that above-mentioned questions. It is notable that 4.9% of subjects receiving romiplostim have developed immunogenic responses against endogenous TPO, albeit non-neutralizing. That leads to the next question, if the identical receptor site were to bind TPO and romiplostim, could not an antibody cross-react as well? Is this why 4.9% of patients receiving romiplostim have developed both anti-romiplostim and anti-TPO antibodies? This is an important question, as TPO is a non-redundant cytokine.

Amgen: Amgen confirmed that TPO and romiplostim compete for the TPO receptor, but they do not have additional data regarding whether the binding epitope for romiplostim is the same as that of TPO. With regard to whether immunogenic responses to romiplostim and TPO were cross-reactive, Amgen replied that validation of the Biacore immunogenicity screening assay demonstrated that neither romiplostim nor TPO inhibit the detection of antibodies to the other.



(2) Dr. Frucht mentioned that the figure legends for report #102177 were labeled incorrectly.

Amgen: noted

(3) Dr. Frucht confirmed with Amgen that the abbreviation PBPC mentioned in study report # PP01104 designates "peripheral blood progenitor cells".

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**Moore, Florence O**

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**From:** Hughes, Patricia  
**Sent:** Tuesday, January 15, 2008 7:45 AM  
**To:** 'Erickson, Lisa'  
**Subject:** RE: BLA 125268  
**Attachments:** 125268.dp.IR.1-15-08.doc

Lisa,

thank you. Please see attached word document for the information requests. If you have any additional questions, please don't hesitate to call or e-mail me.

Thank you.

Patricia

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**From:** Erickson, Lisa [mailto:[lisae@amgen.com](mailto:lisae@amgen.com)]  
**Sent:** Tuesday, January 15, 2008 6:55 AM  
**To:** Hughes, Patricia  
**Subject:** RE: BLA 125268

Patricia,  
e-mail is fine - please send your requests as soon as you can so we can address them.  
Lisa

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**From:** Hughes, Patricia [mailto:[Patricia.Hughes@fda.hhs.gov](mailto:Patricia.Hughes@fda.hhs.gov)]  
**Sent:** Tuesday, January 15, 2008 3:53 AM  
**To:** Erickson, Lisa  
**Subject:** BLA 125268

Lisa,

I received your phone message this morning and thank you for providing me with your contact information. I have been reviewing the drug product sterility ~~processing~~ processing information in part 3.2.P of the BLA and I have some additional questions and information requests. Please let me how you would like this information communicated to you (Fax or e-mail).

Thank you for your prompt response.

Patricia

2   Page(s) Withheld

  X   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Thursday, January 10, 2008 1:49 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** PI Information

Hi Mei-Ling,

These are the minor editorial changes I discussed with you today regarding the PI. If you can make these changes before sending us your updated PI, it would be most appreciated. The rest of the comments regarding the container and carton labels and PI will be coming to you shortly once it is vetted through the review team.

Package Insert Labeling:

b. We recommend expressing the strength of the product consistently throughout the labeling to reduce the potential for confusion between mg and mcg.

c. \_\_\_\_\_

Thanks,

*Florence O. Moore, M.S.  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2381  
Silver Spring MD 20903*

*Tel: 301-796-1423  
Fax: 301-796-9849*

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Amgen Telecon  
BLA 125268  
January 8, 2008  
2:00 p.m. – 2:30 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participant: David Frucht, Kathleen Clouse  
Amgen participants: Lisa Erickson, Bill Gargen

The following issues were discussed:

(1) \_\_\_\_\_ Amgen was queried during the last telecon whether the clearance of \_\_\_\_\_ during the manufacturing process had been validated. Neither Amgen participant was aware whether this had been performed. They were requested to provide this information at this January telecon. If this validation has not been performed, it is likely that it will be requested by FDA, \_\_\_\_\_

Amgen: Amgen stated that they are preparing a risk assessment regarding the potential for \_\_\_\_\_ that should be completed by the time of the facility inspection in late January. They are aware of commercial kits that are available to \_\_\_\_\_ but do not know if analytical data on DS or DP intermediates will be available at the time of the inspection (this will depend on the results of the risk assessment).

FDA: Dr. Clouse also remarked that Amgen should provide detailed information regarding the \_\_\_\_\_

\_\_\_\_\_ She recommended the following course of action: (1) provide detailed information regarding the preparation \_\_\_\_\_ (2) perform risk assessment regarding the \_\_\_\_\_ (3) confirm \_\_\_\_\_ DS and DP intermediates using \_\_\_\_\_ and ultimately, (4) validate the \_\_\_\_\_ during the manufacturing process.

Amgen: Amgen understood the request and will discuss this request internally. They also requested that at some point in the near future, this request be submitted in written form to Amgen.

(2) Amgen was requested to provide information, preferably also including a figure, regarding the binding site of romiplostim, along with the signal transduction pathway(s) that it activates in target cells in the December 12<sup>th</sup> telecon.

Amgen: This slide was sent today by email.

FDA: Dr. Frucht acknowledged receipt of the slide. He inquired why the slide showed a role for JAK1, and not JAK2, in signal transduction. Dr. Erickson remarked that this could be a typographical error. Dr. Frucht and Dr. Clouse then clarified more details regarding what FDA information was requesting:

1. Data confirming whether romiplostim binds to the same site on the TPO receptor as does TPO.
2. Epitope mapping data

Amgen: Amgen proposed to set up a new meeting on January 15<sup>th</sup>, where the Amgen team would discuss what they have learned about the mechanism of action of romiplostim, specifically the questions listed above.

(3) Please clarify why strict reject limits have not been adopted for in-process testing. Amgen was informed in the December 12<sup>th</sup> telecon that it is DMA's general practice to require strict reject limits for in-process testing.

Amgen: Amgen stated that it is general policy at Amgen not to adopt strict reject limits, especially those based primarily on confidence limits generated from manufacturing experience.

FDA: FDA stated that the Agency generally recommends strict reject limits for during the manufacturing process. These reject limits are based on safety concerns and are not necessarily based on confidence limits generated from manufacturing experience.

Amgen: Amgen understood the request and will discuss this request internally. They also requested that at some point in the near future, this request be submitted in written form to Amgen.

(4) Please clarify if your email from November 16, 2007, which identified the three consecutive consistency lots for both upstream and downstream DS process validation, has been entered as a formal amendment to the BLA.

Amgen: These data are already present in the BLA. In addition, this information will be provided during the inspection as well.

FDA: The Agency agreed.

(5) Please indicate the method through which the extinction coefficient for romiplostim was calculated.

Amgen: These data, or the location of these data in the BLA submission, will be provided in the January 16<sup>th</sup> telecon.

(6) Amgen should provide more data regarding the source used to produce the used in the DS manufacturing process.

Amgen: These data will be provided in the January 16<sup>th</sup> telecon.

(7) Amgen is proposing to drop the \_\_\_\_\_ assay as a DS release test, stating the HPLC methods are redundant with this assay. Amgen should indicate if there are any product quality attributes that could be captured by \_\_\_\_\_ but not be the HPLC methods (e.g., smaller fragments or contaminating proteins).

Amgen: Amgen understood the request and will discuss this question internally. They will respond at a later date. They also requested that at some point in the near future, this question be submitted in written form to Amgen.

(8) Romiplostim DP is reconstituted at a concentration of 500 mcg/mL. This would indicate that volumes as low as 100 microliters may be required to deliver appropriate doses to patients. Amgen will be required to validate that recommended syringes are capable of reliably delivering the lowest possible anticipated doses to patients.

Amgen: Amgen understood the request and will discuss this request internally. They also requested that at some point in the near future, this request be submitted in written form to Amgen.

Action Items (in addition to above)

1. A new information request meeting was scheduled for January 22<sup>nd</sup> at 2:00 p.m.

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Amgen Telecon  
BLA 125268  
December 12, 2007  
2:00 p.m. – 2:30 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participant: David Frucht  
Amgen participants: Lisa Erickson, Bill Gargen

The following information requests were discussed:

(1)  

Amgen: Neither Amgen participant was aware of whether this had been performed.

FDA: Please provide this information at our January telecon. If this validation has not been performed, it is likely that it will be requested by FDA,

(2) Please provide information, preferably also including a figure, regarding the binding site of romiplostim, along with the signal transduction pathway(s) that it activates in target cells.

Amgen: Amgen will provide this information.

(3) Please clarify why strict reject limits have not been adopted for in-process testing.

Amgen: Currently Amgen just has action levels that trigger an investigation.

FDA: The Sponsor was informed that it is DMA's general practice to require strict reject specifications for in-process testing.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING ISSUES**

Our STN: BL 125268/0

**DEC 10 2007**

Amgen, Inc.  
ATTENTION: Mei-Ling Chang-Lok, Ph.D., RAC  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799

Dear Dr. Chang-Lok:

This letter is in regard to your biologics license application (BLA) dated October 23, 2007, received October 23, 2007, submitted under section 351 of the Public Health Service Act, for Nplate™ (romiplostim).

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your application today. The review classification for this application is Priority. Therefore, the user fee goal date is April 23, 2008. 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.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 7, 2008.

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

The proposed labeling contains multiple problems in format, grammar and content. Our preliminary review reveals many components of the labeling that need extensive, thoughtful and timely revision. We are especially concerned that the extent of problems within the proposed labeling may delay our review and we request that you submit revised labeling that addresses our concerns. Attached to this letter is a version of your proposed Full Prescribing Information that contains annotated FDA comments in italics. These comments are based upon our initial review and we anticipate the need for additional modifications, contingent upon your response and our review findings. For more information regarding labeling proposals, please see *Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the New Content and Format Requirements*; also refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.

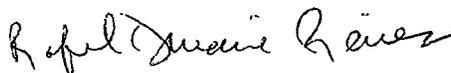
We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or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

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

If you have any questions, call Florence O. Moore, Regulatory Project Manager, at (301) 796-2050.

Sincerely,



Rafel (Dwaine) Rieves, M.D.  
Acting Director  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure: Draft FDA Version 1 of Package Insert

22 Page(s) Withheld

       Trade Secret / Confidential

X Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative-12



Food and Drug Administration  
Center for Drug Evaluation and Research  
5515 Security Lane  
Rockville MD 20852-1448

**Date:** November 16, 2007  
**To:** Administrative File, STN 125268  
**From:** Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/MAPCB/BMT, HFD-328  
**Through:** Edwin Rivera, Branch Chief, CDER/OC/DMPQ/MAPCB, HFD-322,  
**Subject:** Filing Memo for STN 125268  
**US License:** # 1080  
**Applicant:** Amgen, Inc.  
**Product:** Nplate (romiplostim, AMG 531)  
**Dosage:** Lyophilized for SC, 250 mcg (5mL vial), 500 mcg mL vial)  
**Due Date:** 20 November 2007

*Pat F. Hughes*  
*11/16/07*  
*Edwin Rivera*  
*11/20/07*

**SUMMARY:**

The old OTRR filing memo is used to assess of BLA STN 125268 from Amgen, Inc. for the licensure of romiplostim (proprietary name, Nplate). The new templates are inadequate and do not capture the main elements that are necessary to determine the filability of the BLA application from CMC microbial control, product quality microbiology perspective. In addition, the sections of the CFR referenced in the new templates are for NDAs, not BLAs.

Using the OTRR Filing Review Memo from CBER as a template, I have determined that the application is filable from a microbial control, product quality microbiology perspective and CMC facility perspective. The manufacturing facilities listed in the application are ready for a PAI inspection.

Please see Part B Product/CMC/Facility section of the Regulatory Filing Review Memo for BLA.

CC:  
HFD-322: Rivera  
HFD-328: Hughes  
HFD-123: Moore

# CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

11/20

BLA Number: 125268/0

Applicant: Amgen

Submitted Date: 10/23/07

Drug Name: Nplate  
(romiplostim)

BLA Type: Original

Stamp Date: 10/23/07

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. <u>electronic CTD</u> .	✓			
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	✓			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	✓			
5.	Are all documents submitted <u>in English</u> , or are English translations provided when necessary?	✓			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	✓			
<b>LABELING</b>					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 <sup>1</sup> and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	✓			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	✓			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓			
11.	Has the applicant submitted a benefit-risk analysis for the product?	✓	<del>   </del>		
12.	Indicate if the Application is a <u>505(b)(1)</u> or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			✓	
<b>DOSE</b>					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: <u>20000137</u> <del>20010218, 20050118</del> Study Title: <u>(see below *)</u>	✓			

<sup>1</sup> [http://www.access.gpo.gov/nara/cfr/waisidx\\_01/21cfr201\\_01.html](http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html)

\* 20010218: 6 sequential dose cohorts; 24 subjects (section 5.3)  
 20000137: 3 arms; 21 subjects (section 5.3)

## CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Sample Size: (see above*) Arms: Location in submission:				
<b>EFFICACY</b>					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 20030105 — (ITP refractory to splenectomy) Indication: Pivotal Study #2 20030212 — (ITP prior to splenectomy) Indication:	✓			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✓			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	✓			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		✓		AS4 ITP diagnostic criteria used. (not needed)
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✓			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	✓	✗		QT (clinical) studies not done adequate safety experience consider PMU & study
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	✓			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>2</sup> ) been exposed at the dose (or dose range) believed to be efficacious?		✓		orphan designation expect safety update to augment exposure
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	✓			
23.	Has the sponsor submitted the coding dictionary <sup>3</sup> used for mapping investigator verbatim terms to preferred terms?		✓		can request as needed as review proceeds

<sup>2</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>3</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

## CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✓			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	✓			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	✓			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			✓	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	✓			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			✓	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		✓		<i>see item 17 (not needed)</i>
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	✓			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	✓			
34.	Are all datasets to support the critical safety analyses available and complete?	✓			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	✓			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the	✓			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Division?				
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	✓			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			
<b>CONCLUSION</b>					
40.	From a clinical perspective, is this application fileable? If not, please state why.	✓			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

 (JOHN LEE)	11/16/07
Reviewing Medical Officer	Date
 (KUEVES)	11-20-07
Clinical Team Leader	Date

# CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Appears This Way  
On Original

# Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125268/0 Product: Romiplostin Applicant: Amgen Inc

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 11/20/07 Committee Recommendation (circle one) File RTF

RPM: [Signature]  
(signature/date)

## Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - Part A - RPM
  - Part B - Product/CMC/Facility Reviewer(s): Michelle Hughes Laska
  - Part C - Non-Clinical Pharmacology/Toxicology Reviewer(s): Kokate
  - Part D - Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers John Lee Min Chen
- Memo of Filing Meeting

STN 125268/0

Product Nplate (Y6miplostin)

**Part A. Regulatory Project Manager (RPM)**

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	<input checked="" type="radio"/> Y <input type="radio"/> N	
Form 356h completed	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> If foreign applicant, US Agent signature.	<input checked="" type="radio"/> Y <input type="radio"/> N	
Comprehensive Table of Contents	<input checked="" type="radio"/> Y <input type="radio"/> N	
Debarment Certification with correct wording (see * below)	<input type="radio"/> Y <input type="radio"/> N	
User Fee Cover Sheet	<input type="radio"/> Y <input checked="" type="radio"/> N	NA
User Fee payment received	<input type="radio"/> Y <input type="radio"/> N	NA
Financial certification &/or disclosure information	<input type="radio"/> Y <input type="radio"/> N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	<input type="radio"/> Y <input type="radio"/> N	NA
Pediatric rule: study, waiver, or deferral	<input type="radio"/> Y <input type="radio"/> N	NA
Labeling:	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI –non-annotated	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI –annotated	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> PI (electronic)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Medication Guide	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Patient Insert	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> package and container	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> diluent	<input type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> other components	<input type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> established name (e.g. USAN)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> proprietary name (for review)	<input checked="" type="radio"/> Y <input type="radio"/> N	

\* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge..."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?:	<input checked="" type="radio"/> Y <input type="radio"/> N	
Examples include:		
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y <input type="radio"/> N	

STN 125268/0

Product Nplate (Romiplostim)

Examples of Filing Issues	Yes?	If not, justification, action & status
<input type="checkbox"/> protocols for clinical trials present	<input checked="" type="checkbox"/> Y    N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	<input checked="" type="checkbox"/> Y    N	
companion application received if a shared or divided manufacturing arrangement	Y    N	<u>NA</u>
if CMC supplement:		
<input type="checkbox"/> description and results of studies performed to evaluate the change	<input checked="" type="checkbox"/> Y    N	
<input type="checkbox"/> relevant validation protocols	<input checked="" type="checkbox"/> Y    N	
<input type="checkbox"/> list of relevant SOPs	<input checked="" type="checkbox"/> Y    N	
if clinical supplement:		
<input type="checkbox"/> changes in labeling clearly highlighted	Y    N	<u>NA</u>
<input type="checkbox"/> data to support all label changes	Y    N	
<input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	Y    N	
if electronic submission:		
<input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	<input checked="" type="checkbox"/> Y    N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

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Has orphan drug exclusivity been granted to another drug for the same indication?  
 If yes, review committee informed? NO

Does this submission relate to an outstanding PMC? NA

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: ODAC
- Dates: March 12, 2007

Recommendation (circle one):  File  RTF

RPM Signature: [Signature]

Branch Chief concurrence: Alex Kavube

STN 125268/0

Product Romiplostim (Nplate)

Part D Page 1

**Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical)****Reviewers**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Clinical overview [2.5]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	Y N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y <input type="radio"/> N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Study Reports and related information [5.3]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Biopharmaceutic	Y N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
<input type="checkbox"/> Pharmacokinetics (PK)	Y N	
<input type="checkbox"/> Pharmacodynamic (PD)	Y N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Postmarketing experience	Y N	
<input type="checkbox"/> Case report forms	Y N	
<input type="checkbox"/> Individual patient listings (indexed by study)	Y N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	

STN 125268/0 Product Romiplostim

Examples of Filing Issues	Yes?	If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y    N	
<input type="checkbox"/> protocols for clinical trials present	<input checked="" type="radio"/> Y    N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="radio"/> Y    N	
statement for each clinical investigation:		
<input type="checkbox"/> conducted in compliance with IRB requirements	<input checked="" type="radio"/> Y    N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	<input checked="" type="radio"/> Y    N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	<input checked="" type="radio"/> Y    N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	<input checked="" type="radio"/> Y    N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	<input checked="" type="radio"/> Y    N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	<input checked="" type="radio"/> Y    N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	<input checked="" type="radio"/> Y    N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	<input checked="" type="radio"/> Y    N	
drug interaction studies communicated as during IND review as necessary are included	<input checked="" type="radio"/> Y    N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	<input checked="" type="radio"/> Y    N	
comprehensive analysis of safety data from all current world-wide knowledge of product	<input checked="" type="radio"/> Y    N	

STN 125268/0 Product Romiplostim

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	Y N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	<input checked="" type="radio"/> Y N	
adequate characterization of product specificity or mode of action	<input checked="" type="radio"/> Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	<input checked="" type="radio"/> Y N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	<input checked="" type="radio"/> Y N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="radio"/> Y N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
20030105	<input checked="" type="radio"/> Y	N	Y	N	NR	<input checked="" type="radio"/> Y	N	Y	N	NR
20030212	<input checked="" type="radio"/> Y	N	Y	N	NR	<input checked="" type="radio"/> Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

STN 125268/0

Product Romiplostim

Part D Page 4

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

None

Is clinical site(s) inspection (BiMo) needed?

\_\_\_\_\_

Is an Advisory Committee needed?

To be held on 3/12/07 or 3/13/07

Recommendation (circle one): File RTF

Reviewer: [Signature] 11-20-07  
(signature/ date) Type (circle one): Clinical Clin/Pharm Statistical

Concurrence:

Branch Chief: Jyoti Zalkikar  
(signature/ date) 11-20-07

Division Director: Alaka Chakravarty  
(signature/ date) 11/20/07

6 Page(s) Withheld

X Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative-1A



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**Memorandum**

**From:** Florence Moore, M.S. *FM*  
**To:** File: STN 125268/0  
**Subject:** Filing Meeting Summary  
**Sponsor:** Amgen, Inc.  
**Products:** Nplate (romiplostim)  
**Date:** November 20, 2007

**Purpose:** To discuss the filability of STN: 125268/0 for romiplostim and discuss CMC, Non-Clinical, Clinical Pharmacology, Biometrics and Clinical Studies, deficiencies identified.

**Relevant Milestones:**

Filing Date: December 22, 2007

Day 74 Letter Date: January 5, 2008

Mid-Cycle: January 17, 2008

ODAC Meeting: March 13, 2008

Review Completion Goal Date according to GRMP: March 23, 2008

PDUFA Goal Date: April 23, 2008

## **Summary of Review Status:**

### **Administrative**

- There were no administrative issues identified. The PLR label format was discussed and needs to be addressed in the 74 day letter.

### **CMC**

- DMA had no filing issues but had some review issues regarding stability etc that will be communicated to the Sponsor in the 74 day letter.
- TFRB had no filing issues, but had some issues that they will be identifying for the 74 day and information request letter.

### **Pre-Clinical/Toxicology**

- There were no Preclinical filing issues. Preclinical toxicology issues were presented. GLP compliance and reproductive toxicity issues were identified for the 74 day letter.

### **Clinical Pharmacology**

- There were no Clinical Pharmacology filing issues identified

### **Clinical**

- There were no Clinical filing issues identified. However there was some review issues discussed regarding QT studies needed.

### **Biostatistics**

- There were no Biostatistics filing issues identified

**Conclusion:** The review team was in agreement that BLA 125268/0 is filable.

### **Review Team:**

David Frucht – Product  
Patricia Hughes- DMPQ Drug Substance  
Susan Laski – DMPQ Drug Product  
Tushar Kokate –Pharm/Tox  
Clin Pharm – Angela Men  
Biometrics – Richard Chen  
Clinical- John Lee  
RPM- Florence Moore

Consult Review Team:

DDMAC- Sean Bradley

DSRCS- Sharon Mills

DMETS- Richard Abate

DSI- Karen Storms

RiskMAP- Suzanne Berkman

Pediatrics-Richardae Araojo

DDRE- Betsy Scroggs

Team Leaders

Rafel Rieves- CDTL/DD

Jyoti Zalkikar- Biometrics

Hong Zhao- Clin Pharm

Adebayo Lanionu- Pharm Tox

Alice Kacuba- RPM

Kathleen Clouse CMC

Gilbert Salud- Facilities

Attached- Attendance List



STN 125268/0 Filing Meeting  
Sponsor: Amgen  
Product: Nplate (romiplostim)

## AGENDA

1. Introduction of application, including important dates

**Summary Description of Product:** romiplostim is a peptibody that activates intracellular transcriptional pathways to increase platelet production, as a prescription drug intended for the treatment of thrombocytopenia in adult patients with chronic Immune (idiopathic) Thrombocytopenic Purpura (ITP). The anticipated trade name for romiplostim is Nplate™.

Stamp Date: October 23, 2007

Filing Date: December 22, 2007

Day 74 Letter Date: January 5, 2007

ODAC Meeting: March 11/12/13, 2007 (date not confirmed)

Review Completion Goal Date according to GRMP: March 23, 2007

PDUFA Goal Date: April 23, 2007

2. Identification of RTF Issues by Discipline

- |  |           |
|--|-----------|
| a. CMC – David Frucht                        | 4 minutes |
| b. DMPQ/Micro- Patricia Hughes/Gilbert Salud | 4 minutes |
| c. P/T – Tushar Kokate                       | 4 minutes |
| d. Clin Pharm – Angela Men                   | 4 minutes |
| e. Clinical – John Lee                       | 4 minutes |
| f. Stats – Richard Chen                      | 4 minutes |
| g. Labeling – All                            | 4 minutes |

3. Identify Interim Deliverables by Discipline with Timelines for Completion

- |                            |           |
|----------------------------|-----------|
| a. CMC – David Frucht      | 3 minutes |
| b. DMPQ- Patricia Hughes   | 3 minutes |
| c. P/T – Tushar Kokate     | 3 minutes |
| d. Clin Pharm – Angela Men | 3 minutes |
| e. Clinical – John Lee     | 3 minutes |
| f. Stats – Richard Chen    | 3 minutes |

4. Overview of Application by Discipline
  - a. Studies/info submitted
  - b. Identification of Info Requests
  - c. Day 74 letter items
  
5. Reach agreement on filing decision

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Memorandum**

**From:** Florence O. Moore, M.S.

**To:** File: STN 125268/0

**Subject:** Application Orientation Meeting Summary

**Sponsor:** Amgen, Inc.

**Product:** Nplate (romiplostim)

**Date, Location, & Time of Meeting:** November 20, 2007  
WO Rm 1419 and 1421  
1:00 p.m. – 2:30 p.m.

**Purpose:**

Application Orientation Meeting to support the use of Nplate indicated for the treatment of thrombocytopenia in adult patients with chronic Immune (idiopathic) Thrombocytopenic Purpura (ITP)

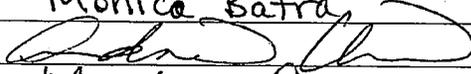
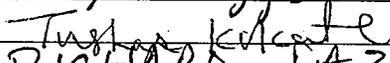
**Meeting Summary:**

The Application Orientation Meeting was held for Amgen to give an overview of their BLA Application to support the use of Nplate which has been the subject of IND 10205 for the treatment of anemia treatment of thrombocytopenia in adult patients with chronic Immune (idiopathic) Thrombocytopenic Purpura (ITP). See attached Amgen's presentation and attendee list.

# MEETING ATTENDANCE LIST

Meeting between Amgen, Inc. and  
the Center for Drug Evaluation and Research.

DATE: Nov. 20, 2007 TIME: 1-2:30 PM ROOM: 1421

NAME - Please print	AFFILIATION
Florence Moore	OODP/DMIHP
PATRICIA F. HUGHES	OC/DMPQ
SUSAN LASKA	OC/DMPQ/BTM
Yow-Ming Wang	Amgen
LISA ERICKSON	AMGEN
Steven Cha	AMGEN
Wende Davis	Amgen
MEI LING CHANG-LOK	AMGEN.
Janet Nichol	AMGEN
Jietmar Berger	AMGEN
Susan Beynon	Amgen
ROY BAYNES	Amgen
Monica Batra	Amgen
	Amgen
Matthew Gled	Amgen
Mark Rütstein	Amgen
GIL SAUD	OC/DMPQ/RMT
Angela Men	DEPS/OTS/CDER
Hong Zhao	DEPS/OTS/CDER
Richard Arango	PMHS
David Frucht	DMA/OBP/OPS/CDER
KATHLEEN CLOUSE	DMA/OBP/OPS/CDER
Karen Feibus	PMHS/ONDIO/CDER
Man Who CHEN	FDA/OB/DBV
Jyoti Zalkikar	FDA/OB/DBV
Kathy Robie-Suh	FDA/OODP/DMIHP
Betsy Scroggs	FDA/OSE/DDRE
	FDA/DMIHP
RICHARD PAZDUR	FDA

# Attendee List

Alice Kacuba	DMITLP
Steven Lemery	DBOP
Andree Furia	OSHI
Yash M Chopra	DMITLP
Satish Misra	Statistics
Susan Cummins	ONDIO-PMHS
Schelden Kiese	DMITLP

Amgen Telecon  
BLA 125268  
November 29, 2007  
2:00 p.m. – 2:15 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference toll/international phone number: 1-706-679-0931  
Conference Code: 8054472146

FDA participant: David Frucht  
Amgen participants: Lisa Erickson, Bill Gargen

The following information requests were discussed:

(1) Table from face-to-face meeting regarding submission of stability updates.

Amgen: Lisa Erickson reported that the stability study analysis would be accelerated such that 30 month DS primary data for lot #1, 24 month DS Primary 250 mcg data from lot #3, 13 month DP from all 500 mcg validation lots, and all 12 month DP data from 250 mcg validation lots would be submitted to the BLA during January. These data would be supplied as an amendment to the BLA and would be the last stability data to be submitted during the review cycle for this BLA.

FDA: This plan submission plan was acceptable, and the data would be reviewed in this BLA cycle.

(2) Regular information request meetings were scheduled for the following dates:

December 12, 2007 at 2:00 p.m.  
January 8, 2008 at 2:00 p.m.  
January 16, 2008 at 2:00 p.m.



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**Memorandum**

**From:** Florence Moore *FM*  
**Subject:** First Committee for STN 125268/0  
**Sponsor:** Amgen, Inc.  
**Products:** Nplate (romiplostim)  
**Date:** November 6, 2007

**Summary:**

The following was relayed to the review team during the First Committee Meeting. This serves as the First Committee meeting memo.

STN: 125268/0  
Drug: Nplate (romiplostim)  
Sponsor: Amgen, Inc.  
Type: Original Application (6 month clock)

Short Summary: BLA- treatment \_\_\_\_\_ of thrombocytopenia in adult patients with chronic Immune (idiopathic) Thrombocytopenic Purpura (ITP).

Action Due Dates:

Filing meeting: November 20, 2007

Please discuss any issues with Dwaine Rieves and me by this date.

Filing action: January 5, 2008

The filing review memo is attached to this e-mail. It should be sent to me indicating if there are no filing issues. If there are filing issues, they should be identified before December 22, 2007, and either be resolved or be in the process of being resolved or it will be a RTF.

## Final Action Due: April 23, 2008

This application will serve as the pilot for the new GRMP/CDTL process.

The review team indicated they are using the old OTRR filing memo because they have found that the new Good Review Management Process (GRMP) checklist does not meet the needs for a biologic product. The review team was tasked to track specifics and forward those to the RPM to be forward to the GRMP team as part of the pilot feedback.

### Review Team:

David Frucht – Product  
Patricia Hughes- DMPQ Drug Substance  
Susan Laski – DMPQ Drug Product  
Tushar Kokate –Pharm/Tox  
Clin Pharm – Angela Men  
Biometrics – Richard Chen  
Clinical- John Lee  
RPM- Florence Moore

### Consult Review Team:

DDMAC- Sean Bradley  
DSRCS- Sharon Mills  
DMETS- Richard Abate  
DSI- Karen Storms  
RiskMAP- Suzanne Berkman  
Pediatrics-Richardae Araojo  
DDRE- Betsy Scroggs

### Team Leaders

Rafel Rieves- CDTL/DD  
Jyoti Zalkikar- Biometrics  
Hong Zhao- Clin Pharm  
Adebayo Lanionu- Pharm Tox  
Alice Kacuba- RPM  
Kathleen Clouse CMC  
Gilbert Salud- Facilities

# DSI CONSULT: Request for Clinical Inspections

**Date:** November 9, 2007

**To:** Leslie K. Ball, M.D., Branch Chief, GCP2, HFD-47  
Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46

**Through:** Joseph Salewski, Acting Director  
Division of Scientific Investigations, HFD-45  
Rafel Dwaine Rieves, M.D., Acting Director, Division of Medical Imaging and Hematology Products, HFD-160

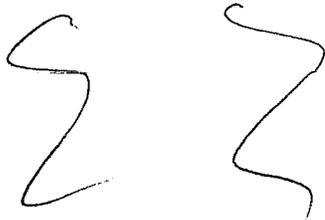
**From:** Florence O. Moore, M.S., Regulatory Health Project Manager  
Director, Division of Medical Imaging and Hematology Products, HFD-160

**Subject:** **Request for Clinical Site Inspections**  
Application: BL STN: 125268/0  
Sponsor: Amgen, Inc.  
Drug: Romiplostim (Nplate™)

**Protocol/Site Identification:**

The following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This BLA provides data for the following: Idiopathic Thrombocytopenic Purpura (ITP)  
This drug is a New Molecular Entity (NME)

Site # (Name, Address, Phone number)	Protocol #	Number of Subjects	Indication
	20030105	6	ITP
	20030212	8	
	20030213	17	
	20030105	3	ITP
	20030212	4	
	20030213	17	
108-Vellenga, Edo Universitair Medisch centrum Groningen Hanzeplein 1, Ingang 23, Terrein Azg, Inwendige Geneeskunde, Groningen, Netherlands (+31 50 3612354; e.vellenga@int.azg.nl)	20030105 20030213	4 4	ITP

**Domestic Inspections:**

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

We have requested inspections because (please check all that apply):

- There are insufficient domestic data. (See "Other" below.)
- Only foreign data are submitted to support an application.
- Domestic and foreign data show conflicting results pertinent to decision-making.
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify): **serial bone marrows were intensively studied to detect any early evidence of potential long-term hematologic safety concerns.**

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) (March 23, 2008). We intend to issue an action letter on this application by (division action goal date) (March 30, 2008). The PDUFA due date for this application is April 23, 2008.

Should you require any additional information, please contact *Florence Moore* at Ph: 301-796-1423

Concurrence: (as needed)

*John Lee*, M.D., Medical Reviewer   
*Rafel Dwaine Rieves*, M.D., Acting Medical Team Leader   
*Rafel Dwaine Rieves*, M.D. Acting Division Director (for foreign inspection request)

Amgen Telecon  
BLA 125268  
November 1, 2007  
11:00 a.m. – 11:40 a.m. EDT

Conference toll-free phone number: 1-888-8046796  
Conference toll/international phone number: 1-706-6790931  
Conference Code: 8054472146

FDA participant: David Frucht  
Amgen participant: Lisa Erickson

The following information requests were discussed:

1. Are there any in-process tests that are not validated (with reports in the assay validation section) or compendial?

Amgen: No

2. Have you validated your \_\_\_\_\_

Amgen: Amgen performed side-by-side testing with \_\_\_\_\_ tests on the initial lots. The results of these studies is either in the submission (Amgen will review submission) or will be submitted.

3. In Section 3.2.R.2., Table 1. it is impossible to “click open” all the methods and validation reports.

Amgen: This will be formally corrected.

4. Are validation reports provided for all of the assays used in DS and DP stability studies? If so, where?

Amgen: All validation reports are provided in 3.2.R, in the methods validation section.

5. Where in the submission are maximum in-process hold times specified? (Description of Manufacturing Process and Process Controls section?)

Amgen: This will be provided in a clear format as a BLA amendment.

6. Where is the data regarding container-closure integrity testing?

Amgen: This is provided in section 3.2.P.2, under microbiological attributes

7. Where is DP comparability data provided?

Amgen: This is provided in section 3.2.P.2, under process comparability

8. Are master files regarding final fill referred to in the submission?

Amgen: Amgen will provide the number of the linked master file. This number was not available at the time of the submission.

9. Please clarify which lots are the 3 lots to be considered the three consecutive consistency lots.

Amgen: Amgen reported that this was a complicated question, as there are \_\_\_\_\_ in the process. However, a flow-chart graphic will be provided explaining which lots are to be considered the consistency lots.

Action Items:

Amgen will provide the following:

- (1) Functional links to all methods and validation reports in 3.2.R.2, Table 1.
- (2) Reports regarding \_\_\_\_\_
- (3) A clear indication of maximal hold times for each process step that will be linked to stability studies supporting these hold times.
- (4) The identification number of the master file linked to drug fill.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 10205

Amgen, Inc.  
ATTENTION: Chris Phillips, Ph.D., RAC  
Director, Regulatory Affairs  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799

Dear Dr. Phillips:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Thrombopoietin Analogue: Fc Fusion Protein (AMG 531).

We also refer to the meeting held on May 22, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 301-796-2050.

Sincerely yours,

*{See appended electronic signature page}*

Florence O. Moore, M.S.  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**Meeting Type:** Type B  
**Meeting Category:** Pre- BLA  
**Meeting Date and Time:** May 22, 2007  
**Meeting Location:** CDER WO 1415 Conf Room Bldg 22  
**Application Number:** IND 10205  
**Product Name:** Thrombopoietin Analogue: Fc Fusion Protein (AMG 531)  
**Received Briefing Package** April 23, 2007  
**Sponsor Name:** Amgen, Inc.  
**Meeting Requestor:** Chris Phillips, Ph.D., RAC  
**Meeting Chair:** Rafel Rieves, M.D.  
**Meeting Recorder:** Florence Moore, M.S.

**Meeting Attendees:**

**FDA Attendees**

Office of Oncology Drug Products

Division of Medical Imaging and Hematology Products

Rafel (Dwayne) Rieves, M.D., Acting Director

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader

Ruyi He, M.D., Ph.D., Medical Team Leader

John Lee, M.D., Medical Reviewer

Adebayo Laniyonu, Ph.D., Pharmacology/Toxicology Team Leader

Tushar Kokate, Ph.D., Pharmacology/Toxicology Reviewer

Alice Kacuba, RN, MSN, RAC, Regulatory Project Manager Team Leader

Florence Moore M.S., Regulatory Health Project Manager

Office of Biotechnology Products  
Division of Monoclonal Antibodies (DMA)  
David Frucht, M.D., Product Quality Reviewer

Office of Clinical Pharmacology  
Division of Clinical Pharmacology V  
Nam Atiqur Rahman, Ph.D., Clinical Pharmacology Director  
Jang-Ik Lee, Ph.D., Clinical Pharmacology Acting Team Leader  
Angela Men, Ph.D., Clin Pharmacology Reviewer

Office of Biostatistics  
Division of Biometrics V  
Satish Misra, Ph.D. Biostatistics Reviewer

Office of Oncology Drug Products  
Division of Biologic Oncology Products  
Steven Lemery

Office of Special Health Issues  
Patty Delaney

**Sponsor Attendees**

Global Development:  
Roy Baynes, M.D., Vice President  
Dietmar Berger, M.D., Executive Director

Global Regulatory Affairs:  
Susan Boynton, Executive Director  
Christine Phillips, Ph.D., RAC, Director  
Mei Ling Chang-Lok, Ph.D., RAC, Senior Manager

Global Regulatory Affairs CMC:  
Lisa Erickson, RAC, Senior Manager

Global Safety Officer:  
Steven Cha, MD, Director

Global Development:  
Janet Nichol, M.S., Executive Director

Pharmacokinetics and Drug Metabolism:  
Yow-Ming Wang, Ph.D., Principal Scientist

Toxicology:

Wende Davis, Ph.D., Scientific Director

Biostatistics:

Mathew Guo, Ph.D., Senior Manager

## 1.0 BACKGROUND

- AMG 531 is an Fc fusion protein (peptibody) that increases platelet production via the thrombopoietin (TPO) receptor, which signals and activates intracellular transcriptional pathways. AMG 531 has no amino acid sequence homology to endogenous thrombopoietin (eTPO). Amgen is preparing a BLA in the Common Technical Document format for the marketing of AMG 531 for the treatment of thrombocytopenia associated with immune (idiopathic) thrombocytopenic purpura (ITP) in adult patients who \_\_\_\_\_ and plans to submit the BLA application in the last quarter of 2007 (October 2007).
- The purpose of this meeting was to obtain FDA feedback and guidance on the proposed clinical content and format for a BLA submission.
- The pre-BLA meeting focused primarily on the two pivotal Phase 3 studies that were conducted under Special Protocol Assessment (SPA) in splenectomized patients and 20030212 in non-splenectomized patients, as well as the interim analysis of the long-term open-label study 20030213, which provides long-term exposure data for the BLA filing.

## 2.0 DISCUSSION

FDA provided draft responses to the questions submitted in the meeting package by Amgen by email communication on May 16, 2007. Amgen presented an overview of their understanding of FDA's preliminary comments for the meeting and provided clarifications for the FDA comments.

### 2.1 Sponsor Questions, FDA Responses and Discussions

**Question 1:**

*A diagram of the studies that comprise the BLA filing is provided, along with patient exposure information (Figure 3-1). The BLA will contain 2 pivotal phase 3 studies that were conducted under Special Protocol Assessment (20030105 in splenectomized patients and 20030212 in non-splenectomized patients). In addition, Amgen will provide an interim analysis of the long-term open-label study 20030213, which provides long-term exposure data for this filing. Amgen is seeking the indication for AMG 531 as a treatment of thrombocytopenia associated with ITP \_\_\_\_\_*

*Does the Agency agree that the proposed data package is adequate to support a BLA filing and the proposed indication?*

**FDA Response (by facsimile):**

It appears that the proposed data package will be adequate to support a BLA submission. Please note the following:

- a. Filing decision will be made after receiving the submission, based on a review of the submitted material.
- b. In the proposed indication, the phrase "\_\_\_\_\_ is unclear. For the BLA submission, it would be helpful to revise the proposed indication in a way that more clearly defines the role of AMG 531 among therapies that are currently available to treat chronic ITP in adults.
- c. The data from study 20060131 and study 20030213 may be needed to adequately evaluate safety and efficacy of AMG 531 in patients with ITP.

**Discussions:**

FDA emphasized that the indication proposed should be based on data collected on patients who participated in the clinical studies. FDA recommended that Amgen use patients' prior history, and to be as specific as possible. FDA advised that Amgen include documentation of prior treatment.

Regarding Study 20030213, Amgen noted that safety data from this open-label extension study will be included in the submission (initial BLA and safety update). Study 20060131 recently began enrollment and is intended to explore the ability of AMG 531 to delay or avoid splenectomy. The final study report is not expected to be available until 2009. This study was not planned as a pivotal study to support the BLA submission. The study will explore the use of AMG 531 in adult ITP in comparison to standard of care.

FDA emphasized that the safety report is very critical and would like to see all the adverse event reports for both the treatment and the placebo arms to determine if there are any safety issues to be monitored.

FDA advised Amgen to separate severe and life threatening adverse events in their safety update. Amgen acknowledged.

**Question 2:**

*Integrated statistical analysis plans for the clinical summary of safety and clinical summary of efficacy were provided to FDA via information amendment on 17 October 2006 (Serial Number 151). Since that time, minor updates have been made to these analysis plans. These integrated statistical analysis plans are provided for review (Appendix 8-1). In addition, an outline of how these analyses will be presented in the clinical summaries of safety and efficacy will be provided. Are these plans acceptable for the BLA filing?*

**FDA Response (by facsimile):**

It is acceptable to pool the data from two pivotal phase 3 studies to estimate a more precise treatment effect as a component of the Integrated Summary of Efficacy. However, merging data to form a single pool may be problematic because the estimated treatment effect applies to two different clinical settings (splenectomy or non-splenectomy), and because of variability within study and unbalanced non-completer's rates. Hence, we do not anticipate the use of these analytical results in labeling or as the sole, cohesive indicator of treatment effects. We encourage additional methods to estimate the robustness of the pooled treatment effects. Substantive evaluation of treatment effects will be based upon individual study results.

**Discussions:**

There was no further discussion on question 2. Amgen acknowledged FDA's response.

**Question 3:**

*A Risk Management Plan (RMP) is provided for review (Appendix 8-2). An initial RMP was provided to the EMEA for comment in October 2006. Their comments were addressed in this version in addition to updating the RMP with the current safety database for AMG 531. Does the Agency agree that the RMP is adequate to address the potential and identified risks so as to minimize safety risks associated with AMG 531 treatment in thrombocytopenic patients with ITP?*

**FDA Response (by facsimile):**



If you 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 FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

- Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>
- Development and Use of Risk Minimization Action Plans: <http://www.fda.gov/cder/guidance/6358fnl.htm>
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: <http://www.fda.gov/cder/guidance/6359OCC.htm>

If you plan to submit a RiskMAP with the original submission, please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.

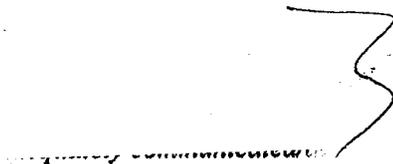
**Discussions:**

Amgen stated that they will include the RiskMAP information requested in the BLA submission. Amgen indicated that they are aware and concerned about off label use and had proposed a proactive language in labeling to prevent off-label use. FDA advised that Amgen should propose and emphasize what they know about the product and the known and potential risks and not focus upon the unknowns regarding the product in a relatively exculpatory manner. FDA recommended that Amgen consider briefly citing the data and potential risks for use of the product among MDS patients in the product labeling. FDA requested Amgen to provide a proposal and justification for Amgen's thinking on MDS. Amgen stated it is difficult to distinguish the two indications (ITP and MDS thrombocytopenia) but will adequately address it in the submission.

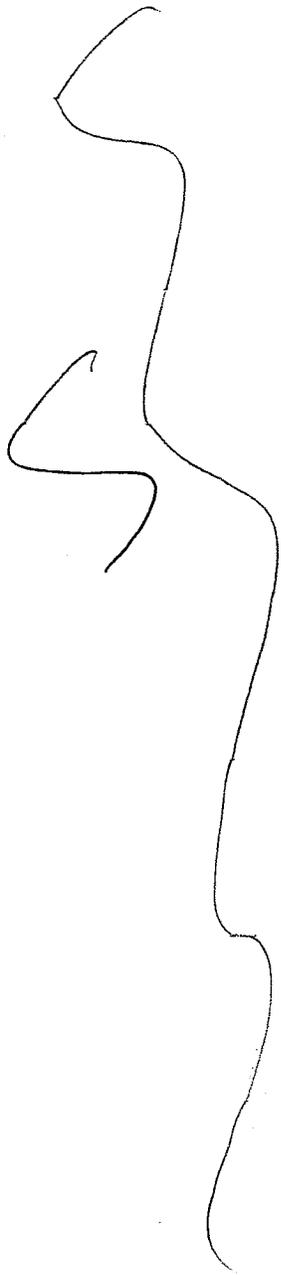
**Question 4:**

*Amgen has prepared a draft proposed package insert (PI) in accordance with the new Physicians Labeling Rule, with the recognition that the clinical data is still being evaluated and is subject to change (Appendix 8-3). At this time, Amgen welcomes the Agency's comments on the placement of information within the structure of the PI, in particular regarding the elements to bring into the Highlights, Warnings & Precautions, Dosage & Administration, and Clinical Studies sections.*

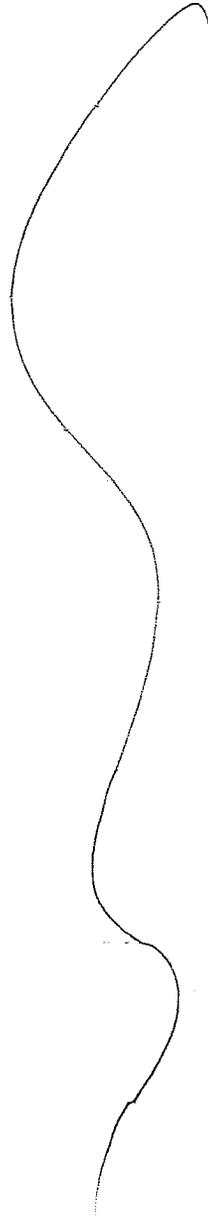
a.



**FDA Response (by facsimile):**

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7.7

A large, stylized handwritten signature in black ink, consisting of several loops and curves.A small, stylized handwritten mark or signature in black ink, consisting of a few loops.

7.7

*Does the Agency agree with Amgen's definition of adverse reactions and the format of the table within this section?*

**FDA Response (by facsimile):**

The adequacy of the PI regarding the definition and description of the adverse reactions associated with the use of AMG 531 will be evaluated after a review of the BLA submission. However, the proposed text does not appear to maintain consistency with the applicable guidance. Specifically, the text should include the "Sample Database Description" described on page 3 of the guidance entitled, "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products--Content and Format."

- c. *As mentioned in Question 1, the 2 pivotal studies are identical with the exception of splenectomy status. Amgen proposes to provide figures that show a similar response was achieved in both populations while high-lighting differences in effective doses required. Does the Agency agree that figures showing the durability of the platelet response over time and at what dose in the 2 pivotal studies are acceptable in the Clinical Studies section of the PI?*

**FDA Response (by facsimile):**

The adequacy of the PI regarding response to AMG 531 and its relationship to splenectomy status will be evaluated after a review of the BLA submission. At this point, we cannot provide definitive feedback regarding the use of figures in labeling.

- d. *During the AMG 531 clinical development program, dose adjustment rules have changed over time in response to input from study investigators. Amgen plans to present simplified dosing rules along with the rationale to support changes from the rules used in the pivotal studies. The dose adjustment rules will be designed to ensure accurate dosing while maintaining the desired response within the target platelet count range with minimal excursions above or below the target range.*
- e. *Does the Agency agree that rules for dose adjustment should be provided in the Dosage & Administration section of the PI?*

**FDA Response (by facsimile):**

We agree that the PI should contain guidelines for adjusting AMG 531 dose based on dose response. Within your BLA, provide detailed analyses to support the proposed dosage and administration text in the labeling. The adequacy of the PI regarding dosage and administration of AMG 531, including dose adjustment guidelines, will be evaluated after a review of the BLA submission.

**Discussions:**

FDA asked if any "reticulin signals" in the placebo group have been observed. Amgen indicated that bone marrow biopsies were not done in patients receiving placebo (because of the risks involved, according to usual clinical practice in ITP). Amgen further stated that all patients were tested for immunogenicity. Only one patient tested positive for antibodies to AMG 531. The patient had a follow up test for neutralizing antibodies, which was negative.

Amgen clarified that they anticipate AMG 531 treatment will be discontinued if there is lack of efficacy. FDA noted that this information should be described in product labeling, especially with respect to dosing, i.e., the label should describe a maximum dose and criteria for identifying "non-responders."

**Question 5:**

*Amgen intends to file this BLA as an eCTD in accordance with "Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, April 2006". Does the Agency agree?*

**FDA Response (by facsimile):**

Yes.

**Discussions:**

There was no further discussion on question 5. Amgen acknowledged FDA's response.

**Question 6:**

*In accordance with 21 CFR 314.50(f)(2), Amgen intends to include hyperlinked Case Report Forms (CRFs) and safety narratives for patients who died, experienced other serious adverse events, or who discontinued the study due to adverse events. In addition, Amgen will provide hyperlinked CRFs and safety narratives for "notable" subjects identified prior to unblinding of the pivotal trials. Please confirm the acceptability of this plan.*

**FDA Response (by facsimile):**

This plan is acceptable, provided that safety narratives are also provided for all patients who discontinue study. Please ensure that the plans also apply to the non-ITP clinical studies. As noted above, we are especially concerned about neoplasia and marrow fibrotic risks.

**Discussions:**

There was no further discussion on question 6. Amgen acknowledged FDA's response.

**Question 7:**

*In accordance with 21 CFR 314.50(d) (5) (vi) (b), Amgen will submit a safety 120-day update 4 months after the original BLA is filed. This safety update will be in the format of the clinical summary of safety and will provide additional data from 2 new studies testing*

*AMG 531 and will report on other ongoing studies of AMG 531. The data provided in this update will be cumulative. Updated labeling will be provided with this update, if changes are needed as a result of the cumulative analysis. Does the Agency agree that this plan is acceptable?*

**FDA Response (by facsimile):**

This plan appears to be acceptable. However, please describe in more detail at the upcoming meeting the "2 new studies testing AMG 531," including the specific roles of studies within your overall product development program and when the studies will be completed.

**Discussions:**

FDA inquired of the number of patients that were enrolled to date in Study 20060131. Amgen noted a total of 39 patients enrolled, with about 20 patients in the treatment arm (2:1 randomization).

**Question 8:**

*The Pediatric Research Equity Act states that "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526." Given that AMG 531 received orphan designation for ITP in March 2003, Amgen interprets this guidance to mean that Amgen has no statutory requirement to perform pediatric studies in ITP. Despite this understanding, Amgen has a pediatric plan and at the time of BLA submission, will submit for a pediatric deferral and will provide details on the pediatric plan. Does the Agency agree with this approach?*

**FDA Response (by facsimile):**

Yes.

**Discussions:**

There was no further discussion on question 8. Amgen acknowledged FDA's response.

**Question 9:**

*In accordance with Fast Track status (granted November 2004), Amgen requests priority review for this BLA because AMG 531 has the potential to fulfill an unmet medical need for patients with ITP. Does the Agency agree that priority review is appropriate for this BLA?*

**FDA Response (by facsimile):**

Based on the priority review policy, for a priority review, the drug product, if approved, would be a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. Based on the information provided in your background package, AMG 531 appears to be unable to provide a significant improvement in the treatment of ITP. In view of the serious long-term risks theoretically associated with the use of AMG 531, safety data are also important to determining the appropriateness of priority review status for this BLA. Limited safety data reported to

date under IND suggest that AMG 531 has the theoretical potential to cause myelofibrosis, bone marrow failure, or hematologic malignancies. The safety experience described in your meeting package does not contain sufficient information regarding animal toxicology studies and human bone marrow studies. The regulatory review status (priority or not) will be determined following submission of the BLA and preliminary examination of the study data.

**Discussions:**

There was no further discussion on question 9. Amgen acknowledged FDA's response.

**2.3 FDA Additional Comments**

- In your pre-BLA meeting package, there is no description of pre-clinical studies that you plan to submit in your BLA. Please provide a list and summary of pre-clinical studies for our review as soon as possible.
- In your pre-BLA meeting package, there is no description of your clinical pharmacology studies that you plan to submit in your BLA. Please provide a list and summary of your clinical pharmacology studies for our review as soon as possible.
- Please include the following information in the BLA submission:
  - a. The summary of pharmacokinetic parameters, immunogenicity, and pharmacodynamic data in a table format;
  - b. Individual concentrations, pharmacokinetic parameters of AMG 531 and PD data in .xpt file;
  - c. Individual immunogenicity data of AMG 531 in both .xpt and .pdf files.
- If there is any information on product medication errors from the premarketing clinical experience, FDA requests that this information be submitted with the BLA application.

**Discussions:**

Amgen acknowledged FDA comments regarding providing summaries of clinical pharmacology and non-clinical studies and noted that they provided these summaries to the FDA a day before the meeting and will also provide the summaries with the full study reports in the BLA submission. FDA asked what was the longest animal study done and if there were any reticulins seen in the animals. Amgen stated that the longest study was done in monkeys for six months. There was some myelofibrosis observed in rats but not in mice bone marrow. In response to a question regarding an animal model of ITP, Amgen noted that there was only one model which was not a "true" ITP model.

FDA questioned the primary end point results with respect to what might be viewed as a relatively low response rate to AMG 531. Amgen explained that the patients studied were very refractory patients. The patients were predominantly post splenectomy patients who had received multiple treatments. FDA noted that the label, especially the indication, should reflect the studied patients.

Amgen indicated they will provide individual platelet graph in the submission to show improvements of patients after treatment with AMG 531 compared to standard of care.

FDA asked if Amgen had any policies on expanded access and if they plan to file this application in ASCO or Europe. Amgen reiterated that they anticipated somewhat restricting distribution of the investigational drug until a risk/benefit has been established and a risk management plan can be established. FDA encouraged Amgen to contact Office of Special Health Issues for advice on their expanded access program if they decide to create one.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussions.

### **4.0 ACTION ITEMS**

- Amgen will revise and propose an indication specifically for patients studied for ITP.
- Amgen will provide all safety data for studies 20030213 and 20060131.
- Amgen will provide an adequate description of the sample database description consistent with the guidance.
- Individual platelet graph in the submission to show improvements of patients after treatment with AG 531 compared to standard o care.
- Amgen will provide a proposal and justification for Amgen's current thinking on MDS.

### **5.0 ATTACHMENTS AND HANDOUTS**

Amgen's slide presentation

10 Page(s) Withheld

X Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative- 13

Linked Applications

Sponsor Name

Drug Name

IND 10205

AMGEN INC

Thrombopoietin Analogue:Fc Fusion  
Protein (AMG 531)(Amgen) to the  
Thrombopoietin Receptor (c-Mpl)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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FLORENCE O MOORE

06/04/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 10205

Amgen, Inc.  
ATTENTION: Lisa Erickson, RAC  
Senior Manager  
Global Regulatory  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799

Dear Ms. Erickson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Thrombopoietin Analogue: Fc Fusion Protein (AMG 531).

We also refer to the meeting held on May 24, 2007, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 301-796-2050.

Sincerely yours,

*{See appended electronic signature page}*

Florence O. Moore, M.S.  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**Meeting Type:** Type B

**Meeting Category:** Pre- BLA

**Meeting Date and Time:** May 24, 2007

**Meeting Location:** CDER WO 1415 Conf Room Bldg 22

**Application Number:** IND 10205

**Product Name:** Thrombopoietin Analogue: Fc Fusion Protein (AMG 531)

**Received Briefing Package** April 24, 2007

**Sponsor Name:** Amgen, Inc.

**Meeting Requestor:** Lisa Erickson

**Meeting Chair:** David Frucht, M.D.

**Meeting Recorder:** Florence Moore, M.S.

**Meeting Attendees:**

**FDA Attendees**

Office of Oncology Drug Products

Division of Medical Imaging and Hematology Products

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader

John Lee, M.D., Medical Reviewer

Florence Moore M.S., Regulatory Health Project Manager

Office of Biotechnology Products  
Division of Monoclonal Antibodies (DMA)  
Patrick Swann, Ph.D., Deputy Division Director  
David Frucht, M.D., Product Quality Reviewer

Office of Compliance  
Division of Manufacturing and Product Quality (DMPO)  
Patricia Hughes, Ph.D., Acting Branch Chief

Office of Clinical Pharmacology  
Division of Clinical Pharmacology V  
Angela Men, Ph.D., Clin Pharmacology Reviewer

**Sponsor Attendees**

Lisa Erickson, Regulatory Affairs  
Jennifer Mercer, Regulatory Affairs  
Chris Phillips, Regulatory Affairs  
Bill Garden, Regulatory Affairs  
Vasuki Satyagal, Operations  
Clea Talley, Process Development  
Mike Akers, Process Development  
Brent Kendrick, Process Development  
Darrin Cowley, Quality  
Dawn Palmer, Quality  
Rick Burdick, Quality  
Jill Crouse-Zeineddini, Analytical Sciences

**1.0 BACKGROUND**

- AMG 531 is an Fc fusion protein (peptibody) that increases platelet production via the thrombopoietin (TPO) receptor, which signals and activates intracellular transcriptional pathways. AMG 531 has no amino acid sequence homology to endogenous thrombopoietin (eTPO). Amgen is preparing a Biologic License Application (BLA) in the Common Technical Document format for the marketing of AMG 531 for the treatment of thrombocytopenia associated with immune (idiopathic) thrombocytopenic purpura (ITP) in adult patients who \_\_\_\_\_ and plans to submit the BLA in the last quarter of 2007 (October 2007).
- The purpose of this meeting was to discuss chemistry, manufacturing and control (CMC) aspects of AMG 531 program in preparation for the submission of the BLA which will be submitted in October 2007.

## 2.0 DISCUSSION

FDA provided draft responses to the questions submitted in the meeting package by Amgen by email communication on May 17, 2007. The following is a summary of the discussion and clarifications sought by Amgen regarding the FDA responses.

### 2.1 Sponsor Questions, FDA Responses and Discussions

#### Question 1:

*Amgen has communicated the analytical comparability approach to FDA over the course of drug substance and drug product development. Drug product comparability results including \_\_\_\_\_ are provided in this document. Does FDA agree that the overall plan for demonstrating analytical comparability for drug product is acceptable for the BLA?*

#### FDA Response (by facsimile):

In general, FDA agrees with Amgen's overall approach for demonstrating analytical comparability for the drug product during the facility \_\_\_\_\_. However, much of the comparability data in the current amendment is provided in summary form, precluding a comprehensive review at this time. In addition, we note that the \_\_\_\_\_ lots utilizing \_\_\_\_\_ DS have \_\_\_\_\_ than historically seen. Amgen hypothesizes that this \_\_\_\_\_ FDA anticipates that additional lots presented in the BLA will confirm this hypothesis. Please comment. In addition, the BLA should include the primary DP comparability data used to support the summary conclusions provided in amendment 0200, including photographic quality images demonstrating \_\_\_\_\_ and spectroscopy results.

#### Discussions:

Amgen clarified that the \_\_\_\_\_ has an assay variability of \_\_\_\_\_. FDA noted a trend in potency measurements for DP produced at \_\_\_\_\_ that exceeded this range, as well as the historical range for lots produced at \_\_\_\_\_. Amgen stated that they do not anticipate manufacturing new lots prior to the \_\_\_\_\_, but committed to provide a more comprehensive data package in the BLA that supports comparable potency of DP made at \_\_\_\_\_.

FDA requested that Amgen submit photographic quality images of chromatography results in the BLA submission. Amgen acknowledged this point and indicated they will do so.

#### Question 2:

*Does the Agency agree with the number and type of tests and their associated acceptance criteria included in the proposed specification for drug substance and drug product?*

**FDA Response (by facsimile):**

In general, FDA agrees with the current approach used to develop the tests for drug substance and drug product quality, as well as the statistical approach used to develop acceptance criteria. However, a final assessment of the appropriateness of these tests and acceptance criteria will not be possible until the BLA submission is comprehensively reviewed.

In addition, we recommend that a container closure integrity test be performed on stability lots in lieu of sterility tests as a means of monitoring the maintenance of microbial product quality attributes during shelf life. The test should be conducted initially, annually and at end of shelf life. The sensitivity of the method should be described.

**Discussions:**

Regarding the \_\_\_\_\_ test comment, Amgen stated that they will provide validation data correlating \_\_\_\_\_ testing results in the BLA.

Amgen elucidated that they will provide container closure data for the production vials using a \_\_\_\_\_ test and a \_\_\_\_\_ test data on media filled vials. Amgen has also developed a physical test for container closure testing of lots on stability. The new test is \_\_\_\_\_ is very reliable in correlation to the microbial test methods. The test will not be available until 2008 and data from this test will not be submitted in the initial BLA submission. Amgen indicated that they would like to provide data and information on the new container closure integrity test method as an amendment to the BLA. FDA advised that Amgen can submit the amendment if it will not have a major impact on the PDUFA clock. Amgen acknowledged this point.

Regarding stability, FDA asked what data will be available in the BLA submission for container-closure stability. Amgen pointed out that it was too early to determine what they will be presenting in the BLA.

**Question 3:**

As previously discussed with the Agency (13 June 2006 Type C CMC Meeting, BB-IND 10205 Serial No. 129), Amgen intends to include the 250 µg vial presentation for licensure in the BLA. The second vial presentation is exactly the same formulation and container closure as that of the 500 µg vial with only a change in fill volume. Would an analytical data package (comparability, validation, stability, specifications) be sufficient to support licensure of the 250 µg vials in the absence of clinical data?

**FDA Response (by facsimile):**

This approach would be acceptable as long as the 250 µg vial had the same specifications and shelf life, and the analytical package to be submitted in the BLA did not reveal product quality differences between DP in the 250 µg vial presentation as compared to the 500 µg vial presentation.

**Discussions:** There was no further discussion on question 3. Amgen acknowledged FDA's response.

**FDA Additional Comments:**

- Please include a letter of authorization to reference the DMF for \_\_\_\_\_ in support of \_\_\_\_\_ of the drug product and include references to the DMF update and sections that specifically support drug product manufacturing. The DMF and BLA should include the type of information described in the 1994 FDA Guidance for Sterilization Process Validation. Additional updated GMP information can be found in the 2004 FDA \_\_\_\_\_ Guidance.
- Please indicate whether a non-proprietary (USAN) name has been established for AMG 531.
- We encourage you to submit all associated labels and labeling for review as soon as available.

**Discussions:**

FDA reminded Amgen that the Sponsor for the drug Master Files (DMF) for AMG 531 must submit a letter of authorization to reference the DMF before FDA can use the information in the DMF. Amgen acknowledged and noted that they are aware that there is a planned inspection for the sponsor holding the DMF in 2008.

Amgen indicated that they will like a three month advance notice from the FDA for the pre-approval inspection (PAI) to be able to coordinate their schedules properly. Amgen plans to schedule production in October, November and December. FDA stated the PAI timeline will be discussed internally and will provide Amgen feedback on the dates for the PAI.

Regarding the USAN non-proprietary name, Amgen explained that they do have a USAN for AMG 531 "Romiplostim" and expects to submit the name to the FDA around August/September 2007.

Linked Applications

Sponsor Name

Drug Name

IND 10205

AMGEN INC

Thrombopoietin Analogue:Fc Fusion  
Protein (AMG 531)(Amgen) to the  
Thrombopoietin Receptor (c-Mpl)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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FLORENCE O MOORE

06/04/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852

Our Reference: BB-IND 10205

**JUL 18 2005**

Amgen Inc.  
Attention: Douglas Hunt  
Manager, Regulatory Affairs  
One Amgen Center Drive  
Thousand Oaks CA 91320-1799

Dear Mr. Hunt:

Please refer to your **Investigational New Drug Application (IND)** for "Thrombopoietin Analogue: Fc Fusion Protein (AMG 531) (Amgen) to Thrombopoietin Receptor (c-Mpl)." and to the telephone conversation held on June 21, 2005, between representatives of your firm and this agency. A copy of our memorandum of that telephone conversation is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, Maryland 20852

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

Florence O. Moore, M.S.  
Regulatory Project Manager  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

Memorandum

Date: JUL 18 2005 FM  
From: Florence O. Moore, M.S., DRMP, HFD-109  
To: Amgen  
Subject: IND 10205 End of Phase 2 (CMC) Meeting Summary

Meeting Date: June 21, 2005

Time: 1:30 - 2:30 p.m.

Location: WOC-2, Conference Room G

Teleconference Requestor/Sponsor: Amgen

Product: Thrombopoietin Analogue: Fc Fusion Protein (AMG 531) (Amgen) to  
Thrombopoietin Receptor (c-Mpl)

Proposed Use: Treatment of chronic immune thrombocytopenia purpura (ITP)

Type of Meeting: End of Phase 2 (IND 10205)

Meeting Purpose: To discuss clinical and preclinical data and submission content related to  
the submission of a BLA.

Note: FDA provided draft responses to the questions submitted in the meeting package by  
Amgen by facsimile transmission on June 21, 2005.

#### Meeting Summary

At the beginning of the meeting, Amgen acknowledged receiving the FDA's responses to the submitted questions. What follows is a summary of specific discussions and clarifications sought by Amgen regarding our responses.

**Sponsor Questions, FDA Response and Discussions**

1. *Data from pilot scale runs demonstrating comparability between the clinical and commercial process are included in this meeting package. Amgen plans to submit a similar comparability data package via an information amendment to the IND comparing material produced at full scale by the commercial process with that produced by the original clinical process. Does the Agency agree with Amgen's plan for evaluating comparability?*

**FDA Response (by facsimile):** Prior to agency concurrence with your comparability plan, the following concerns should be addressed:

- a. Please identify the \_\_\_\_\_ characterized as pilot scale for \_\_\_\_\_ and Amgen Colorado (ACO).
- b. You have not provided data demonstrating that the stability studies proposed as part of the comparability protocol will include conditions that will reveal stability-indicating parameters. For example, the bioassay is stability-indicating for Drug Product stored at 60°C for at least 3 days, but this condition is not included in the proposed comparability protocols. Please identify which parameter(s) is/are stability-indicating in the proposed stability comparability studies and provide data supporting that the proposed stability temperature parameters will be adequate to detect degradation.
- c. The proposed comparability protocol should include a comparison of test results for relevant in-process contaminants \_\_\_\_\_, as well as for other critical in-process testing parameters (e.g. quantity measure of \_\_\_\_\_).
- d. The proposed comparability protocol should include defined acceptance criteria (not "report" results).
- e. Please consider including \_\_\_\_\_ analysis as part of peptide mapping studies.
- f. Please characterize the \_\_\_\_\_ contaminants observed in reverse phase HPLC analysis of drug substance.
- g. Host cell DNA testing should be performed using the original assay for \_\_\_\_\_ content.

**Discussion During the Meeting:** FDA made an overall comment that it is very difficult to answer post-licensure questions for a product prior to submission of the BLA. However, FDA has answered Amgen's questions as detailed as was possible with the given information.

- Regarding question 1a. Amgen reported that the \_\_\_\_\_ for \_\_\_\_\_ and \_\_\_\_\_ respectively.
- Regarding question 1b. FDA advised that it is important for Amgen to determine which parameters in the stability protocols are stability-indicating. Amgen stated that page 29 of the meeting briefing package identifies the first and second stages of Amgen's plans for comparability testing. The first stage will involve a comparison of lots made at the clinical facility using the different manufacturing processes (clinical vs. commercial process). The second stage will involve a comparison of lots made at the clinical facility with those made in the commercial facility, all made using the new commercial process. Information generated from the stage one comparability study will be used to develop a more detailed stage two comparability study. Amgen committed to developing storage conditions for their stability protocols that will .



- Regarding FDA response (by facsimile) to questions 1c and 1d, Amgen acknowledged these deficiencies. Amgen plans to submit a comparability protocol in stage 2 that will include testing for in-process parameters, as well as the use of defined acceptance criteria.
- FDA advised that Amgen must show comparability for the new and old material manufactured using the different process before introducing the new material into the Phase 2 studies. FDA also inquired whether pharmacokinetic (PK) data would be gathered in the Phase 2 extension studies using product made using the new commercial process. Amgen stated that it might be difficult to monitor the pharmacokinetic (PK) activities in the current protocol. Amgen stated that they will provide pharmacodynamic data from the upcoming Phase 2 extension study. FDA asked how Amgen would present results for Phase 1 and 2 comparability studies, especially with regard to clinical data.

Amgen answered that they will examine relevant clinical responses and development of immunogenic responses. Amgen indicated that the new manufactured product will not be introduced in the Phase 2 clinical trials if *in vitro* studies do not indicate comparability with product manufactured using the original process. Amgen stated that they will provide the *in vitro* comparability data in late August. FDA informed Amgen that the CMC reviewers will discuss the results of the *in vitro* comparability studies with the FDA clinical reviewers before the material is introduced in the clinical studies. In addition, FDA requested that Amgen define the acceptance criteria of the comparability parameters prior to initiating stage 2 of the comparability protocol. Amgen agreed to this request.

- Regarding FDA response (by facsimile) to questions 1e. Amgen agreed to perform            analysis as part of peptide mapping studies in the comparability protocols.
- FDA noted on page 64 of the meeting package the RP-HPLC data showed there were



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2. *Does the Agency agree that the appropriate quality attributes have been included in the drug substance and drug product specification? Can the Agency comment on the current specification and the strategy that will be used for establishing the drug substance and drug product specifications to support the license application?*

**FDA Response (by facsimile):** In general, the Agency agrees that the drug substance and drug product specifications are adequate for the current level of product development. Several assays to be used to evaluate the commercial product are currently under development (e.g., excipient testing assays and a new HPLC            method). Moreover, full validation data regarding the analytical procedures used to characterize the drug substance (DS) and drug product (DP) have not yet been submitted, so the adequacy of these procedures cannot yet be assessed. In addition, the following concerns should be addressed:

a.

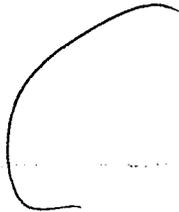


- b. Please note that your acceptance criterion for HCP \_\_\_\_\_ for products that we have reviewed. This specification should be adjusted based on manufacturing history and clinical experience.
- c. Please indicate whether data regarding product reconstitution time have been collected, and strongly consider the merits of this measure as a quality attribute for lot release and/or comparability.
- d. Please note that HPLC < is included in DP stability (Table 37) but not DP lot release (Table 31).

**Discussion During the Meeting:**

- Regarding the drug product specification, Amgen indicated, several assays are currently under development.

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- FDA stated that the acceptance criterion for \_\_\_\_\_ than what has been previously reviewed by the FDA. Amgen acknowledged this concern and stated that they will reassess this issue before filing the BLA.
- Regarding product reconstitution time, Amgen stated they are collecting data but will not include the newly collected data for this parameter included in the package to be submitted with the stage 1 comparability study results. However, Amgen will consider including this parameter in the stage 2 comparability study.
- FDA recommended that HPLC and \_\_\_\_\_ are important and are needed for drug product release testing.

3. *Can the Agency comment on the acceptability of the drug substance and drug product stability programs to support the license application? Specifically,*
- *Does the Agency agree that shelf-life can be established based on lots manufactured at the clinical site with the commercial process?*

**FDA Response (by facsimile):** For determining shelf-life, the Agency would consider



- *Does the Agency agree with Amgen's plan to provide updated stability data during the BLA review period?*

**FDA Response (by facsimile):** Amgen may provide updated stability data during the BLA review period. However, submission of stability data less than three months prior to the decision date may be considered a major amendment and delay the decision timetable.

Please confirm your intent (Tables 35 and 38) to provide no DS or DP stability data from the commercial manufacturing facilities upon BLA submission (or filing?).

**Discussion During the Meeting:** FDA asked Amgen to clarify their intentions of submitting the stability data and stated it would be important that Amgen demonstrate comparability for the stability of material manufactured at the different sites. Amgen agreed to this request. FDA also advised that it is important that Amgen provide information on container closure for the drug product, including detailed information regarding the vials/stoppers and container closure integrity. Amgen agreed to this request. Furthermore, FDA inquired whether any changes would be made to DP container process and/or components. Amgen indicated that they do not intend to change the current vials and stoppers during the transition to the new process and manufacturing site.

4. *Data detailing the cell-based bioassay that is used to determine potency of AMG 531 was previously submitted to FDA in an information amendment. BB-IND 10205 (Serial Number 068) dated 22 December 2004 and is provided in Appendix 2. Following on from data presented in the information amendment on stability and specificity of the bioassay, does the agency concur that the cell-based bioassay is appropriate as the potency assay to support the licensing application?*

**FDA Response (by facsimile):** The data presented by Amgen thus far supports the use of the cell-based bioassay as an appropriate potency assay for AMG 531. However, the Agency will require submission of full validation data for this assay at the time of the BLA submission to confirm that this assay is adequate for licensure.

**Discussion During the Meeting:** Amgen acknowledged FDA's request (by facsimile) and indicated that they will provide all data requested prior to or in the BLA.

Additional Discussion:

FDA informed Amgen that the FDA CMC reviewers and clinical reviewers will have internal discussions to discuss the results of *in vitro* Stage 1 comparability studies, because there could be clinical concerns due to changes in the product that could impact efficacy or immunogenicity. Although Amgen is not obliged to wait for FDA review of the data prior to initiating the use of the new process material in Phase 2 extension studies, it would be preferable for Amgen to obtain FDA's input prior to determining clinical parameters to examine in Phase 2 extension studies. In addition, Amgen was advised to consult FDA regarding the development of Stage 2 comparability parameters and specifications.

**FDA Attendees:**

Office of Drug Evaluation VI  
Division of Review Management and Policy  
Florence Moore, M.S.

Office of Drug Evaluation VI  
Division of Therapeutic Biological Internal Medicine Products  
Ellis Unger, M.D.  
Rafel (Dwayne) Rieves, M.D.  
John Lee, M.D.

Office of Drug Evaluation VI  
Division of Monoclonal Antibodies  
David Frucht, M.D.  
Patrick Swann, Ph.D.

**Sponsor Attendees:**

Lisa Erickson, RAC Manager, Regulatory Affairs CMC  
Pat Green, MS Scientist, Process Development  
Debra Grymkoski, MS Team Leader, Quality  
Brent Kendrick, Ph.D Principal Scientist, Process Development  
Jennifer Mercer, RAC Sr. Manager, Regulatory Affairs CMC  
Venkat Mukku, Ph.D Lab Head, Process and Analytical Sciences  
Janet Nichol, MS Associate Director, Global Development  
Vasuki Satyagal, MS Ch.E Team Leader, Global Operations  
Tom Tarlow, MS Director, Regulatory Affairs



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852

Our Reference: BB-IND 10205

SEP 23 2005

Amgen Inc.  
Attention: Douglas Hunt  
One Amgen Center Drive  
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Please refer to your **Investigational New Drug Application (IND)** for "Thrombopoietin Analogue:Fc Fusion Protein (AMG 531)(Amgen) to the Thrombopoietin Receptor (c-Mpl)," and to your August 19, 2005, **Request For Special Protocol Assessment**, received August 22, 2005. This submission contained the protocol # 20030105 dated August 19, 2005, entitled "A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Refractory to Splenectomy," and the protocol # 20030212 dated August 19, 2005, entitled "A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions:

Questions:

1. Does the agency agree with the definition of a weekly platelet response as a platelet count  $\geq 50 \times 10^9 /L$  on a weekly scheduled dose day from week 2 to week 25, inclusive? This measure provides for a clinically meaningful increase of  $20 \times 10^9/L$  above the highest possible mean baseline value. In the previous version of this study protocol, ~~the week 2 to week 25 interval was incorporated to align with 'intent to treat' definition of weekly platelet response.~~ The week 2 to week 25 interval was incorporated to align with 'intent to treat' definition of weekly platelet response.

FDA Response:

As a definition of the "weekly platelet response," the change in the applicable time interval is reasonable. As previously noted in our May, 2005 letter, we regard this secondary endpoint as essentially a sensitivity analysis of the primary endpoint. The primary endpoint provides the clinically meaningful outcome measure for both studies.



- 
- 
4. Does the Agency agree that the attached Case Report Forms and Eligibility Worksheet are adequate to capture the required data to support licensure?

FDA response:

Yes, for both studies.

5. Does the Agency agree that the attached Statistical Analysis Plan is adequate to support registration?

FDA response:

Yes, for both studies.

6. Does the Agency agree that study 20030105 is designed such that positive results would support an indication for AMG 531 for the treatment of thrombocytopenia associated with ITP in patients refractory to splenectomy?

Does the Agency agree that study 20030212 is designed such that positive results would support an indication for AMG 531 for the treatment of thrombocytopenia                     

FDA response:

Yes, however please be aware that the specific text used in an indication statement is contingent upon the evidence supporting safety and efficacy of the study agent.

We have determined that the design and planned analysis of your studies does adequately address the objectives necessary to support a regulatory submission. This special protocol assessment can be modified to improve the study, if you submit a revised special protocol assessment and, FDA agrees in writing to the modification. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

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

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Therapeutic Biological Products Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Katherine Needleman, M.S., at (301) 827-4358.

Sincerely yours,

A handwritten signature in black ink that reads "Kay Schneider" with a stylized flourish at the end.

Wendy Aaronson, M.S.  
Acting Director  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Center for Drug Evaluation and Research

**FOOD AND DRUG ADMINISTRATION  
 CENTER FOR DRUG EVALUATION AND RESEARCH  
 OFFICE OF NEW DRUGS  
 OFFICE OF DRUG EVALUATION VI  
 DIVISION OF REVIEW MANAGEMENT AND POLICY**

Woodmont Office Complex II, 6<sup>th</sup> Floor  
 1451 Rockville Pike  
 Rockville, Maryland 20852-1448  
 FAX #: 301-827-5397

**FACSIMILE TRANSMISSION RECORD**

TOTAL NUMBER OF PAGES: 6 (Including Cover Page)

FAX TO: Douglas Hunt / Amgen, Inc.

Facsimile Telephone No. 905-480-1330 Voice Telephone No. \_\_\_\_\_

FROM: Kathryn A. Neuchlenn / FDA / ODEVI / DRMP

Facsimile Telephone No. 301-827-5397 Voice Telephone No. \_\_\_\_\_

DATE: 5/2/05 TIME: 3:30pm

MESSAGE: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852

Our Reference: BB-IND 10205

MAY 02 2005

Amgen Inc.  
Attention: Douglas Hunt  
One Amgen Center Drive  
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Please refer to your Investigational New Drug Application (IND) for "Thrombopoietin Analogue:Fc Fusion Protein (AMG 531)(Amgen) to the Thrombopoietin Receptor (c-Mpl)," and to your March 18, 2005, Request For Special Protocol Assessment, received March 18, 2005. The protocol # 20030212 dated March 2, 2005, is entitled "A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions:

## Questions:

1. Does the agency agree with the definition of a weekly platelet response as a platelet count  $\geq 50 \times 10^9/L$  on a weekly scheduled dose day from \_\_\_\_\_ to week 25, inclusive? This provides for a clinically meaningful increase of  $20 \times 10^9/L$  above the highest possible mean baseline value.

FDA Response:

Yes.

2. Amgen proposes that the primary endpoint of protocol 20030212 is the incidence of durable platelet response. A subject with durable platelet response is defined as achieving at least 6 weekly platelet responses \_\_\_\_\_

Does the Agency agree that this primary endpoint is appropriate?

FDA Response:

Page 2 - BB-IND 10205

For the primary endpoint, the definition of a "response" includes responses observed following administration of rescue medication. The use of rescue medication may have unpredictable effects on platelet counts, and could confound interpretation of the primary endpoint. We acknowledge receipt of your facsimile, dated April 25, 2005, revising the definition of a durable platelet response to classify, as non-responders, subjects who receive rescue medication at any time during the study. Please submit a revised protocol incorporating this change. With this change, we find the primary endpoint to be appropriate.

3. Amgen proposes that the key secondary endpoints of protocol 20030212 are:

a.

b.

c.

d.

[Handwritten scribbles and lines, possibly representing redacted or illegible text]

Does the Agency agree that these key secondary endpoints are appropriate?

FDA Response:

[Handwritten scribbles and lines, possibly representing redacted or illegible text]

4. Amgen plans to initiate protocol 20030212 with a starting dose of 1  $\mu\text{g}/\text{kg}$ . The primary endpoint platelet target is  $50 \times 10^9/\text{L}$ . The platelet count maintained is  $50 \times 10^9/\text{L}$ .

[Handwritten scribbles and lines, possibly representing redacted or illegible text]

Does the Agency agree that the starting dose and dosage adjustment rules are appropriate?

Page 3 - BB-IND 10205

FDA Response:

Yes.

5. Does the agency agree with a mean of 3 pre-treatment platelet counts of  $\leq 30 \times 10^9/L$  with no individual count to exceed  $35 \times 10^9/L$ , as the inclusion criterion for baseline platelet values?

FDA Response:

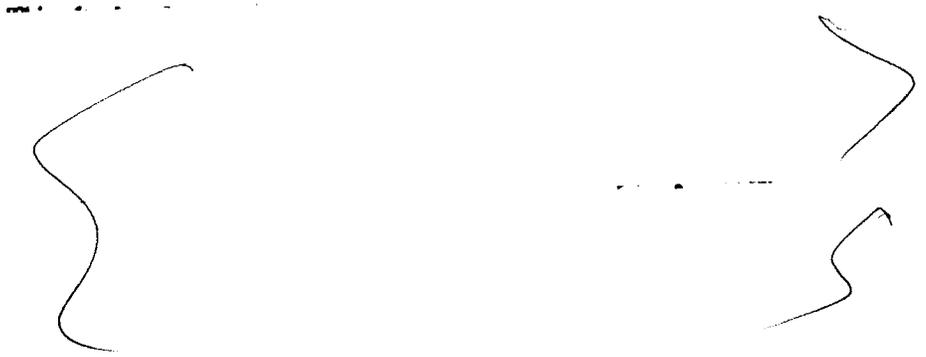
Yes.

6.



FDA Response:

.....



Please comment.

7. Does the Agency agree that the attached Case Report Forms, Eligibility Worksheet and electronic data capture as described in the attached Data Capture Explanation are adequate to capture the required data to support licensure?

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FDA Response:

Yes.

8. Does the Agency agree that the attached Statistical Analysis Plan is adequate to support registration?

FDA Response:

Yes.

9. Does the Agency agree that protocol 20030212 is designed such that positive results would support an indication for AMG 531 for the treatment of thrombocytopenia

FDA Response:

The protocol design is adequate to support the submission of a Biologics License Application. FDA would review the study data to evaluate your proposed indication for AMG 531 for the treatment of thrombocytopenia

We have determined that the design and planned analysis of your study does adequately address the objectives necessary to support a regulatory submission. This special protocol assessment can be modified to improve the study, if you submit a revised special protocol assessment and, FDA agrees in writing to the modification. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

We also have the following comment:

10. Your protocol specifies the measurement of baseline endogenous thrombopoietin level without specifying additional measurements after the initiation of investigational therapy. Investigation of the effect of AMG 531 administration on endogenous thrombopoietin levels may prove useful in defining how AMG 531 is to be used as a clinical therapy. We recommend revising your protocol to specify the measurement of endogenous thrombopoietin level at end of the study. Please comment.

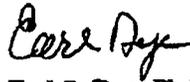
Page 5 - BB-IND 10205

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, Maryland 20852

If you have any questions, please contact the Regulatory Project Manager, Katherine Needleman, M.S., at (301) 827-4358.

Sincerely yours,



Earl S. Dye, Ph.D.  
Director  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Center for Drug Evaluation and Research



**FOOD AND DRUG ADMINISTRATION  
 CENTER FOR DRUG EVALUATION AND RESEARCH  
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 1451 Rockville Pike  
 Rockville, Maryland 20852-1448  
 FAX #: 301-827-5397

**FACSIMILE TRANSMISSION RECORD**

TOTAL NUMBER OF PAGES: 9 (Including Cover Page)

FAX TO: Douglas Hunt / Bonnie Saffyunt Co / Angen, Inc.

Facsimile Telephone No. 805-480-1336 Voice Telephone No. \_\_\_\_\_

FROM: Kathryn Reed Leman / FDA / CDER / DRMP

Facsimile Telephone No. 301-827-5397 Voice Telephone No. \_\_\_\_\_

DATE: 2/3/05 TIME: 2:15 pm

MESSAGE: \_\_\_\_\_  
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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852

Our Reference: BB-IND 10205

FFB 03 2005

Amgen Inc.  
Attention: Douglas Hunt  
One Amgen Center Drive  
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Please refer to your Investigational New Drug Application (IND) for "Thrombopoietin Analogue:Fc Fusion Protein (AMG 531)(Amgen) to the Thrombopoietin Receptor (c-Mpl)," and to your December 21, 2004, Request For Special Protocol Assessment, received December 21, 2004. The protocol # 20030212 dated December 1, 2004, is entitled "A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions:

## Questions:

1. Amgen plans to initiate protocol 20030105 with a starting dose of 1  $\mu\text{g}/\text{kg}$ . Additionally, dosage adjustment rules are included in protocol sections 6.2.1 and 6.2.2. Does the Agency agree that the starting dose and dosage adjustment rules are appropriate?

## FDA Response:

- a. The proposed starting dose is acceptable.
- b.

- c. The Startup Dose Adjustment Rules chart does not use mutually exclusive ranges for platelet counts. To reduce the potential for misinterpretation, we recommend that the ranges be non-overlapping, e.g.,  $< 10$ ,  $\geq 10$  to  $< 50$ ,  $\geq 50$  to  $< 100$ , etc.

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- d. We suggest that you combine the Startup Dose Adjustment Rules chart and the Maintenance Dose Adjustment Rules chart into a single chart, thereby reducing the potential for error from using the wrong chart.

- 2. Does the Agency Administration "Dosage and Administration" section of the package insert

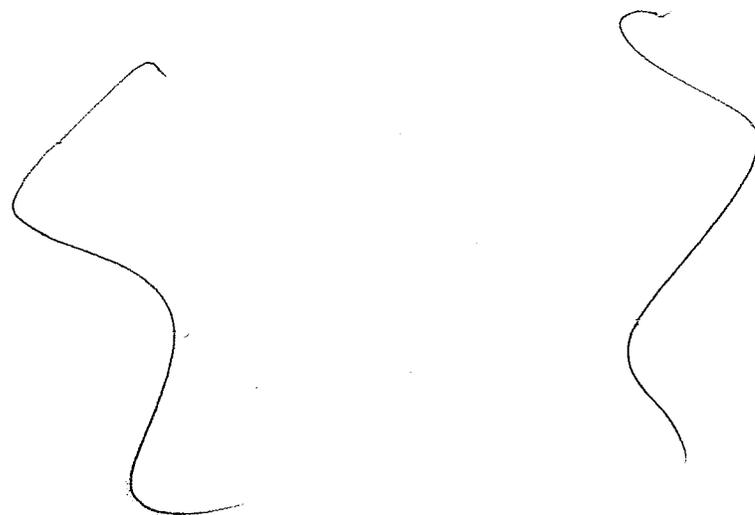
FDA Response:

Two large, irregular handwritten scribbles, one on the left and one on the right, appearing to be redactions or placeholder marks.

- 3. Does the Agency agree that study 20030212 is designed such that positive results would support an indication for AMG 531 for the treatment of thrombocytopenia

FDA Response:

a.

Two large, irregular handwritten scribbles, one on the left and one on the right, appearing to be redactions or placeholder marks.

b.

Page 3 - BB-IND 10205

following recommendations regarding the baseline platelet count:

- i. Apply an upper criterion limit to individual counts obtained during the screening period;
- ii. Increase the number of samples used to establish the mean baseline platelet count to at least three, to be obtained under reasonably similar conditions for each subject;
- iii. Apply an upper criterion limit to the mean baseline platelet count for each subject. The criterion limit for the mean could be different from the limit applied to the individual platelet readings in (i), above. The criterion limit for the mean could be a statistical confidence bound.

You may consider including only one or two of options (i), (ii), and (iii) in the protocol, or propose alternative methods for reducing within-subject variability in baseline platelet count.

4. Does the Agency agree that a sustained positive platelet count response in non-splenectomized patients (from study 20030212) \_\_\_\_\_

FDA Response:

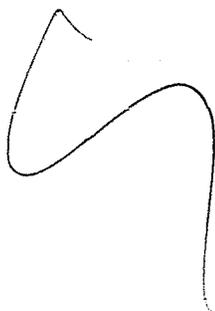


5. Does the Agency agree that the attached statistical analysis plan is adequate to support registration?

FDA Response:

a.

b.



Page 4 - BB-IND 10205

c.

d.

6. Does the Agency agree that the attached Case Report Forms are adequate to capture the required data to support licensure?

FDA Response:

The Case Report Forms have the inadequacies outlined below:

- a. The Case Report Form (CRF) for subject screening is not designed to capture reasons for screening failures. Such knowledge is critical to a thorough understanding of the study population, and critical to placing the study population in the context of the intended clinical target population.
- b. The CRF packet does not include forms for eligibility criteria, physical examination, complete blood count, chemistry studies, P-selectin assay, endogenous thrombopoietin level, and anti-platelet antibody test.
- c. The CRFs for platelet count monitoring and study drug administration are not designed to record the actual time at which the platelet count is obtained. Date and time of sampling could provide important information germane to the analysis and interpretation of study results, and these data should be included in the CRFs.

Page 5 - BB-IND 10205

- d. The CRFs are not designed to capture the identity, date, time, or personnel who perform a given evaluation or record information on the CRFs.
  
- 7. Does the FDA agree that the SF-36 and the attached Patient Assessment Questionnaire are appropriate to capture the required data to ~~assess~~ of health-related quality of life in subjects with thrombocytopenia ~~assess~~

FDA Response:

a.

b.

c.

We have determined that the design and planned analysis of your study does not adequately address the objectives necessary to support a regulatory submission. In addition to the responses to your questions, we have the following comments:

Page 6 - BB-IND 10205

8.



9. Your protocol states that bone marrow stem cell disorders and malignancies are causes for subject exclusion. Please note that exclusion of subjects with these conditions has implications for eventual product labeling. You may wish to comment on the status and impact of the ongoing study in the Netherlands (effect of AMG 531 on bone marrow) on selecting subjects for the pivotal study, and finalize subject selection criteria after considering available data regarding tumorigenesis. You may also want to consider performing bone marrow examination in a subset of subjects after extended (over 6 months) exposure to AMG 531, either as part of the pivotal study or as part of the ongoing open-label study.
10. Duration of platelet response is identified as a secondary endpoint, and it is defined in  
This definition is unclear when applied to periods for which monitoring is less frequent than weekly. We recommend that you clarify the definition of platelet response duration.
11. Your protocol states that approximately 40 centers in the United States and the European Union will participate in the study. Please indicate the estimated numbers of centers in each country.

You will need to submit a revised protocol that addresses all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to the FDA "Guidance for Industry; Formal Meetings with Sponsors and Applicants for PDUFA Products" available at <http://www.fda.gov/cber/guidelines.htm>). This meeting would be limited to discussion of this protocol.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, Maryland 20852

Page 7 - BB-IND 10205

If you have any questions, please contact the Regulatory Project Manager, Katherine Needleman, M.S., at (301) 827-4358.

Sincerely yours,



Earl S. Dye, Ph.D.

Director

Division of Review Management and Policy

Office of Drug Evaluation VI

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852

Our Reference: BB-IND 10205

DEC 17 2004

Amgen Inc.  
Attention: Douglas Hunt  
One Amgen Center Drive  
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Please refer to your **Investigational New Drug Application (IND)** for "Thrombopoietin Analogue:Fc Fusion Protein (AMG 531)(Amgen) to the Thrombopoietin Receptor (c-Mpl)" and to the meeting held on November 23, 2004, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

Katherine Needleman, M.S.  
Regulatory Project Manager  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

Memorandum

Date: **DEC 17 2004**  
From: Katherine Needleman, M.S., DRMP, HFD-109 **KN**  
To: Amgen Inc.  
Subject: IND 10205 EOP2 Meeting Summary

Meeting Date: November 23, 2004

Time: 2:30 - 4:00 p.m. EST

Location: WOC-2, Conference Room G

Meeting Requestor/Sponsor: Amgen Inc.

Product: Thrombopoietin Analogue:Fc Fusion Protein (AMG 531)(Amgen) to the Thrombopoietin Receptor (c-Mpl)

Proposed Use: Treatment of chronic immune thrombocytopenia purpura (ITP)

Type of Meeting: End of Phase 2 (EOP2)

Meeting Purpose: To discuss and reach agreement on the design of the Phase 2/3 planned pivotal study designs to demonstrate efficacy and safety of AMG 531.

*Note: Preliminary comments by FDA were faxed to Heidi Marchand on November 23, 2004, prior to the meeting, and they are included as an Appendix to these meeting minutes. Some of FDA's comments were modified in the course of discussions at the meeting. These minutes supercede FDA's prior preliminary comments.*

**Sponsor questions and FDA response:**

1. Based on the results of Study 20000137B and study 20030213, Amgen plans to initiate these trials with a starting dose of            Does the FDA agree that this starting dose is appropriate?

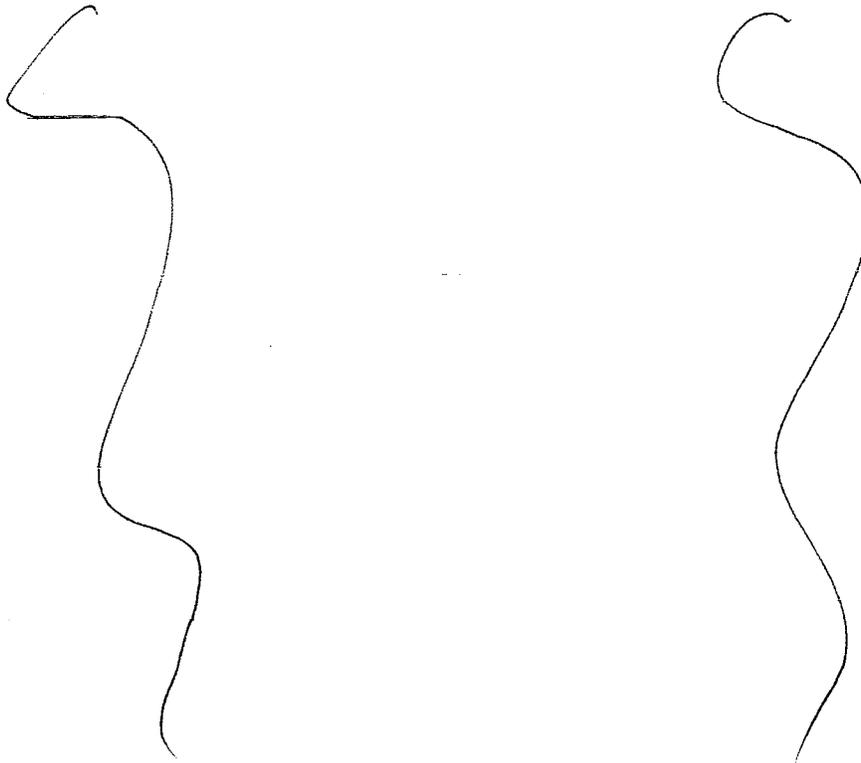
- A starting dose of 1 µg/kg is acceptable. However, FDA is not convinced that the higher starting dose is a better choice. The data in support of a higher dose are limited

and are derived from subjects who have been previously treated with AMG 531, not therapy-naïve subjects as would be treated in the proposed pivotal studies and/or “real world.” The lower dose may be a better choice for many subjects in the proposed studies. FDA recommends starting at the 1 µg/kg and escalating more quickly in selected subjects who appear to be less responsive to AMG 531, as proposed in the revised dose titration rules. Amgen agreed.

- Amgen noted that the maximum dose would be \_\_\_\_\_

2. *Does the FDA agree that the 2 protocols (Study 20030105 and Study 20030212) are appropriately designed to adequately demonstrate safety and efficacy of AMG 531 in thrombocytopenia associated with ITP, an orphan indication?*

FDA has the following comments regarding the design of the protocols:



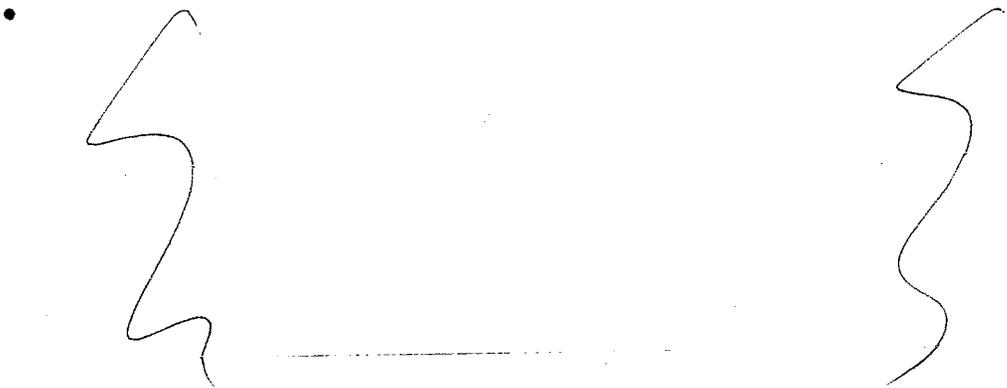
3 Page(s) Withheld

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       Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative- 14



**NOTE: The following FDA comment on Question #2 was faxed to Amgen prior to the meeting as part of FDA's draft responses, but there was no additional discussion of them at the meeting:**



*3. Does the Agency agree that if Study 20030105 and Study 20030212 are adequate, AMG 531 may be indicated for the treatment of thrombocytopenia associated with ITP in nonsplenectomized and splenectomized patients?*

- In principle, if adequate studies are performed in non-splenectomized and splenectomized subjects, then AMG531 may be indicated for the treatment of thrombocytopenia associated with ITP in nonsplenectomized and splenectomized patients.

4. *The AMG 531 safety registration database will consist primarily of subjects participating in*

*Does the FDA agree that this represents an adequate number of subjects for a safety database in this orphan indication?*

- The adequacy of the number of patients would depend on the results available at time of the BLA submission, for both safety and efficacy. The proposed number may or may not be adequate.

5. *Does FDA agree that the Biacore-based immunogenicity screening assay combined with the neutralizing antibody bioassay have been validated appropriately and are suitable for monitoring and detecting immunogenic responses?*

- The immunogenicity screening assay and neutralizing antibody test are sufficient to proceed to Phase 3 studies. However, the following issues should be addressed prior submission of the licensure application:
  - Please provide data supporting the ability of the anti-human F(ab')<sub>2</sub> used in the BIACORE assay to bind different human Ig subclasses.
  - The validation of the Biacore assay should include data showing that the difference (in RUs) between the binding levels of negative control samples and

positive control samples does not vary beyond acceptable limits following multiple cycles of use.

- Amgen agreed to provide these data prior to or at the time of a potential BLA submission.

6. *Due to clinical differences and the small number of pediatric patients diagnosed with thrombocytopenia associated with ITP, Amgen is requesting a deferral of pediatric development at this time but plans to develop AMG 531 in pediatric patients in the future. Does the Agency agree with this approach?*

- This approach is acceptable.

7. *Does FDA recommend that a special protocol assessment be submitted for each proposed pivotal protocol (Study 20030105 and Study 20030212), and does the FDA consider these protocols filed to the IND during this procedure?*

- FDA encourages Amgen to submit a Special Protocol Assessment (SPA) to the IND, and would be glad to comment on a draft protocol, incorporating the recommendations from FDA, prior to submission of an SPA.

#### **Additional Comments/Recommendations**

- FDA noted that AMG 531 is a growth factor, and asked what data Amgen would be generating to put in the "Carcinogenesis, Mutagenesis..." section of labeling.
  - Amgen said they are conducting a separate clinical study in the Netherlands that will look at the effects of AMG 531 on bone marrow.
  - FDA asked Amgen also to provide any preclinical data that could address the question of whether or not AMG 531 has potential to promote tumor growth.

#### **Addendum**

**Follow-up comment to Amgen not discussed at the meeting regarding Question 2:**

- 



Page 10 - BB-IND 10205

**FDA Attendees:** Ellis Unger, John Hyde, John Lee, David Frucht, Anne Pilaro, Janice Derr, Brad Glasscock, Katherine Needleman

**Sponsor Attendees:** Heidi Marchand, Gene Koren, James George, Janet Nichol, Daniel Stepan, Linda Paradiso, Lisa Erickson, Chien-Feng Chen, David Parkinson, Yu-Nien Sun, Jennifer Mercer, Rick Remmele, Bonnie Safyurtlu, Kathy Jelaca-Maxwell

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**OFFICE OF NEW DRUGS**  
**OFFICE OF DRUG EVALUATION VI**  
**DIVISION OF REVIEW MANAGEMENT AND POLICY**

Woodmont Office Complex II, 6<sup>th</sup> Floor  
 1451 Rockville Pike  
 Rockville, Maryland 20852-1448  
 FAX #: 301-827-5397

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TOTAL NUMBER OF PAGES: 3 (Including Cover Page)

FAX TO: Doug Hunt

Facsimile Telephone No. ~~301-827-5397~~ Voice Telephone No.

FROM: Kathy Noel Loman / FDA/CDER/DRMP

Facsimile Telephone No. 301-827-5397 Voice Telephone No. 301-827-5099

DATE: 11/23/04 TIME: 1:45pm

MESSAGE:

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DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852**NOV 23 2004**

Our Reference: BB-IND 10205

Amgen, Incorporated  
Attention: Douglas Hunt  
Director, Regulatory Affairs  
One Amgen Center Drive  
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Reference is made to your Investigational New Drug Application (IND) for "Thrombopoietin Analogue: Fc Fusion Protein (AMG 531)(Amgen) to the Thrombopoietin Receptor (c-Mpl)." We also refer to your submissions of September 28, 2004 and November 17, 2004, received on September 28, 2004 and November 17, 2004 respectively, requesting designation as a Fast Track Product pursuant to Section 506 of the Food, Drug, and Cosmetic Act.

We have reviewed your request and concluded that it meets the criteria for the Fast Track designation. Therefore, we are designating as a Fast Track development program the investigation of Thrombopoietin Analogue: Fc Fusion Protein (AMG 531) in the treatment of immune thrombocytopenic purpura

Please note that if the clinical development program you pursue does not continue to meet the criteria for Fast Track designation, the application will not be reviewed under the Fast Track program.

Under the FDA Modernization Act of 1997, designation as a Fast Track product for a new drug or biological product means that FDA will take such actions as are appropriate to expedite the development and review of the application for approval of such product. FDA may also evaluate for filing and commence review of portions of an application for approval of a Fast Track product under certain conditions.

For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review". This document is available on the internet at <http://www.fda.gov/cder/guidance/index.htm> or may be requested from the Office of Training and Communications, Division of Drug Information at (301) 827-4570.

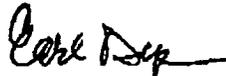
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Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, Maryland 20852

We look forward to working with you to expedite the development and review of this promising proposed use of the product. If you any have questions, please contact Katherine Needleman, M.S., Division of Review Management and Policy, at (301) 827-4358.

Sincerely yours,



Earl S. Dye, Ph.D.  
Director  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Center for Drug Evaluation and Research

**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**OFFICE OF NEW DRUGS**  
**OFFICE OF DRUG EVALUATION VI**  
**DIVISION OF REVIEW MANAGEMENT AND POLICY**

Woodmont Office Complex II, 6<sup>th</sup> Floor  
 1451 Rockville Pike  
 Rockville, Maryland 20852-1448  
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**FACSIMILE TRANSMISSION RECORD**

**TOTAL NUMBER OF PAGES:** 8 (Including Cover Page)

**FAX TO:** Doug Hunt

**Facsimile Telephone No.** 805-480-1330 **Voice Telephone No.** 805-447-1753

**FROM:** Kathy Needleman

**Facsimile Telephone No.** ~~301-827-4358~~ **Voice Telephone No.** 301-827-4358

**DATE:** 1/28/04 **TIME:** \_\_\_\_\_

**MESSAGE:** \_\_\_\_\_

Meeting summary enclosed.

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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852

Our Reference: BB-IND 10205

JAN 8 2004

Amgen Inc.  
Attention: Douglas Hunt  
One Amgen Center Drive  
Thousand Oaks, CA 91320

Dear Mr. Hunt:

Please refer to your **Investigational New Drug Application (IND)** for "Thrombopoietin Analogue:Fc Fusion Protein (AMG 531)(Amgen) to the Thrombopoietin Receptor (c-Mpl)" and to the teleconference held on December 18, 2003, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cder/biologics/default.htm>. Until further notice, however, all correspondence regarding this IND should continue to be addressed to:

CBER Document Control Center  
Attn: Office of Therapeutics Research and Review  
HFM-99, Room 200N  
1401 Rockville Pike  
Rockville, Maryland 20852-1448

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

Katherine Needleman, M.S.  
Regulatory Project Manager  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

Memorandum

Date: **JAN 8 2004**  
From: Katherine Needleman, M.S., DRMP, HFM 588 **KN**  
To: Amgen Inc.  
Subject: **IND 10205 End of Phase 1 Meeting Summary**

Teleconference Date: December 18, 2003

Time: 3:00 - 4:30 p.m. EST

Location: WOC-2, 6-FL Conference Room I

Meeting Requestor/Sponsor: Amgen Inc.

Product: Thrombopoietin Analogue:Fc Fusion Protein (AMG 531)(Amgen) to the Thrombopoietin Receptor (c-Mpl)

Proposed Use: Treatment of chronic immune thrombocytopenia purpura (ITP)

Type of meeting: End of Phase 1

Meeting Purpose: To discuss the patient population with chronic ITP, an appropriate primary endpoint for efficacy assessment and the use of AMG within adult, chronic ITP therapy.

**Chemistry, Manufacturing, and Controls (CMC) Information:**

- Prior to initiation of Phase 2 studies, FDA requires that Amgen develop and validate a sensitive assay for detecting immunogenic responses that are generated against AMG-531, the binding peptide component of AMG-531, Fc, and endogenous TPO. Antibodies that bind to TPO and/or AMG-531, but do not neutralize in the bioassay might still clear TPO from the circulation and have clinical consequences, highlighting the need for a sensitive and specific binding assay for both TPO and AMG-531. Thresholds for these binding assays should be based on ITP patient sera (not normal controls). In addition, it will be critical to consider the possibility that pre-existing antibodies to AMG-531, AMG-531 binding peptide, Fc, and endogenous TPO might be present, especially in patients with ITP. These latter samples should not be used to

generate background thresholds. If these requirements are technically infeasible using the current BIAcore method, a new screening assay must be developed.

Please provide FDA with the raw data related to immunogenicity testing already conducted for normal controls, ITP controls, and each patient that has received AMG 531 (BIAcore and/or bioassay). Also, please indicate what Amgen considers to be the potential source of the high background when using ITP patient sera in the BIAcore assay. Finally, please outline in detail your future plans for developing a suitable screening assay for immunogenicity. It would be preferable if Amgen submitted the full validation package for the screening assay prior to re-testing old patient samples.

FDA also requests more data regarding your neutralizing antibody bioassay. Specifically, please provide a complete validation package supporting background cutoffs for determining positive results and the sensitivity of the assay. In addition, please address the fact that the

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- FDA has the following additional questions and comments regarding your specific responses to FDA comments and questions concerning the original IND submission:
  - (Response to point 8e) Currently, Amgen's stability testing program has no assay that detects changes in Fc function. As this region of AMG 531 likely plays a major role in its pharmacokinetics, FDA strongly recommends that Amgen develop an assay that would address this concern.
  - (Response to point 14a) FDA previously requested that Amgen establish a binding assay for AMG 531, set specifications, and incorporate a binding assay into lot release and stability testing. Amgen responded to the Agency that the cell-based potency assay used for lot release

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Please provide evidence that there is a direct correlation between potency and binding (e.g., in accelerated stability studies).
- Amgen has developed a new and improved BIAcore-based immunogenicity screening assay and has agreed to provide validation data concerning this new immunogenicity assay, as well as the neutralizing antibody assay. Amgen has agreed not to pursue Phase 2 studies until FDA has reviewed these data and agreed that suitable immunogenicity assays have been developed.

**Sponsor questions and FDA response, in order of discussion:**

1



- The primary endpoint is acceptable for the proposed Phase 2 studies.

2. *Various secondary endpoints are under consideration such as:*



*does the Agency agree that these secondary endpoints are adequate?*

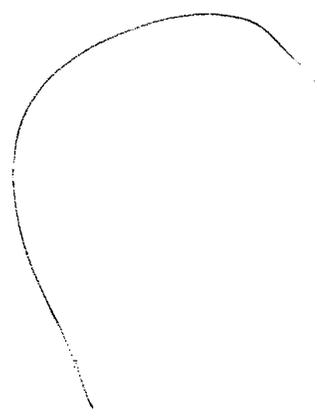
- FDA has no objection to the secondary endpoints proposed but recommends the addition of lab assays such as platelet function tests and mean time to dose stabilization (see Additional Comments below).

3. *AMGEN proposes that the adult subjects entering these studies*



- Yes.

4. *With regard to the Open Label Extension Study (Study 20030213), subjects entering this*



5. AMGEN proposes that subjects may enter the planned studies (Studies 20030105 and 20030212)

- This is a possibility but it is too premature to comment at this time. Amgen may need to evaluate results from the proposed and/or additional Phase 2 or Phase 3 studies.

6. Does the Agency agree that adults with chronic ITP refractory to splenectomy represents a

- There is little information in the literature about the natural history of ITP, and it may be difficult to evaluate the clinical effectiveness of the currently available therapies for ITP. Amgen should provide supportive information, to the extent possible, regarding the natural history of ITP and the effectiveness of currently utilized therapies. This information may be submitted for FDA review according to the agency recommendations outlined in Guidance for Industry: Fast Track Drug Development Programs - Designation, Development, and Application Review.

7. AMGEN proposes a Safety and Efficacy Data Set in the proposed indication of

- FDA is not able to comment at this time. This question would be more appropriate for discussion at an End of Phase 2 meeting after substantial clinical data have been collected.

**Additional Comments/Recommendations:**

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1   Page(s) Withheld

  X   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

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**FDA Attendees:** John Lee, Ellis Unger, John Hyde, Anne Pilaro, David Frucht, Anthony Mire-Sluis, Ferrin Harrison, Aloka Chakravarty, Bradley Glasscock, Katherine Needleman

**Sponsor Attendees:** Julie Lepin, David Parkinson, Janet Nichol, James Matcham, Thomas Tarlow, Jim Navratil, Wende Davis, Gene Koren, Bing Wang, Ross Lobell, James George (Consultant)