



NDA 22-291

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Dennis Williams
1250 South Collegeville Road
Collegeville, PA 19426

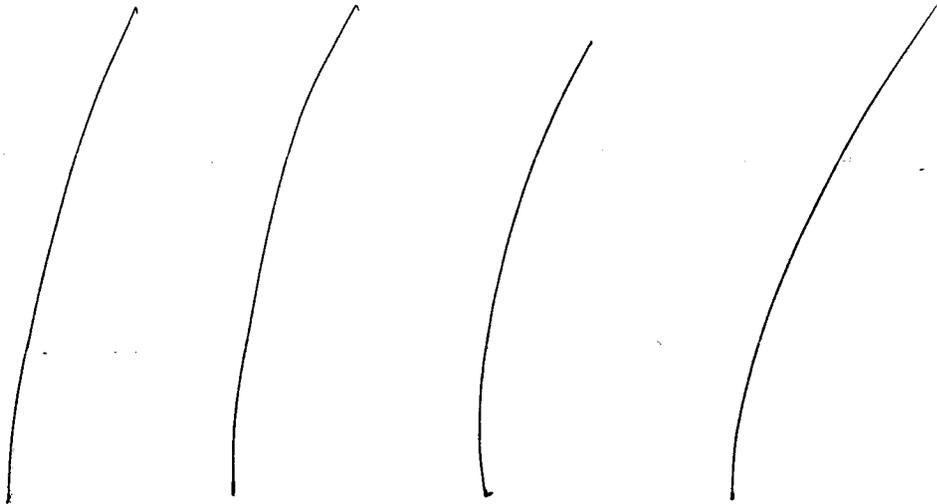
Dear Mr. Williams,

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta™ (eltrombopag) Tablets, 25 mg and 50 mg.

We also refer to your submission dated May 20, 2008, containing "Amendment to Pending Application: CMC, Labeling. Response to FDA Request/Comment: CMC, Labeling."

We are reviewing your submission and have the following comments in response to the information provided in your amendment. Please respond by June 3, 2008 in order to continue our evaluation of your NDA.

1.



2.

b(4)

3. Except as noted above and in the May 28, 2008 FDA letter regarding container labels, you may update the appropriate sections of the NDA with the new information provided in your amendment dated May 20, 2008.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at
301-796-2050.

Sincerely,

{See appended electronic signature page}

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
5/30/2008 03:53:20 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-291

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Dennis Williams
1250 South Collegeville Road
Collegeville, PA 19426

Dear Mr. Williams,

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta™ (eltrombopag) Tablets, 25 mg and 50 mg.

We also refer to your submissions dated May 13, 2008 and May 20, 2008, containing "Amendment to Pending Application: CMC, Labeling. Response to FDA Request/Comment: CMC, Labeling."

We are reviewing your submissions and have the following comments in response to the information provided in your amendment. Please respond by May 30, 2008 in order to continue our evaluation of your NDA.

Revise the container label according to the following consolidated comments from Chemistry, Manufacturing, and Controls (CMC) and the Division of Medication Errors and Prevention (DMEDP):

[Redacted content]

b(4)

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
5/28/2008 06:24:57 PM

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, May 27, 2008 2:06 PM
To: 'dennis.q.williams@gsk.com'
Subject: NDA 22-291 Promacta: Your submission dated April 4, 200
Importance: High

Mr. Williams,

We are reviewing your submission dated April 4, 2008, "Amendment to Pending Application: Clinical – Clinical Pharmacology". In your response to the "highlights of clinical pharmacology", you stated that "For HCV, plasma eltrombopag exposures at the 75mg QD dose were approximately 2.3-fold those observed in patients with ITP at the same dose".

Please submit all available information used to justify the 2.3-fold difference in the HCV population including a descriptive (non-dose-normalized) table of exposure (AUC, Cmax) by race. We understand these data may be preliminary.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

Hyon.Lee@fda.hhs.gov

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5/27/2008

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/s/

Hyon Z Lee
5/27/2008 02:13:03 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, May 27, 2008 10:24 AM
To: 'dennis.q.williams@gsk.com'
Subject: Promacta datasets
Attachments: Whosa_GSK.txt; to GSK 5.23.doc

Mr. Williams,

Please see attached the datasets.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
Hyon.Lee@fda.hhs.gov

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5/27/2008

Dear Bhabita,

Please find the enclosed dataset that I used for the analysis of WHO Bleeding Scale for the 773B.

I used different ways to impute the missing data. None of them are statistically significant. The best result is $P=0.067$. $P\text{-value}=0.09$ if I add 7 days for end of event day from starting event day. And Hazard Ratio=0.798. I also tried to include different covariates. But I didn't get any significant results.

Please let me know if you have any question.

Qing

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Hyon Z Lee
5/27/2008 01:36:39 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-291

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Dennis Williams
1250 South Collegeville Road
Collegeville, PA 19426

Dear Mr. Williams,

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We also refer to your submission dated May 13, 2008, containing "Amendment to Pending Application: CMC, Labeling. Response to FDA Request/Comment: CMC, Labeling."

We are reviewing your submission and have the following comments in response to the information provided in your amendment:

[Redacted content]

b(4)

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
5/15/2008 05:35:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-291

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Dennis Williams
1250 South Collegeville Road
Collegeville, PA 19426

Dear Mr. Williams,

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta™ (eltrombopag) Tablets, 25 mg and 50 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests in addition to our information request letter dated April 29, 2008. We request a prompt written response by May 20, 2008 in order to continue our evaluation of your NDA.

1. The scope and role of the manufacturing process descriptions for the drug substance (S.2.2) and that of the drug product (Section P.3.3) are unclear.
 - a. Describe how these documents relate to the process knowledge gained in the pharmaceutical development report via design of experiments (DoE).
 - b. State whether these are to be considered viable documents amenable to revisions with increased process understanding and improvement.
 - c. State clearly how these documents are related to the master production batch records.
2. It is important to establish a clear linkage between the pharmaceutical development report, the manufacturing process descriptions, and the master production batch records. In their current form, the manufacturing process descriptions for the drug substance and the drug product do not adequately capture the design space information from the pharmaceutical development report. Therefore, revise these sections with the pertinent design space information from the development report. Additional details should include design space for critical and quality process parameters and be based on the findings from the DoEs and process knowledge. Also, it would be desirable to indicate which parameters were found not to influence any critical quality attributes within the range studied in the DoEs and manufacturing experience. Therefore, address the following concerns.

Drug substance manufacturing process description section:



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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
5/13/2008 04:51:35 PM

MEMORANDUM OF TELECONFERENCE

Date: April 30, 2008

Time: 4-4:30 PM

Location: White Oak Bldg 22, Rm 2327

Application: NDA 22-291: Promacta™ (eltrombopag) Tablets

Between

FDA Attendees:

Ravi Harapanhalli, Ph.D., Chief, Branch V (CMC-Premarketing)
Sue Ching Lin, Ph.D., CMC Reviewer, Branch V
Ying Wang, Ph.D., CMC Reviewer, Branch V
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager, DMIHP

And

External Constituent Attendees and Titles:

GlaxoSmithKline

Bekki Komar, Director, Global CMC Regulatory Affairs
Fran Muller
Shiva Kapsi

The Agency sent an information request letter to GSK on April 29, 2008 regarding the Chemistry, Manufacturing and Controls section of the NDA submission, and requested that the sponsor respond in ten days of receipt of the letter.

GSK called the Agency on April 30, 2008 requesting a teleconference to discuss some of the questions included in the letter.

After the introduction, the sponsor stated that they wanted to discuss the question number 5 of the April 29, 2008 letter, i.e., provide dissolution data at earlier time points (e.g. 15, 30 minutes, etc.) for all the clinical and stability batches of 25 mg and 50 mg strength tablets manufactured to date. They stated that this was provided in the March 20, 2008 submission with 15, 30 and 45 minute time points with the mean results only but will provide clarification which batches are clinical and which batches are stability.

The sponsor then asked for clarification on the question number 14 of the April 29, 2008 letter, i.e., the response to FDA comments, as provided in the March 20, 2008 amendment, should also be placed in appropriate drug substance and drug product sections in your CTD submission. Therefore, submit revised sections to the NDA. GSK stated that if they have to edit all sections, it

would be hard for them to meet the ten day timeline, and that they agree to edit the impurity and the characterization sections, but that they have not been editing the development type sections, such as S 2.6 and P 2. They stated that they will edit responses to question numbers 1, 2, 3 and 4, but not provide edits on responses to question numbers 5,6 and 7 of the March 20, 2008 submission. They will submit the revisions to the Gateway on May 13, 2008. The Agency agreed that it is acceptable to provide revised documents in appropriate CTD sections for questions 1 through 4 only.

The teleconference ended.

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/s/

Hyon Z Lee
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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-291

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Dennis Williams
1250 South Collegeville Road
Collegeville, PA 19426

Dear Mr. Williams,

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We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in ten days of receipt of this letter in order to continue our evaluation of your NDA.

Drug Substance:

[Redacted content]

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Ravi Harapanhalli
4/29/2008 02:23:24 PM

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, April 28, 2008 2:09 PM
To: 'dennis.q.williams@gsk.com'
Subject: NDA 22-291 Promacta: Information request

Mr. Williams,

Please provide the following information as soon as possible and preferably no later than one week from today:

- 1) Please provide summary analyses and text description of the ITP bleeding scale results for the 773 A and 773 B studies;
- 2) Please comment upon the basis for the extent of missing "bleeding" data in the analyses of the WHO bleeding scale results for 773 A and 773 B; apparently more than 20% of patients in each study did not have "end of study" bleeding data obtained.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
Hyon.Lee@fda.hhs.gov

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4/28/2008

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Hyon Z Lee
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MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 8, 2008
TIME: 12:00 – 1:00 PM
LOCATION: Conference Room 2201 (White Oak)
APPLICATION: NDA 22-291
DRUG NAME: Eltrombopag Olamine (SB-497115-GR)
TYPE OF MEETING: Risk Management Plan meeting

MEETING CHAIR: Rafel Rieves, M.D.

MEETING RECORDER: Hyon-Zu Lee, Pharm.D.

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel Rieves, M.D., Acting Division Director
Andrew Dmytrijuk, M.D., Medical Reviewer
Yash Chopra, Ph.D., Pharmacology/Toxicology Reviewer
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Qing Xu, Ph.D., Statistics Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager
Florence Moore, M.S., Acting Team Leader, Project Management

Office of Surveillance and Epidemiology (OSE)

Claudia Karwoski, Pharm.D., Acting Director, Division of Risk Management
Janet Anderson, Pharm.D., Regulatory Project Manager
Suzanne Berkman, Pharm.D., Risk Management Analyst, Division of Risk Management

EXTERNAL CONSTITUENT ATTENDEES:

Michael Arning, M.D., Ph.D., Group Director, Oncology MDC
Sophia Goodison, M.P.H., Associate Director, Global Clinical Safety
Josephine Comisky, Risk MAP, Senior Director
Randy Batenhorst, Pharm.D., V.P., US Regulatory Affairs
Manuel Aivado, M.D., Associate Director, Clinical Development, Oncology MDC
Julian Jenkins, M.S., Global Project Leader, Oncology MDC
Rezvan Rafi, M.D., Oncology Medical Director, Global Safety/Clinical Pharmacovigilance
Debasish Roychowdhury, M.D., V.P., Clinical Development, Oncology MDC, US
Nicole Stone, Ph.D., Associate Director, Clinical Development, Oncology MDC, US
Dennis Williams, R.Ph., Assistant Director, Regulatory Affairs, Oncology
Mary Wire, Pharm.D., Pharmacokinetics

BACKGROUND:

The Agency had a meeting with GSK on March 31, 2008 to discuss the risk management plan (RMP) for Promacta. The Agency arranged a follow up teleconference with the sponsor.

DISCUSSION POINTS:

The Agency indicated that the proposed labeling submitted with the initial NDA appears deficient and needs extensive revisions in formatting as well as the clinical contents. There is

b(4)

The sponsor stated that the revised risk management plan (RMP) will incorporate the feedback received from the Agency on the March 31, 2008 meeting, and that they are proposing many changes. The program will include _____

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They stated that they are planning to submit the 120 safety update on April 18, 2008 which includes 330 subjects with chronic ITP (155 subjects exposed to the drug for six months and 44 subjects for one year). They will address adverse reactions regarding hepatotoxicity, phototoxicity, renal toxicity, thromboembolic events and cataracts consistent with the initial NDA submission. They will also do their best to include data regarding bone marrow effects of the drug. The sponsor asked the Agency what they need to do to change the proposed indication to long term with the available long term data.

The Agency responded that the sponsor needs to fully analyze the interim study reports for the clinical trials in patients with chronic ITP, and asked how many patients continued to enroll into the extension studies from the six weeks studies.

The sponsor stated that approximately 70% of the patients who participated in an initial study chose to enroll in the extension study. FDA noted that loss of more than 20% of these patients raised special concerns regarding the inherent selection bias for the extension study.

The Agency indicated that in general, the patients that continued to take the drug longer than six weeks may be healthier, and that the study reports for the extension studies as well as six weeks studies should be analyzed. The FDA's briefing document for the Advisory Committee (AC) scheduled on May 30, 2008 will be based on the original NDA submission, not on data submitted with the 120 day safety update. Hence, FDA noted that the review will continue with detailed data analyses focused upon the proposed short term use indication.

The sponsor agreed that they will prepare their briefing document based on the original submission and not include substantive new data.

The Agency asked for clarifications on the following issues related to clinical pharmacology:

- The Agency asked the sponsor to clarify the discrepancy between drug exposure in East Asian/Japanese subjects from clinical pharmacology studies conducted in the west and

those conducted in Japan. FDA further highlighted specific concerns regarding quality of the data from the 104603 & 105580 trials conducted in Japan given the formulation, high variability and upper limit of quantification of the assay used to determine eltrombopag concentrations. FDA stated these issues may have contributed to some of the higher exposures noted in the trials conducted in Japan. FDA further stated that the limited number of East Asian/Japanese subjects studied in the western trials did not show this higher exposure and cited examples from the 105122 trial. The sponsor agreed with FDA's concerns regarding the single dose 104603 trial, but still felt the repeat dose trial reported higher exposure in the East Asian/Japanese. The sponsor stated that they were preparing another report on the effect of ethnicity on the clinical pharmacology of eltrombopag which would be sent to FDA in the next few days.

- The Agency stated that while reviewing the effect of East Asian/Japanese race on eltrombopag it was noted that African Americans appears to display higher exposure in the 105122 and 105120 studies. FDA also noted the sponsor's statement in the ethnicity report that African Americans were genetically similar to Asians. The FDA asked the sponsor why they had not addressed this issue. The sponsor stated that they would address this issue in a report on the effect of ethnicity on the clinical pharmacology of eltrombopag which would be sent to FDA in the next few days.
- FDA found that smokers were included in the repeat dose PK study 105580 (Japan); however, this factor was not addressed by the sponsor in their analysis. A preliminary analysis by FDA suggested a trend toward lower exposure in smokers. FDA was interested in this factor given smoking may induce UGT1A1 which is a metabolic pathway for eltrombopag. FDA asked if this analysis was conducted by the sponsor. The sponsor stated this analysis was not conducted but they would conduct an analysis across studies to evaluate the effect of smoking on eltrombopag PK/PD.
- FDA found that two patients in the 497115/001 study who had received acetaminophen during the PK sampling were in the 75th percentile for drug exposure. Given glutathione conjugation is a metabolic pathway for both acetaminophen and eltrombopag, FDA asked if the sponsor had investigated this potential drug interaction. The sponsor stated this analysis was not conducted but they would conduct an analysis across studies to evaluate the effect of acetaminophen on eltrombopag PK/PD and vice versa.
- FDA noted that studies that utilized formulations made from substance batch TPO-E-02C appeared to have a higher incidence of liver function test (LFT) elevations compared to formulations from other substance batches used in the clinical pharmacology studies. Given this formulation was also used in the pivotal trial, FDA asked the sponsor to evaluate the effect of this substance batch on the incidence of elevated LFT's. The sponsor agreed to evaluate this issue across studies.
- The sponsor committed to submitting the ethnicity report within several days of the meeting and the other analyses within ten business days of the meeting.

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The sponsor then asked if the data in the extension studies are supportive to modify the indications in the labeling.

The Agency responded that all options will be considered and that the strengths and limitations of the two six weeks studies and the limited data from the extension and repeat dose studies will be discussed or summarized at the AC. The Agency asked the sponsor to provide information regarding the number of patients and their specific patient identifier numbers that completed or

were withdrawn or discontinued from the pivotal studies and then were enrolled into the EXTEND, RAISE or any other long term treatment study and into which long term study specifically they were enrolled. The Agency also asked that the sponsor provide a table which shows the distribution of patients into the various studies, i.e., EXTEND, RAISE, etc.

The sponsor asked how they should prepare the briefing document for the AC regarding data of the EXTEND and RAISE studies and supporting indication statement.

The Agency stated that the general format of the questions to the AC panel will probably be similar to the ones in the recent advisory committee regarding another product that is proposed for use in the treatment of ITP.

The sponsor asked when the Agency would like to have the revised labeling.

The Agency responded that some components of the boiler plate of the labeling are deficient and need to be revised. We will start working on the labeling after the ODAC since the discussions at the AC might be relevant and affect the labeling.

The sponsor understood and stated that they will submit the revised RMP within five business days.

**APPEARS THIS WAY
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/s/ -----

Hyon Z Lee
4/21/2008 02:01:00 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 31, 2008
TIME: 1:00 - 2:30 PM
LOCATION: Conference Room 1417 (White Oak)
APPLICATION: NDA 22-291
DRUG NAME: Eltrombopag Olamine (SB-497115-GR)
TYPE OF MEETING: Risk Management Plan meeting

MEETING CHAIR: Rafael Rieves, M.D.

MEETING RECORDER: Hyon-Zu Lee, Pharm.D.

FDA ATTENDEES:

Office of Oncology Drug Products (OODP)

Karen Weiss, M.D., Deputy Director

Division of Medical Imaging and Hematology Products (DMIHP)

Rafael Rieves, M.D., Acting Division Director

Andrew Dmytrijuk, M.D., Medical Reviewer

Minh Ha Tran, D.O., Medical Reviewer

Jyoti Zalkikar, Ph.D., Statistics Team Leader

Qing Xu, Ph.D., Statistics Reviewer

Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer

Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

Diane Leaman, Acting Safety Project Manager

Office of Surveillance and Epidemiology (OSE)

Claudia Karwoski, Pharm.D., Acting Director, Division of Risk Management

Janet Anderson, Pharm.D., Regulatory Project Manager

Suzanne Berkman, Pharm.D., Risk Management Analyst, Division of Risk Management

Walter Fava, Pharm.D., Safety Evaluator, Division of Medication Error and Technical Support

EXTERNAL CONSTITUENT ATTENDEES:

Michael Arning, M.D., Ph.D., Group Director, Oncology MDC

Sophia Goodison, M.P.H., Associate Director, Global Clinical Safety

Josephine Comisky, Risk MAP, Senior Director

Randy Batenhorst, Pharm.D., V.P., US Regulatory Affairs

Manuel Aivado, M.D., Associate Director, Clinical Development, Oncology MDC

Julian Jenkins, M.S., Global Project Leader, Oncology MDC

Rezvan Rafi, M.D., Oncology Medical Director, Global Safety/Clinical Pharmacovigilance

Debasish Roychowdhury, M.D., V.P., Clinical Development, Oncology MDC, US

Nicole Stone, Ph.D., Associate Director, Clinical Development, Oncology MDC, US

Dennis Williams, R.Ph., Assistant Director, Regulatory Affairs, Oncology

BACKGROUND:

An Application Orientation meeting was held on March 13, 2008 for Promacta. During that meeting, the Office requested a separate meeting be held to discuss the risk management plan (RMP). For the preparation of the meeting, GlaxoSmithKline submitted the risk management briefing document on March 24, 2008.

DISCUSSION POINTS:

The meeting started with the sponsor presenting the slides attached below.

The Agency asked to provide updates on the extension studies including the EXTEND and RAISE studies.

The sponsor responded that they have 207 patients in the EXTEND study and that they are planning to submit the data in the 120 safety update in three weeks. The study report of the RAISE study will be submitted in the 4th quarter of 2008. They stated that the median continuous exposure in the extension studies is 70 days and mean 134 days.

The Agency commented that the proposed indication is for the short term treatment, but because the drug product is administered orally, it may be administered "off label" in both a chronic and repeated manner. The Agency then indicated that long term safety is an important issue, and that we have concerns about hepatotoxicities and potential bone marrow toxicities (among other concerns) when the drug will be administered both short term and chronically.

The sponsor responded that they have seen abnormalities in the nucleated blood cells in four subjects in the RAISE study and six subjects in the REPEAT study but it did not appear that these changes were permanent. No other bone marrow abnormalities have been observed to date. As part of the risk management plan the sponsor proposes that all Phase IV studies incorporate bone marrow biopsy evaluation for those patients that develop peripheral blood smear abnormalities suggestive of bone marrow toxicity.

The Agency asked if GSK had performed chronic dosing studies in animals.

The sponsor responded that they have two year carcinogenicity studies.

The Agency expressed concerns that the drug can, in effect, be used continuously with multiple ("back to back") cycles of six weeks and that there is an apparent disconnect of the proposed indication and the how the drug may be used, _____ The Agency stated that the pharmacovigilance plan ? _____ s). The indicated treatment duration is apparently for a single six weeks of drug use in a setting of a chronic disease and, at present, there is little long term safety data to support the safety of the drug when used for more than six weeks or in a repeated manner.

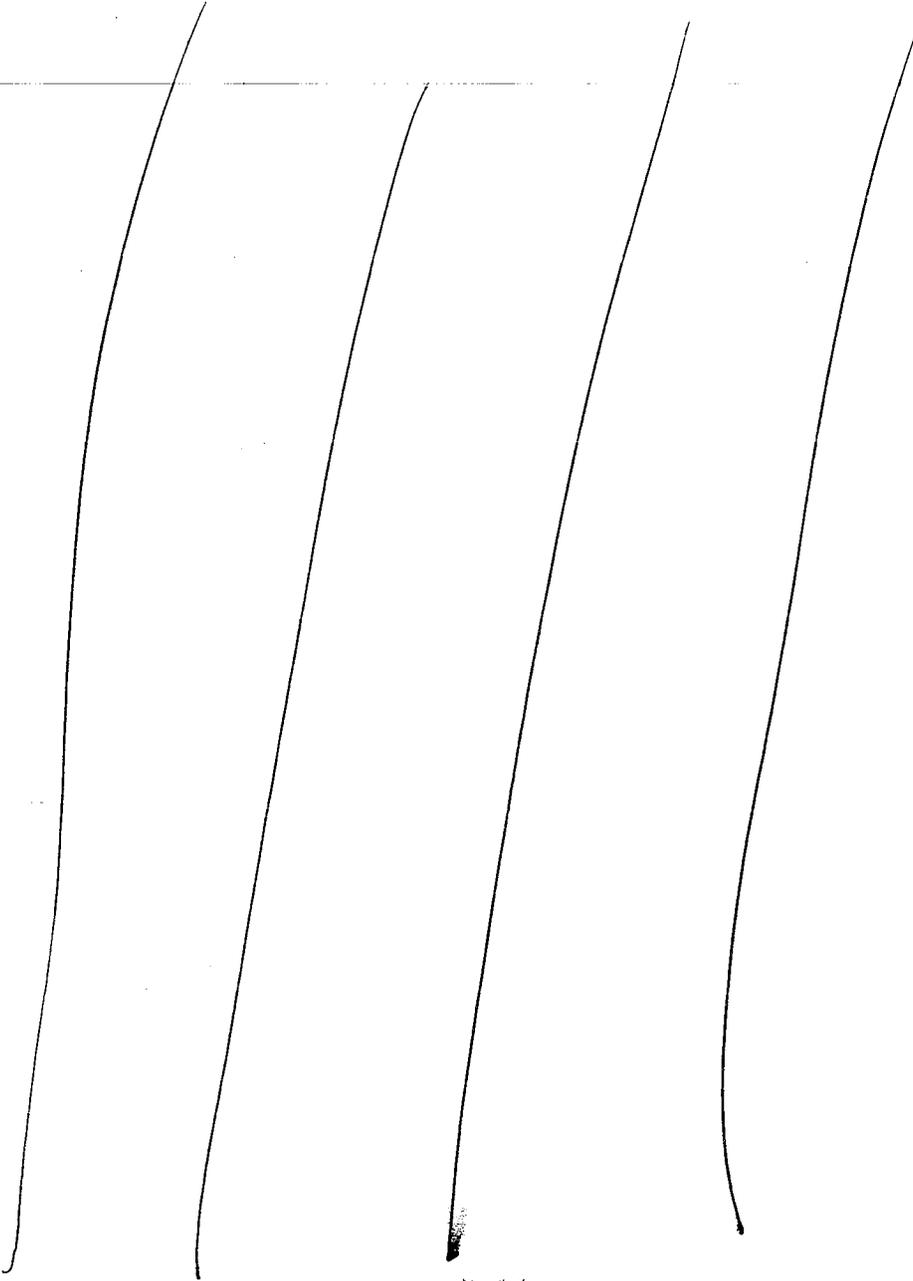
b(4)

The sponsor stated that they understand the problem and that the plan is eventually to treat the patients long-term, but until they have more data, that the current RMP _____

b(4)

The Agency indicated that the RMP plan states that _____

b(4)



b(4)

The sponsor stated that they are working on the East Asian population and that they would submit the study report on the Japanese population. The sponsor then stated that they considered the chronic use issue and that they thought of modifying the proposed indication to treatment of previously treated patients with chronic ITP to increase platelet counts and to decrease or prevent bleeding.

The Agency responded that the sponsor should make the call for appropriate action plans, and that we welcome additional analyses.

The meeting concluded.

**APPEARS THIS WAY
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Draft Labeling (b4)

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Deliberative Process (b5)

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/s/

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Hyon Z Lee  
4/11/2008 11:52:17 AM  
CSO

**Lee, Hyon-Zu**

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**From:** Lee, Hyon-Zu  
**Sent:** Friday, April 04, 2008 10:45 AM  
**To:** 'dennis.q.williams@gsk.com'  
**Subject:** NDA 22-291 Promacta: Pre-clinical information request  
**Importance:** High

Mr. Williams,

We are performing the statistical review of the carcinogenicity studies. Please submit the tumor datasets of the studies in FDA data format as soon as possible. If the datasets have been submitted please let us know the location.

Thank you,

Hyon-Zu Lee, Pharm.D.  
Regulatory Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

[Hyon.Lee@fda.hhs.gov](mailto:Hyon.Lee@fda.hhs.gov)

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4/4/2008

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/s/

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Hyon Z Lee  
4/4/2008 10:58:12 AM  
CSO

**Lee, Hyon-Zu**

**From:** Lee, Hyon-Zu  
**Sent:** Wednesday, April 02, 2008 2:46 PM  
**To:** 'dennis.q.williams@gsk.com'  
**Subject:** NDA 22-291 Promacta: clinical pharmacology information request

Mr. Williams,

In following up on the March 31, 2008 meeting discussion regarding dosing and ethnicity, please submit the validation report for the assay Method for the Determination of SB-497115 in Human Plasma for the Study TRA104603 (Japan). You have only submitted the validation for the urine.

Please submit by the end of the week so that we can discuss this at the teleconference on April 8, 2008.

Thank you,

Hyon-Zu Lee, Pharm.D.  
Regulatory Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Office: 301-796-2050  
Fax: 301-796-9849  
[Hyon.Lee@fda.hhs.gov](mailto:Hyon.Lee@fda.hhs.gov)

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4/2/2008

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/s/

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Hyon Z Lee  
4/2/2008 03:09:46 PM  
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**Lee, Hyon-Zu**

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**From:** Lee, Hyon-Zu  
**Sent:** Wednesday, March 26, 2008 4:15 PM  
**To:** 'dennis.q.williams@gsk.com'  
**Subject:** NDA 22-291 Promacta: Clinical Pharmacology information request  
**Importance:** High  
**Attachments:** HighlightsofClinicalPharmacology.doc

Mr. Williams,

Please complete the attached ClinPharm table and submit as soon as possible. Also, please submit all related ECG waveforms to the ECG warehouse at [www.ecgwarehouse.com](http://www.ecgwarehouse.com), and submit the most recent Investigator's Brochure for this application.

Please let me know when you are able to submit the requested information.

Thanks,

Hyon-Zu Lee, Pharm.D.  
Regulatory Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Office: 301-796-2050  
Fax: 301-796-9849  
[Hyon.Lee@fda.hhs.gov](mailto:Hyon.Lee@fda.hhs.gov)

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3/26/2008

### Highlights of Clinical Pharmacology

|                                           |                                                                               |                                                                                                                         |
|-------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| Therapeutic dose                          | Include maximum proposed clinical dosing regimen.                             |                                                                                                                         |
| Maximum tolerated dose                    | Include if studied or NOAEL dose                                              |                                                                                                                         |
| Principal adverse events                  | Include most common adverse events: dose limiting adverse events              |                                                                                                                         |
| Maximum dose tested                       | Single Dose                                                                   | Specify dose                                                                                                            |
|                                           | Multiple Dose                                                                 | Specify dosing interval and duration                                                                                    |
| Exposures Achieved at Maximum Tested Dose | Single Dose                                                                   | Mean (%CV) C <sub>max</sub> and AUC                                                                                     |
|                                           | Multiple Dose                                                                 | Mean (%CV) C <sub>max</sub> and AUC                                                                                     |
| Range of linear PK                        | Specify dosing regimen                                                        |                                                                                                                         |
| Accumulation at steady state              | Mean (%CV); specify dosing regimen                                            |                                                                                                                         |
| Metabolites                               | Include listing of all metabolites and activity                               |                                                                                                                         |
| Absorption                                | Absolute/Relative Bioavailability                                             | Mean (%CV)                                                                                                              |
|                                           | T <sub>max</sub>                                                              | <ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul> |
| Distribution                              | V <sub>d</sub> /F or V <sub>d</sub>                                           | Mean (%CV)                                                                                                              |
|                                           | % bound                                                                       | Mean (%CV)                                                                                                              |
| Elimination                               | Route                                                                         | <ul style="list-style-type: none"> <li>• Primary route: percent dose eliminated</li> <li>• Other routes</li> </ul>      |
|                                           | Terminal t <sub>1/2</sub>                                                     | <ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>         |
|                                           | CL/F or CL                                                                    | Mean (%CV)                                                                                                              |
| Intrinsic Factors                         | Age                                                                           | Specify mean changes in C <sub>max</sub> and AUC                                                                        |
|                                           | Sex                                                                           | Specify mean changes in C <sub>max</sub> and AUC                                                                        |
|                                           | Race                                                                          | Specify mean changes in C <sub>max</sub> and AUC                                                                        |
|                                           | Hepatic & Renal Impairment                                                    | Specify mean changes in C <sub>max</sub> and AUC                                                                        |
| Extrinsic Factors                         | Drug interactions                                                             | Include listing of studied DDI studies with mean changes in C <sub>max</sub> and AUC                                    |
|                                           | Food Effects                                                                  | Specify mean changes in C <sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)                      |
| Expected High Clinical                    | Describe worst case scenario and expected fold-change in C <sub>max</sub> and |                                                                                                                         |

|                   |                                                                                |
|-------------------|--------------------------------------------------------------------------------|
| Exposure Scenario | AUC. The increase in exposure should be covered by the supra-therapeutic dose. |
|-------------------|--------------------------------------------------------------------------------|

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/s/

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Hyon Z Lee  
3/26/2008 04:51:38 PM  
CSO



NDA 22-291

**INFORMATION REQUEST LETTER**

GlaxoSmithKline  
Attention: Sandra L. Bihary-Waltz, MSN  
2301 Renaissance Boulevard,  
PO Box 61540  
King of Prussia, PA 19406

Dear Ms. Bihary-Waltz:

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta (eltrombopag).

We are reviewing the labeling section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following information is requested:

[Redacted content]

(b)(4)

[Redacted content]

b(4)

If you have any questions, call Hyon-Zu Lee, Pharm.D. at 301-796-2192.

Sincerely,

*{See appended electronic signature page}*

Alice Kacuba, RN, MSN, RAC  
Regulatory Project Manger Team Leader  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/

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Alice Kacuba  
3/14/2008 10:36:45 AM



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-291

**INFORMATION REQUEST LETTER**

GlaxoSmithKline  
Attention: Sandra L. Bihary-Waltz, MSN  
2301 Renaissance Boulevard,  
PO Box 61540  
King of Prussia, PA 19406

Dear Ms. Bihary-Waltz:

Please refer to your December 19, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta™ (eltrombopag olamine) Tablets; 25 mg and 50 mg.

We also refer to your submission dated March 3, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in two weeks in order to continue our evaluation of your NDA.

*[Three large, curved, handwritten lines, likely indicating redactions or specific points of interest.]*

(X)

  1   Page(s) Withheld

  /   Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

Ravi Harapanhalli
3/6/2008 01:58:38 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Medical Imaging and
Hematology Products

FACSIMILE TRANSMITTAL SHEET

DATE: February 29, 2008

To: Sandra L. Bihary-Waltz, MSN	From: Alice Kacuba, R.N., MSN, RAC Regulatory Project Management Team Leader Alice.Kacuba@fda.hss.gov
Company: GSK	Division of Medical Imaging and Hematology Drug Products
Fax number: by email	Fax number: 301-796-9849
Phone number: 610-787-3796	Phone number: (301) 796-1381
Subject: Information Requests from biopharm reviewer	

Total no. of pages including cover: ____

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Hi,

The following are Information requests from the stats reviewer:

We received your response to our Biopharm IR. However, the following information was not addressed. Please provide an expeditious response:

The NONMEM analysis dataset for Report Number: RA018135 Population Pharmacokinetic and Pharmacodynamic Analysis of Eltrombopag in Healthy Subjects and Subjects with Chronic Idiopathic Thrombocytopenic Purpura (SAS transfer file format).

Thank you.

Alice Kacuba

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Alice Kacuba
2/29/2008 08:49:19 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-291

GlaxoSmithKline
Attention: Sandra L. Bihary-Waltz, MSN
2301 Renaissance Boulevard,
PO Box 61540
King of Prussia, PA 19406

Dear Ms. Bihary-Waltz:

Please refer to your new drug application (NDA) dated December 19, 2007, received December 19, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Promacta™ (eltrombopag olamine) Tablets; 25 mg and 50 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is June 19, 2008.

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

1. The pivotal studies are small in terms of number of enrolled patients.
2. The indication that is sought for Promacta is that of short term treatment of ITP, which is a chronic disease. There is a reasonable potential that Promacta may be used off label to treat ITP on a long-term (chronic) basis.
3. We are concerned that there is a difference in dosing recommendation based on patient ethnicity, i.e., a dose of 25 mg once daily might need to be considered for patients of East Asian ancestry. The scientific basis for the difference in recommended dosing is not obvious and particular directions for implementing the recommended dosing (i.e., clarifying the population) may need to be elaborated.
4. Although Promacta appears to decrease bleeding overall, little data have been supplied to support a claim that _____
5. The safety analyses revealed that 3 patients with ITP who were treated with Promacta developed significant hepatobiliary abnormalities with elevation of aminotransferases to

≥ 3 fold the upper limit of normal and total bilirubin > 1.5 fold the upper limit of normal and an additional 5 patients developed hyperbilirubinemia. Overall, there appear to be 16 of 164 patients from the pivotal trials who were treated with Promacta, compared to 5 of 67 placebo treated patients that developed hepatobiliary abnormalities. Your proposed risk management plan may not adequately address the potential safety concern for hepatotoxicity.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

If you have any questions, call Alice Kacuba, Regulatory Project Manager Team Leader, at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

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

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/s/

Rafel Rieves
2/28/2008 03:19:08 PM



NDA 22-291

NDA ACKNOWLEDGMENT

GlaxoSmithKline
Attention: Sandra L. Bihary-Waltz, MSN
2301 Renaissance Boulevard,
PO Box 61540
King of Prussia, PA 19406

Dear Ms. Bihary-Waltz:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Promacta™ (eltrombopag olamine) Tablets; 25 mg, 50 mg

Date of Application: December 19, 2007

Date of Receipt: December 19, 2007

Our Reference Number: NDA 22-291

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-1381.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Regulatory Project Manager Team Leader
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Alice Kacuba
1/8/2008 06:12:23 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 63,293

GlaxoSmithKline
Attention: Sandra Bihary-Waltz
2301 Renaissance Boulevard, Building 510
P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Ms. Bihary-Waltz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Eltrombopag Olamine (SB-497115-GR) Tablets.

We also refer to the meeting between representatives of your firm and the FDA held on August 2, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm. D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 2, 2007
TIME: 11:00 AM– 12:30 PM
LOCATION: Conference Room 2376 (White Oak)
APPLICATION: IND 63,293
DRUG NAME: Eltrombopag Olamine (SB-497115-GR) Tablets
TYPE OF MEETING: Pre-NDA meeting

MEETING CHAIR: Rafael Rieves, M.D.

MEETING RECORDER: Hyon-Zu Lee, Pharm.D.

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Rafael Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
Andrew Dmytrijuk, M.D., Medical Reviewer
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Richard Chen, Ph.D., Statistics Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Yash Chopra, Ph.D., Pharmacology/Toxicology Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Sandi Bihary-Waltz, M.S.N., Director, US Regulatory Affairs, Oncology
Robert S. Watson, M.B.A., Vice President, US Regulatory Affairs, Oncology
Michael Arming, M.D., Ph.D., Group Director, Oncology MDC
Nicole Stone, Ph.D., Associate Director, Oncology MDC
Bhabita Mayer, Ph.D., Principle Statistician, BDS
Teresa Sellers, M.S., Manager, Clinical Safety/Safety Assessment
Ron Eydelloth, D.V.M., Director, WorldWide Safety Assessment
Susan Cousounis, M.S., Director, Medical Writing/Clinical Sub.Planning
Kenneth Lord, Ph.D., Lead Medical Writing Scientist, Clin. Submissions
David Donohue, M.B.A., Manager, Regulatory Operations
Roya Behbahani, M.B.A., Director, Strategic Labeling
Bin Peng, Ph.D., Director, Clinical Pharmacology
Rezvan Rafi, M.D., TA Director, Global Clinical Safety
Dennis Williams, R.Ph., Assistant Director, US Regulatory Affairs, Oncology
Manuel Aivado, M.D., Associate Director, Oncology MDC
Richard Rogers, Project Manager, Global Project Management

BACKGROUND AND MEETING OBJECTIVES:

GlaxoSmithKline (GSK) submitted a Pre-NDA meeting request on May 31, 2007 to discuss the format and content proposal of the eltrombopag NDA for the treatment of previously treated adults with chronic Idiopathic Thrombocytopenic Purpura (ITP)

DISCUSSION POINTS:

In response to the questions in the July 5, 2007, background package, the following comments were faxed to GSK on July 31, 2007:

Questions:

1. *Does the Division agree with the proposed format of presentation in the submission dossier for TRA100773A, TRA100773B, TPL102357, SB497115/003, EXTEND and REPEAT?*

FDA Response:

The format of presentation of the trials used to support the registration of eltrombopag appears to be appropriate. You should submit data in XML file format for review.

2. *Does the Division agree with the proposed format of presenting RAISE, LENS and TRA109678 as summary reports in m5 and synopses in m2.7.6 in the CTD?*

FDA Response:

All available data that will be used to support the registration of Eltrombopag for the proposed indication should be submitted for review and also refer to the response for question 1. We understand RAISE, LENS and TRA109678 are on-going clinical studies and that summary reports will be supplied in m5 and synopses supplied in m2.7.6. In general, this plan appears reasonable. The safety data from these on-going studies (that include some subjects without ITP) should be summarized separately from that for ITP patients enrolled in the completed studies (including the interim lock for EXTEND and REPEAT). For both completed and on-going studies, patient narratives and case report forms should be submitted for all patients who died, experienced serious adverse events and/or discontinued study medication due to adverse events.

3. *Does the Division agree with the proposed format and data presentation as short summaries for the eltrombopag Liver/HCV, CIT and Japanese ITP studies?*

FDA Response:

In general, the approach appears reasonable. Please see responses to questions 1 and 2.

4. *GSK proposes to present the final data from the pivotal studies and the available efficacy data from REPEAT and EXTEND in the Summary of Clinical Efficacy (SCE), and to pool data from the two pivotal studies. Does the Division find this proposal acceptable for the SCE?*

FDA Response:

Your plan of pooling data from the two pivotal studies is acceptable as long as the data for each of the two studies has also been analyzed and presented individually for efficacy analysis. Pooled dataset tables should include a variable to indicate the specific study for each patient.

5. *Does the Division agree with the proposed ITT population for the summary analyses?*

FDA Response:

In the protocols, the ITT population was apparently defined as all randomized subjects who received at least one dose of study medication and at least one platelet count post-dose. Now, for the summary analyses of efficacy, you propose to redefine the ITT population as all subjects randomized. Please explain why you would like to change the primary efficacy analysis population. Summary analyses of pooled efficacy data will largely be used for illustrative review purposes and is highly unlikely to impact the definitive determination of eltrombopag efficacy or product labeling.

You may provide the proposed summary analysis as an exploratory analysis or supportive analysis with pre-specified method of missing data imputation for those who did not receive at least one dose of study medication or without any platelet count post-dose. The extent and handling of missing data in these analyses will be considered during the review.

6. *GSK proposes to present the final data from the pivotal studies and the available safety data from REPEAT, EXTEND and RAISE, and to pool only data from the pivotal studies. Does the Division find the above proposal acceptable for the Summary of Clinical Safety?*

FDA Response:

The proposal appears to be acceptable. However you should analyze the safety data of the pivotal trials separately as well (these analyses should be provided in the individual study reports). Regarding safety data in non-ITP subjects, see responses to questions 1 and 2.

7. *Does the Division find the above proposal acceptable for the Summary of Clinical Safety regarding the contents of the SCS, reporting of SAEs, the provision of narratives and all other identified safety data?*

FDA Response:

The proposal appears to be generally acceptable. However, also see responses to questions 1 and 2.

8. *Does the Division agree with GSK's proposal of not providing platelet data in the presentation of safety data in RAISE due to the blinded nature of this ongoing study?*

FDA Response:

Blinded platelet count data should be included in the presentation of safety data from the RAISE study. We are especially interested in the detection of any marked elevations in platelet counts and/or marked elevations that are followed by marked decreases in platelet counts.

9. *Does the Division agree with the proposed approach for the Clinical Summaries to be satisfactory and to not require a traditional ISS or ISE?*

FDA Response:

The proposal appears to be acceptable. The safety summary should include comparison of safety across treatment arms in the completed controlled clinical trials for ITP.

10. *Does the Division agree that at the time of the initial submission, antiplatelet antibody testing from approximately 70 subjects in EXTEND is acceptable to the Division to determine the effect of eltrombopag on the development of antiplatelet antibodies?*

FDA Response:

The proposal appears to be acceptable for submission. If needed, additional information may be requested during review. We are concerned that the available data appears minimal, especially since these data do not assess the development/or elevation of platelet antibodies among all subjects in any randomized, controlled clinical study. The EXTEND population is a selected group of patients; hence, bias is not controlled and the data may not fully assess the potential for worsening of anti-platelet antibody responses.

11. *Does the Division agree that the proposed dataset of functional characteristics of platelets produced in response to eltrombopag is acceptable for the initial NDA?*

FDA Response:

The proposal appears to be acceptable for the initial NDA submission. The detection of "activation" of platelets based upon cell surface markers is probably less informative than measures of aggregation. Your clinical development program apparently produced little platelet aggregation data and the available data will be from selected patients. The importance of this limitation will be determined during the NDA review.

12. *Does the Division agree that the ocular safety data proposed will be acceptable to define the ocular safety profile of eltrombopag for the proposed indication?*

FDA Response:

The proposed data to support the ocular safety profile of eltrombopag appears to be acceptable for NDA submission.

13. *Does the Division agree with the above plan to assess the effects of withdrawal from eltrombopag treatment?*

FDA Response:

The proposed plan appears to be acceptable. However, the sufficiency of the supplied data to address eltrombopag withdrawal concerns will be contingent upon the review findings.

14. *Does the Division agree that data from the described non-clinical studies will provide an acceptable non clinical safety database to support an NDA for eltrombopag?*

FDA Response:

You have submitted full reports of toxicity studies by oral route of administration in rodent and non-rodent species. The chronic toxicity studies were 28-week study in rats and 52-week toxicity study in dogs and these were acceptable in reviewable format.

The oral gavage carcinogenicity studies in rats and mice are ongoing. The final and full reports of the studies should be submitted with NDA package.

The mutagenicity and reproductive toxicity (segment I, II and III in rats and Segment II in rabbits) studies with the parent compound were completed in acceptable manner. No additional studies are needed. You have been exempted to perform the additional genotoxicity studies on ~~some~~ impurities in accordance to the FDA draft guideline on genotoxic impurities.

b(4)

Investigative cataractogenesis study in CD-1, BC3F1 mice is completed. The other special toxicity studies including a cataractogenesis study in CD-1 mice, immunotoxicology study in rats which are planned or ongoing should be completed. The full reports of the studies should be submitted with NDA package.

If the full and complete reports of the studies are submitted, no additional preclinical studies may be needed; the sufficiency of these data will be determined during the review.

15. *Does the Division agree with the proposed format for the submission datasets?*

FDA Response:

Please see response to question 1.

Also, please refer to all pertinent guidance for electronic Common Technical Document (eCTD) including: www.fda.gov/cder/regulatory/ersr/.

16. *Does the Division agree with GSK's proposal to submit CRFs for the pivotal studies (TRA100773A and TRA100773B) for those subjects who died or withdrew due to an AE in electronic format?*

FDA Response:

For the entire eltrombopag database, you should include the CRFs and patient narratives for all patients who died or withdrew due to adverse events or had a serious adverse event or who had platelet counts >400,000 or ≤ 10,000.

Additional Comments:

- If possible, please submit a desk copy of your proposed draft SPL labeling as soon as possible. This will allow the review team to begin looking at the label and possibly provide some feedback on the formatting promptly during the review cycle."

GSK emailed the following request for clarifications on August 1, 2007, and agreements were reached after the discussion (the format provides the firm's request for clarifications in regular font followed by DMIHP in bolded font):

Clarification for questions 1 and 5 (combined), 5,14,16, and additional comment:

GSK would like to provide clarity and attain understanding between GSK and the Division regarding eCTD comments provided by FDA for our NDA for eltrombopag. The following are the FDA comments with the GSK explanation/clarification.

Question 1: You should submit data in XML file format for review.

GSK plans to submit this NDA in accordance with "Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications. (4/19/2006)". This guidance dictates methods and specifications for submission of eCTD format submissions. GSK will provide the Division with a combination of PDF, XML and XPT files.

Each study report will be submitted with a XML Study Tagging File (STF). The study reports will be provided in PDF format. Supporting study data if applicable will be provided based on the ISDL specification (XPT and SAS files) and not in the CDISC SDTM format.

FDA Response:

Your plan appears acceptable.

Question 15: (see #1)

Please see response to question 1.

Also, please refer to all pertinent guidance for electronic Common Technical Document (eCTD) including: www.fda.gov/cder/regulatory/ersr/.

GSK has proposed to submit the Eltrombopag NDA in eCTD format. In the briefing document response, the FDA referred GSK to the Electronic Regulatory Submissions and Review website. This website contains links to the Electronic Submission Guidance and Specifications. GSK has the capability of submitting the application following the published eCTD Guidance "Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications" (<http://www.fda.gov/cder/guidance/7087rev.pdf>) with the exception of the documents reference to datasets.

GSK will not be providing the datasets in the CDISC Study Data Tabulation Model (SDTM) format as detailed in the Study Data Specification Document (<http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.3.pdf>). GSK understands that SDTM is currently not required and the data can be provided using the legacy ISDL format in the appropriate location in the eCTD application.

Question 5:

GSK wishes to provide the Division with additional clarity regarding the ITT analysis:

For studies TRA100773A and TRA100773B, the primary population for analysis is the Efficacy Population, comprised of all subjects randomized, treated with at least one dose of study treatment and with a baseline platelet count <30G/L. GSK is not proposing to modify the definition of this population.

Question 5 was seeking the acceptability of modifying the definition of the ITT population in studies TRA100773A and TRA100773B from all subjects randomized, treated with at least one dose of study treatment and with at least one post-baseline platelet count to all subjects randomized.

GSK accepts Divisions response that 'Summary analyses of pooled efficacy data will largely be used for illustrative review purposes and is highly unlikely to impact the definitive determination of eltrombopag efficacy or product labeling' and will therefore not be making any changes to the definition of the ITT population.

Question 14:

GSK wishes to provide the Division with additional clarity regarding the availability of non-clinical studies at the time of NDA submission:

FDA response

Investigative cataractogenesis study in CD-1, B6C3F1 mice is completed. The other special toxicity studies including a cataractogenesis study in CD-1 mice, immunotoxicology study in rats which are planned or ongoing should be completed. The full reports of the studies should be submitted with NDA package.

If the full and complete reports of the studies are submitted, no additional preclinical studies may be needed; the sufficiency of these data will be determined during the review.

GSK clarification

Complete and final reports of completed studies will be provided to the Division within the NDA. Additionally, GSK proposes to provide interim information on one ongoing and one planned study. GSK would like to clarify that the investigative cataractogenesis study in CD-1 vs. B6C3F1 was initiated but was recently discontinued due to unexpectedly low systemic exposure in B6C3F1 mice that would not have allowed us to achieve the study objective. Instead, the photo-ocular study, which is planned to initiate at a phototoxicology CRO later this year, will be modified to include an assessment of cataractogenesis in CD-1 vs. B6C3F1. A validation study in CD-1 mice (I07079) is ongoing at this laboratory. This experiment is being conducted to confirm the development of cataracts under experimental conditions similar to those of previously conducted repeat-dose toxicity studies in which cataracts were observed. In the briefing document submitted to the Division, GSK indicated that results from completed or ongoing investigative studies would be included in the NDA. As the timing of some experiments would not allow for the submission of full reports, it was our intent that interim data from these studies would be submitted. In the Division's recent communication, it is suggested

that full reports from investigative studies would be required at the time of submission. Therefore, GSK seeks clarification as to whether the Division will accept interim information from the ongoing/planned studies at NDA submission with full reports provided as soon as they are available.

FDA Response:

It is acceptable to submit the interim data with your initial NDA, but the full final reports of the discontinued study in B6C3F1 mice and other ongoing studies should be submitted within 45 days of your initial NDA submission including the planned photo-ocular study, which is to be initiated this year. You will as agreed, include additional groups of animals in photo-toxicity study for the assessment of cataractogenesis potential of the drug in CD-1 vs. B6C3F1 in mice.

GSK stated that they will submit the complete final reports at least by February of 2008.

Question 16:

GSK would like to obtain clarity regarding the Division's responses to Question 16, which appears to request CRFs and narratives for a broad range of different subjects.

- GSK requests clarification regarding the reference to "entire eltrombopag database" in the Division's response to Question 16. It is unclear to GSK if this terminology refers to all subjects from all ITP studies, or to all subjects across the program, which would include subjects from ongoing and completed studies from other indications and the studies with healthy volunteers
- In the response, the Division states "that GSK should include the CRFs and patient narratives for all patients who died or withdrew due to adverse events or had a serious adverse event or who had platelet counts >400,000 or <=10,000". GSK would like to clarify that the text "or who had platelet counts....." was intended by the Division rather than "and who had platelet counts....."?
- If the word "or" is correct, GSK would like to state that many patients with ITP have baseline platelet counts below 10,000 due to severity of the disease studied. Approximately 120 patients in the pivotal studies experienced this low platelet value at least once during the study periods. GSK would like to confirm that the Division indeed requests CRFs and narratives in these patients not experiencing an AE, SAE or who died while having this low platelet count.
- GSK will provide CRFs and patient narratives for all ITP subjects who have had a platelet count $\leq 10\text{Gi/L}$ AND drop to a level $\geq 10\text{Gi/L}$ below their baseline platelet count during the follow-up period.
- GSK requests similar clarification regarding subjects who experience platelet counts >400,000 Gi/L. Are narratives and CRFs to be provided to the Division if there were no adverse events observed in this group of subjects while subjects experienced high temporary platelet counts?
- Many healthy volunteers in clinical pharmacology studies also reached platelet counts $\geq 400\text{Gi/L}$ after single or repeat doses of eltrombopag because they started with baseline

values of platelet counts >300Gi/L. Although these subjects withdrew due to the threshold of platelet counts ≥ 400 Gi/L defined in the protocols, these events were not considered an AE by investigators because it is an intended pharmacological effect. Thus, GSK proposes not to include narratives and CRFs for healthy volunteers who simply had platelet counts ≥ 400 Gi/L.

With regard to the Division's request for CRFs and narratives in Questions 2, 3 and 16, GSK's proposal for the summary of subject narratives and CRFs is summarized below. GSK believes the subject narratives and CRFs for the studies proposed will provide relevant information regarding the evaluation of the safety for the indication of short-term treatment of patients with ITP.

Does the following proposal satisfy the request of the Division?

FDA Response:

No. Please provide narratives and CRF for the "broader" ITP indication population (patients with ITP and healthy volunteers that contribute to the ITP indication database). This "broader" population includes patients who, at any time, had platelet counts $\leq 10,000$ /mcL or counts $> 400,000$ /mcL. Regarding the "entire eltrombopag database", we refer to the population for the ITP indication including the healthy volunteers. Hence, we do not anticipate (at NDA submission) the need for CRF/narratives from other indications (cancer, hepatitis). The ITP indication database is the population most applicable to labeling and risk-benefit analysis although important findings from the study of eltrombopag in other indications may, depending upon the nature of the findings, impact these decisions. Final (for completed) and interim (for on-going) reports should be submitted to the NDA for all studies examining eltrombopag use (any indication).

GSK stated that they would provide safety information from all population, but provide narratives and CRFs for the ITP population and other population as supportive.

Regarding your clarification for our comments "or/and who had platelet counts.....", we prefer the broader ITP population including the healthy volunteers, but we might request information for the cancer and the hepatitis C indication during our review if needed. We request that your medical officers develop the narratives in a manner that will focus upon clinically important correlates and considerations for the detection of eltrombopag effects.

SUMMARY OF SUBJECT NARRATIVES AND CRFS PROPOSED TO BE INCLUDED IN NDA

Subject/patient category	Completed ITP studies	Ongoing ITP studies	Completed studies-other indications	Ongoing studies-other indications	Healthy Volunteer studies
Died- narratives and CRFs	X	X	X	X	X
AE leading to withdrawal from study or discontinuation of study medication- narratives and CRFs	X	X	X	X	X
SAE- narratives	X	X	X	X	X
SAE and platelets >400Gi/L- CRFs	X	X			X
SAE and platelet ≤10Gi/L - CRFs	X	X	X		X
Platelets ≤10Gi/L- narratives and CRFs			X		X
Platelets ≤10Gi/L and a drop to a level ≥10Gi/L from baseline for analysis of withdrawal effect of cltrombopag- narratives and CRFs	X	X			
Platelets >400Gi/L narratives and CRFs					

Additional Comment:

Labeling

GSK requests clarification of the Division's additional comment on the draft labeling. Given that the label is in its early stages of development, and not all sections are populated, would the Division accept a WORD version of our current draft labeling? This would not be in XML format (SPL). The SPL labeling will be provided at the time of NDA submission. GSK will provide a draft label to the Division as soon as possible, but reminds the Division that the label will evolve as the data and summaries are provided.

FDA Response:

We understand that the label will evolve, however, we strongly recommend that you focus on the guidance and language to include in the Physician Labeling Rule (PLR) so that we can provide feedback on the formatting issues and optimize the review cycle.

FDA additional comments:

- Regarding your plan on question number 15, please contact the electronic submissions coordinator at esub@fda.hhs.gov directly.
- Please note that for question number 14, if the NDA submission is determined to be a priority review, the complete final report has to be submitted within 30 days of your initial NDA submission.

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/s/

Hyon Z Lee

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: April 24, 2006

To: Anne-Margaret Martin	From: James Moore
Company: GlaxoSmithKline	Division of Medical Imaging and Hematology Products
Fax number: (610) 787-7062	Fax number: (301) 796-9849
Phone number: (610) 787-3725	Phone number: (301) 796-2050
Subject: Fax of Responses to IND 63, 293, Serial 076, March 13, 2006, GSK Response to 1/24/06 Meeting Minutes)	

Total no. of pages including cover: 5

Comments:

Document to be mailed: YES NO

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April 24, 2006

IND 63,293

Eltrombopag olamine (SB-497115-GR)

**April 20, 2006 FDA Responses to Sponsor's Comments and Corrections in the
March 13, 2006 submission (N-076) regarding Minutes of the January 24, 2006
Meeting**

We have numbered the items to which you provided comments (we highlight the subject in parentheses). We provide this communication in order to facilitate our subsequent discussion regarding your clinical development program. Responses to your submitted comments follow:

1. (Errors) Corrections and clarifications to the patient numbers planned for the ITP database are noted. We acknowledge our errors within the January 24, 2006 minutes regarding the subject numbers and study numbers. Note that the division does not re-issue meeting minutes. This current correspondence serves as documentation of our acknowledgement of the errors in subject numbers and study numbers in the official meeting minutes.
2. (ITP rarity) No further comment.
3. (Safety data submission timing) Submission and review of preliminary data from an adequately designed clinical development program is needed before we can provide a definitive FDA response regarding the timing and the nature of the clinical data to be submitted with your NDA. Based upon the supplied information, we do not concur with your clinical development program, especially with respect to the nominal "short term" indication. (See comments under "5" below). With regard to questions regarding the ophthalmic data, based upon the supplied information, we anticipate that the complete ophthalmic data (including 6 month follow-up data for all patients) should be included in the initial NDA submission.
4. (Size of safety database) We remain very concerned about the limited amount of safety data available for the product. In the limited data you presented, there were serious adverse events, including a case of pulmonary embolism, hepatitis and renal failure at the 50mg dose (a dose planned for Phase 3 study) and some patients discontinued the study drug because of unacceptably high platelet counts. It is not clear how many patients completed the full 6 week treatment in Study TRA100773. Also, you have not provided a comprehensive analysis of the exposure/response relationship for platelet counts or safety (e.g., thrombosis). Considering the available data, Agency comment on the acceptability of a specific set of safety data to include in an NDA is premature.

The safety database becomes of even greater concern because of the lack of clarity regarding the target indication. Though you intend the initial NDA to be

for a short-term (6 weeks) treatment, because eltrombopag is an oral agent, we do not believe that even strong labeling statements or a risk management program will adequately address the toxicity risks associated with off-label, long term use. We regard the potential for off-label, long term use as a major concern, given the nature of chronic ITP. Hence, based upon the available information regarding your clinical development program, we regard sufficient evidence of safety during long term usage as essential to support the acceptability of a marketing application for short term usage. Also, you have proposed no plan to address use of eltrombopag for repeated courses, a situation that also must be addressed in order to support a short term usage. Because of this, it is likely that substantial evidence for safety of long-term use will be needed for any approval, even for a short-term indication.

5. (Proposed indication) You state the initial indication is to be for short-term treatment

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The potential risks and benefits of the study agent will likely vary depending upon the specific usage. Data to allow adequate assessment of the study agent's benefits and risks must be provided for any clinical settings in which the drug is to be indicated

6. ("Success" determination) We acknowledge that attainment and retention of an adequate platelet count is an acceptable efficacy endpoint in a clinical protocol that is appropriately designed to evaluate efficacy and safety for the study agent. Regarding the definition of how changes in platelet counts will be analyzed as a measure of efficacy, we intended to convey that, based upon the supplied information, the measure of effect on platelet counts used (whatever it is) will need to be supported as providing a clinically meaningful benefit in the context of the specific indication. As noted above, based on the supplied information, your planned phase 3 study does not appear to be appropriately designed to allow an assessment of the risks and benefits of your study agent for any use. Clarification of the overall clinical development program will allow us to provide more specific comment on your proposed endpoints for your clinical studies.
7. (Patient population) See comments under "5" and "6" above.
8. (Drug interaction studies, etc.) No further comment.
9. (Ocular examinations) You have detailed the ocular database you intend to submit for the initial NDA submission. Our comment was intended to convey that for

safety, any studies of eltrombopag that are underway or to be initiated should include ocular evaluations (evaluations at baseline, during and at end-of-treatment, at a minimum). We acknowledge your commitment to obtain these data.

10. (Single study) We acknowledge your comments and reiterate our comments above regarding your clinical development program. Based on the available information, we continue to advise at least two adequate and well-controlled trials for each indication.
11. (LOCF) Your proposal for statistical analysis will be reviewed as part of your revised protocol.
12. (mouse carcinogenicity) As indicated under "4" and "5" above, safety with chronic use needs to be clearly defined and supported before any approval of the drug. Therefore, final results and complete reports of the two-year mouse carcinogenicity studies should be submitted with the initial NDA.
13. (Summary comments: study indication, population, time period) See comments under "5" and "6" above.
14. (Summary comments: Clinically meaningful definition of success/failure) See comments under "6" above.
15. (Summary comments: plan for safety evaluation) The safety assessments will be reviewed in the review of the SPA for your Phase 3 protocol that is currently under review. Also see comments under "4" and "5" above.
16. (Summary comments: indication) Noted. See also comments under "5" above.
17. (Summary comment: antibody/immune response) The safety assessments will be reviewed in the review of the SPA for your Phase 3 protocol that is currently under review. Also, see comments under "4" and "5" above.
18. (Summary comment: two trials) See comments under "10" above.
19. (Summary comment: Safety Update) See comments under "4" above.
20. (Summary comment: revised Phase 3 protocol) Please be aware that your protocol submitted for SPA (letter date April 3, 2006; received April 6, 2006) is currently under review.

Additional comment:

You should examine the protocol for your short-term (6-week) Phase 3 study submitted previously in light of the comments from the January 24, 2006 meeting and the comments in this current communication to determine if revisions are needed.

Any additional protocols for Phase 3 studies also should be submitted for review.

If you have questions, contact James Moore, Project Manager at (301) 796-2050.

James Moore, PharmD, M.A.
Project Manager, DMIHP

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/s/

James Moore
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CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2006

To: Paula Bursztyn Goldberg	From: James Moore
Company: SmithKline Beecham Corporation d/b/a GlaxoSmithKline	Division of Medical Imaging and Hematology Products
Fax number: (610) 787-7062	Fax number: (301) 796-9849
Phone number: (610) 787-3722	Phone number: (301) 796-2050
Subject: Fax of Meeting Minutes January 24, 2006, 1 63,293	

Total no. of pages including cover: 15

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Document to be mailed: YES NO

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Minutes of Industry Meeting between the Division of Medical Imaging and Hematology Products and GlaxoSmithKline, Tuesday, January 24, 2006, 10:00AM-11:00AM, White Oak Conference Room 1417

Subject: I 63,293 (SB497-115-GB)

GlaxoSmithKline Attendees:

Paula B. Goldberg, Ph.D., Executive Director, US Regulatory Affairs
Anne-Margaret Martin, M.A., Senior Director, Therapeutic Area Regulatory Affairs, US Regulatory Affairs
Robert S. Watson, M.B.A., Vice President Oncology, US Regulatory Affairs
Andrew Provan, Director, MDC* Oncology, EU
Nicole Stone, Ph.D., Assistant Director, Oncology, MDC Oncology, US
Julian Jenkins, M.S, Global Project Leader, MDC Oncology, US
Debasish F. Roychowdhury, M.D., Vice President Clinical Development, MDC Oncology
Habib Hassani, Director, Statistics and Programming
Daphne Williams, Ph.D., Senior Clinical Pharmacokineticist, Clinical Pharmacokinetics, US
Kelly Grotzinger, Director Therapeutic Area, Global Health Outcomes
Teresa S. Sellers, M.S., Manager Clinical Pathology, Safety Assessment

FDA Attendees:

Rafel Rieves, M.D., Clinical Team Leader, DMIHP
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, DMIHP
Andrew Dmytrijuk, M.D., Clinical Reviewer, DMIHP
Yuan Chen, Ph.D., Statistical Reviewer, DMIHP
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, OCP
Yash Chopra, Ph.D., Pharmacology/Toxicology Reviewer, DMIHP
Adebayo Lanionu, Ph.D., Pharmacology/Toxicology Reviewer
James Moore, PharmD., M.A. Project Manager, DMIHP

Background

Prior to the meeting the Division's responses to questions from GSK's meeting package were faxed to GlaxoSmithKline. Here are GSK's questions and FDA's responses. After introductions the meeting began.

Question 1. Does the division agree with the dose and regimen selected for the progression into the Phase 3 studies described in this document?

FDA Response-

Yes, the dosing regimen selected appears to be appropriate, based on the data presented.

Question 2: Does the division agree with the primary analysis using the last observation on randomized treatment carried forward as described above?

FDA Response-

- It is difficult to evaluate the appropriateness of using the LOCF method for the Phase III study. For example, based on the information provided in the background package, the numbers of early dropouts in the Phase II study were unbalanced in the two treatment arms [1 (4%) and 9 (38%) for placebo and the 50 mg arm, respectively]. The proportion of responders of those 10 subjects was not given. If the response rate of the 9 subjects in the 50 mg arm was high at the last recorded visit, the LOCF method would be biased in favor of the treatment group. Please provide more information regarding the percent of responders based on the last observation carried forward method in studies that you have already completed.
- You should propose additional sensitivity analyses in order to assess the robustness of the primary efficacy analysis results. This should include treating the dropouts as failures as an alternative outcome for consideration.
- The primary efficacy analysis should be on the modified intent-to-treat population (i.e., all patients who receive any study drug). Secondary efficacy analyses may be done using evaluable populations.
- During conduct of the study every effort should be made to minimize missing data.

Question 3: Does the division agree that, given the above, Part A and Part B of study TRA100773 can be considered as two independent studies?

FDA Response-

- In principle, this appears acceptable. Although the efficacy results of Part A seem compelling (response rates of 16% and 67% for placebo and the 50 mg arm, respectively), you should recognize that Part A was designated and reviewed for the objective of proof of concept for eltrombopag in ITP patients. The primary data for the study has not been submitted or reviewed for important considerations, such as internal consistency across centers, subpopulations and related endpoints, comparability of treatment arms at baseline, etc.
- Assurance is needed that a favorable outcome for the eltrombopag treatment in Part A does not influence inclusion of study sites in Part B, i.e., Part A and Part B should be as independent as possible.
- Also, see response to Question 11.

Question 4: Does the division concur that the use of validated and reliable instruments would be appropriate for the purpose of evaluating symptom severity and quality-of-life endpoints?

FDA Response-

- Validated and reliable instruments should be used for evaluating these endpoints. In the NDA you should provide information to substantiate the validity of the evaluation instruments used for these analyses.

- These endpoints would be appropriate as secondary endpoints only.

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Question 5: Does the division agree that based on the findings to date, the plan for continued monitoring of safety is appropriate?

FDA Response-

Your reporting of safety data from part A in the background material is not sufficiently complete to allow determination whether the proposed safety monitoring plan for the Phase 3 study is appropriate. Provide additional detail regarding the safety results so far obtained when you submit the complete Phase 3 protocol for review. We will provide additional comments then.

Question 6: Does the division agree with the use of the Generalized Estimating Equations for the analysis of the primary endpoint as described above?

FDA Response-

Yes. The Agency does not object to the use of any appropriate analytical method for the primary efficacy analysis. Please clearly specify the GEE model and the definition of each variable of the model in the Phase 3 protocol for review.

Question 7: Does the division agree that the

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FDA Response-

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Question 8: Does the division agree that due to stringent type 1 error (1%) for TRA 102537, this single study will be adequate for approval of eltrombopag as long term treatment of adult ITP patients?

FDA Response-

No. In general, two adequate and well-controlled trials are needed to support each indication. Refer to Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 15, 1998)" on why two studies are recommended and what otherwise would be needed. There is a risk in performing a single study, that study may not have convincingly positive results.

Question 9: Does the division agree that based on the findings to date, the plan for monitoring of safety in this study is appropriate?

FDA Response-

It is unclear if the plan for monitoring of safety in the study is appropriate. Please see the answer to question number 5.

Question 10: Does the division agree that TRA 100773 (short-term use Phase III study) and TRA 102537 (long-term use Phase III study) subjects who wish to participate in TRA 105325 (open label extension study) do not need to have a six-month follow-up ophthalmologic examination as ophthalmologic examinations will be performed throughout the trial.

FDA Response –

No. Due to toxicity seen in the preclinical studies, ophthalmologic examinations should be performed throughout the trial and at the conclusion of the studies. In your studies ophthalmic examination for cataract should be done at least twice during the treatment period in addition to the proposed testing regimen.

Question 11: Based on the observed compelling platelet response results already obtained, does the division agree that the data from both independent parts of the adequate and well-controlled phase 2/3 adaptive design study will be sufficient to support approval of eltrombopag in the short-term treatment of adults with immune thrombocytopenic purpura?

FDA Response –

- It is not clear what the short-term indication is from your background package. A short-term use may not be appropriate for treatment of chronic ITP.
- Considering that chronic ITP is a chronic condition, please explain what is intended for treatment after six weeks and what the initial indication will be, given the short time course (6 weeks) for treatment for this chronic condition in your proposed studies.
- Durability of response and safety information regarding platelet levels after discontinuation of the study drug will need to be provided.
- Because treatment with eltrombopag may indirectly enhance sensitization of patients to platelets, immunogenicity to platelet antigens should be assessed in

the clinical trials. The total number of patients enrolled in Part A and B may not be sufficient for the review of safety issues.

Question 12: Does the division agree that the safety database, as summarized above, will be adequate to support approval of eltrombopag for the short-term treatment of chronic ITP patients?

FDA Response –

No. Based on your background package, currently in ITP there are only a total of 144 eltrombopag exposed patients of which 117 received ≥ 50 mg. This safety database appears too small. We reiterate the importance of clearly identifying the target indication in order to more rigorously evaluate your clinical development program. The determination of sufficiency of a safety database is contingent not only upon the sample size but also upon the demonstrated treatment benefit (i.e., the assessment of overall risk-benefit). For example, a "smaller" sample size database may reasonably support an important treatment benefit among refractory ITP patients. In the absence of a clear definition of the target indication, we recommend that you conceptualize approximately 500-1000 patients receiving eltrombopag in order to support the safety of this new molecular entity. This conceptualization may change, contingent upon the specific target indication and the on-going findings from clinical studies.

Question 13: Is the proposed plan of clinical pharmacology studies acceptable for supporting approval of the short-term use ITP indication?

FDA Response-

In addition to the sponsor's clinical pharmacology studies currently planned, the following information will be needed from a clinical pharmacology perspective to support the approval of the drug:

- (i) The pharmacokinetic (PK) information in the target patient population.
- (ii) PK information in special populations, i.e., gender differences, age effect, hepatic insufficiency, renal insufficiency if deemed necessary, geriatrics, and pediatrics if deemed necessary.
- (iii) The information on the assay methodology for the parent drug as well as the metabolite(s) if deemed necessary.

Please note that the above recommendation is not limited and more information may be needed based on the information that will be obtained from ongoing studies.

Question 14: Does the division agree to accepting results of the six-month follow-up ocular examinations for the final patients in the Phase 3 study in safety updates during NDA review?

FDA Response-

No. All safety results, including ocular examinations, should be included in the initial NDA submission.

Nonclinical

Question 1: Does the Division agree that data from the above described studies will provide an acceptable nonclinical safety database in support of an initial NDA application for short term treatment with eltrombopag (SB-497115-GR) of chronic ITP patients?

FDA Response-

No. The available toxicity studies in the rodent and non-rodent species are not sufficient to support an application for an NDA. The full reports of the following studies should also be available at the time of the submission of the new drug application.

1. For a short duration of treatment:

(i) Prenatal and post-natal development toxicity study in pregnant rats (Segment III).

(ii) Full and final study reports of the 2-year carcinogenicity studies in mice and rats.

(iii) Full and final report of cataract examination of animals in the mouse carcinogenicity study and in the 28-week oral rat study.

(iv) Full and final reports of the Ames test and chromosomal aberration test of the impurities in the drug product.

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3. The immunotoxicity potential of the compound should be evaluated particularly when a compound is intended to be used for a prolonged period.

Additional comments:

1. Please submit the initial Phase 3 protocol for our review.

2. Although short-term toxicity studies did not show an immune toxicity, it is possible that a rebound immune thrombocytopenic response could occur after long term exposure to eltrombopag. Therefore, long-term immune toxicity evaluation should be performed particularly in those patients with a decrease in platelet count after treatment has ceased.

3. Please clarify the initial short-term indication since ultimately you have planned a six-month trial and indeed it is expected that this drug will be used long-term.
4. Concomitant medications and changes in concomitant medication requirements for patients with ITP should be evaluated in your Phase 3 studies. Please provide information on what changes were seen in concomitant medication requirements in the Phase 1/2 studies.
5. Please also see the minutes of the IND 63,293 Teleconference dated January 13, 2006 for responses regarding chemistry issues that need to be addressed for this NDA.

After receiving the Division's responses to questions from the GSK meeting package, GSK selected questions for further discussion at the industry meeting. Those questions are listed below in GSK's order of priority.

GSK Question	FDA Response
<p>Question 11: Based on the observed compelling platelet response results already obtained, does the Division agree that the data from both independent parts of the adequate and well controlled, Phase II/III adaptive design study will be sufficient to support approval of eltrombopag in the short-term treatment of adults with immune thrombocytopenic purpura (see Section 1.4.4)?</p>	<ul style="list-style-type: none"> • It is not clear what the short-term indication is from your background package. A short-term use may not be appropriate for treatment of chronic ITP. Please see our prior comments regarding the importance of clearly describing the proposed indication, including the treatment benefit. • Considering that chronic ITP is a chronic condition, please explain what is intended for treatment after six weeks and what the initial indication will be, given the short time course (6 weeks) for treatment for this chronic condition in your proposed studies. • Durability of response and safety information regarding platelet levels after discontinuation of the study drug will need to be provided. • Because treatment with eltrombopag may enhance sensitization of patients, immunogenicity to platelets should be assessed in the clinical trials. • The total number of patients enrolled in Part A and B may not be sufficient for the review of safety issues.

<p>Question 12: Does the Division agree that the safety database, as summarized above, will be adequate to support approval of eltrombopag for the short-term treatment of chronic ITP patients?</p>	<p>No. Based on your background package, currently in ITP there are only a total of 144 eltrombopag exposed patients of which 117 received ≥ 50 mg. This safety database appears too small. We recommend that approximately 500-1000 patients receiving eltrombopag be studied to support the safety of this new molecular entity, contingent upon the proposed treatment benefit. Please see our prior comments regarding sample size considerations.</p>
<p>Question 13: Is the proposed plan of clinical pharmacology studies acceptable for supporting approval of the short-term use ITP indication?</p>	<p>In addition to the sponsor's clinical pharmacology studies currently planned, the following information will be needed from a clinical pharmacology perspective to support the approval of the drug:</p> <ul style="list-style-type: none"> (i) The pharmacokinetic (PK) information in the target patient population. (ii) PK information in special populations, i.e., gender differences, age effect, hepatic insufficiency, renal insufficiency if deemed necessary, geriatrics, and pediatrics if deemed necessary. (iii) The information on the assay methodology for the parent drug as well as the metabolite(s) if deemed necessary. <p>Please note that the above recommendation is not limited and more information may be needed based on the information that will be obtained from ongoing studies.</p>
<p>Question 14: Does the Division agree to accepting results of the six-month follow up ocular examinations for the final patients in the phase III study in safety updates during NDA review (see Section 1.4.4)?</p>	<p>No. All safety results, including ocular examinations, should be included in the initial NDA submission.</p>

<p>Question 8: Does the Division agree that due to the stringent type I error (1%) for TRA102537, this single study will be adequate for approval of eltrombopag as long-term treatment of adult ITP patients (see Section 1.4.2.5)?</p>	<p>No. In general, two adequate and well-controlled trials are needed to support each indication. Refer to Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (My IS, 1998)" on why two studies are recommended and what otherwise would be needed. There is a risk in performing a single study, that study may not have convincingly positive results.</p>
<p>Question 2: Does the Division agree with the primary analysis using the last observation on randomized treatment carried forward as described above (see Section 1.4.1.4)?</p>	<ul style="list-style-type: none"> • It is difficult to evaluate the appropriateness of using the LOCF method for the Phase III study. For example, based on the information provided in the background package, the numbers of early dropouts in the Phase II study were unbalanced in the two treatment arms (1 (4%) and 9 (38%) for placebo and the 50 mg arm, respectively). The proportion of responders of those 10 subjects was not given. If the response rate of the 9 subjects in the 50 mg arm was high at the last recorded visit, the LOCF method would be biased in favor of the treatment group. Please provide more information regarding the percent of responders based on the last observation carried forward method in studies that you have already completed. • You should propose additional sensitivity analyses in order to assess the robustness of the primary efficacy analysis results. This should include treating the dropouts as failures as an alternative outcome for consideration. • The primary efficacy analysis should be on the modified intent-to-treat population (i.e., all patients who receive any study drug). Secondary efficacy analyses may be done using evaluable populations. • During conduct of the study every effort should be made to minimize missing data.

Nonclinical	
<p>Question 1: Does the Division agree that data from the above described studies (see Section 1.1) will provide an acceptable nonclinical safety database in support of an initial NDA application for short-term treatment with eltrombopag (SB-497115-GR) of chronic ITP patients?</p>	<p>No. The available toxicity studies in the rodent and non-rodent species are not sufficient to support an application for an NDA. The full reports of the following studies should also be available at the time of the submission of the new drug application.</p> <ol style="list-style-type: none"> 1. <u>For a short duration treatment:</u> <ol style="list-style-type: none"> (i) Prenatal and post-natal development toxicity study in pregnant rats (Segment III). (ii) Full and final study reports of the 2-year carcinogenicity studies in mice and rats. (iii) Full and final report of cataract examination of animals in the mouse carcinogenicity study and in the 28-week oral rat study. (iv) Full and final reports of the Ames test and chromosomal aberration test of the impurities in the drug product. 2. For the use of the compound in other than the adult population, 2/4-week toxicity studies in neonatal and juvenile and non-rodent species. 3. The immunotoxicity potential of the compound should be evaluated particularly when a compound is intended to be used for a prolonged period.

	<p>Additional FDA Comments:</p> <p>2. Although short-term toxicity studies did not show an immune toxicity, it is possible that a rebound immune thrombocytopenic response could occur after long term exposure to eltrombopag. Therefore, long-term toxicity evaluation should be performed particularly in those patients with a decrease in platelet count after treatment has ceased.</p> <p>3. Please clarify the initial short-term indication since ultimately you have planned a six-month trial and indeed it is expected that this drug will be used long-term.</p> <p>4. Concomitant medications and changes in concomitant medication requirements for patients with ITP should be evaluated in your Phase 3 studies. Please provide information on what changes were seen in concomitant medication requirements in the Phase 1/2 studies.</p>
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Discussion

FDA queried GlaxoSmithKline (GSK) about the number and characteristics of patients that would be included in the trial for idiopathic thrombocytopenic purpura. GlaxoSmithKline replied that there were two studies in which patients were enrolled; one was study 821 and the other study 679. According to GSK, 117 patients are in the safety database and these patients would be exposed to the product for 6 weeks to obtain safety data. GSK also stated that eighty patients with hepatitis are enrolled in the trial and would be followed for 16 weeks.

According to GlaxoSmithKline, Idiopathic Thrombocytopenic Purpura (ITP) is a rare disorder and it is difficult to recruit patients for this trial. GlaxoSmithKline stated that annually there are only about cases reported in the U.S.

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During the discussion of NDA safety data, GlaxoSmith Kline stated that they planned to submit all of the safety data for the conducted studies when the safety update was submitted. FDA stated that all available safety data must be submitted at the time of NDA submission not afterwards.

FDA was very concerned about the limited amount of safety data that has been collected, and the possibility that inadequate safety data would be available when the NDA is submitted. This concern was conveyed to GSK.

FDA also sought clarification of the wording of the indication and stated that the indication should be clear so that practitioners may use the product appropriately. FDA asked about chronic versus short term use of Eltrombopag and noted that FDA was concerned about the potential for off label use of this product, especially with respect to a potential "short term" usage. GSK responded that they understood this concern but were confident that the labeling would be clear so that the potential for off label use would be minimal.

In light of the apparent absence of a clearly defined target indication for short term usage, FDA expressed its concern that there is no clear clinical endpoint for the measure of success for the product. GlaxoSmithKline responded that success would be achieving a platelet count of $\geq 50,000/\mu\text{L}$. FDA pointed out that maybe there should be an upper limit of the platelet count for success. The Sponsor's target range for platelet counts is $\geq 50,000$ to $200,000/\mu\text{L}$. Rate of success should be clinically meaningful to support approval. It is not clear what amount of increase in "success" over placebo will be considered clinically meaningful in the trial. FDA stated that the measure of success or failure should be clearly stated in the Phase 3 protocol submitted to the Agency.

FDA also stated that GSK should clarify the patient population in which the drug would be used, provide information on the risk/benefit of the product, what constitutes clinical success, clearly state the period of treatment for patients, provide information on platelet sensitization and long term effects, provide data on antibody and antiplatelet effects, provide information on the level of antibody production observed during treatment with the agent and after withdrawal, clearly define the proposed patient population, and provide the overall plan for clinical development of the product.

FDA reminded GSK of the need to include drug-drug interaction studies, metabolic/enzyme studies, metabolites of the product, gender, age assessments and all required pharmacokinetic/pharmacodynamic studies in their Phase 3 development plans for the product.

FDA expressed its concern about GSK's proposal to eliminate ocular examinations at followup for patients treated with Eltrombopag. FDA stated that based on the cataract formation seen in preclinical studies that it was not acceptable to exclude ocular examination at the six month time point of the study as part of the clinical assessment plan for Eltromopag. FDA also stated that there should be baseline ocular examinations and periodic ocular assessments at different time points in the trial and recommended that this be included as part of the Phase 3 drug development plan. The timing of these exams should be clearly stated in the Phase 3 protocol.

GSK again requested that FDA respond to GlaxoSmithKline's request to conduct a single trial to support the efficacy of Eltrombopag. FDA advised again that 2 adequate and

well-controlled trials should be conducted in support of a proposed indication. There is a risk in performing a single study, that study may not have convincingly positive results. GSK remarked that based on the stringent p-value of 0.01 imposed on the trial that a single adequate and well controlled study should be adequate to support the efficacy of this product. FDA referred GSK to the Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 15, 1998)".

FDA did not concur with GlaxoSmithKline's proposal for use of the LOCF method for missing data imputation. The sponsor agreed to re-define the responders in the protocol for review so that subjects who left the trial early with treatment effect would not be counted as failures.

FDA reminded GSK that the results of the 2 year mouse carcinogenicity could be submitted with the NDA but interim reports completed for this study should be submitted to the IND.

Summary

FDA reemphasized and clarified the following during the meeting.

- GSK must clearly define the proposed indication, the patient population in which the product will be used and the time period that patients will be exposed to the product. This should be clearly stated in the Phase 3 protocol.
- GSK must state in their Phase 3 protocol what constitutes failure or success for individual patients in the idiopathic thrombocytopenic purpura population treated with this drug and for achieving a clinically meaningful amount of success in the study.
- GSK must clearly define in their Phase 3 design a comprehensive plan for evaluation of safety including ocular examination of subjects at specified intervals.
- GSK must clearly state the indication for this product (short term vs long term use and the nature of the proposed treatment benefit).
- There must be a comprehensive plan for assessment of the platelet antibody/immune response in the Phase 3 protocol.
- GSK was referred to the Guidance for **Industry** entitled "**Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 15, 1998)**" and encouraged to consider evaluation of safety and efficacy of this product in two clinical trials rather than one as proposed by GSK.

- All safety data collected during the clinical trial must be included at the time of submission of the NDA and it is not acceptable to submit safety data from the clinical trial at the time of the Safety Update.
- A revised Phase 3 protocol should be submitted that incorporates the changes to the protocol recommended by FDA.

The minutes were prepared by James Moore, Project Manager.

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Project Manager, DMIHP

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/s/

James Moore
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