

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Friday, September 19, 2008 3:39 PM
To: 'dennis.q.williams@gsk.com'
Subject: Promacta: REMS comments
Attachments: FDA REMS Comments 9 19 08.doc

Mr. Williams,

Please see attached FDA comments of the REMS submission.

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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9/19/2008

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Hyon Z Lee
9/19/2008 04:43:20 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 12, 2008
TIME: 10 AM – 11 AM (Eastern Standard Time)
LOCATION: White Oak Conference Room 1313
APPLICATION: NDA 22-291
DRUG NAME: Promacta® (eltrombopag) Oral Tablets
TYPE OF MEETING: Pre-Approval Safety 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., Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Andrew Dmytrijuk, M.D., Clinical Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Ira Krefting, M.D., Associate Director for Safety
Diane Leaman, Safety Regulatory Project Manager
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

Office of Surveillance and Epidemiology (OSE):

Mary Dempsey, Pharm.D., Risk Management Programs Coordinator, DRISK
Susan Lu, Pharm.D., Team Leader, DPV
Timothy Lape, Pharm.D., Safety Reviewer, DPV
Janet Anderson, Pharm.D., Project Manager

BACKGROUND OF THE MEETING:

This application was submitted on December 18, 2007 for the short term treatment of previously treated patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding initially, and was revised during the course of the review to the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag is classified as a new molecular entity and was discussed at the Oncologic Drugs Advisory Committee (ODAC) on May 30, 2008.

The Risk Evaluation and Mitigation Strategies (REMS) requirements and the final labeling are currently being worked on.

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/s/

Hyon Z Lee
9/19/2008 02:37:09 PM
CSO

MEMORANDUM OF TELECONFERENCE

Date: September 9, 2008

Time: 3:30 – 4:30 PM

Location: White Oak Bldg 22, Rm 2376

Application: NDA 22-291 Promacta

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products

Rafel Rieves, M.D., Division Director

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

Andrew Dmytrijuk, M.D., Medical Reviewer

Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer

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

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

And

External Constituent Attendees and Titles:

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

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

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, Clinical Pharmacology

The Agency arranged the teleconference as part of labeling negotiations with the sponsor and also to discuss the anticipated timeline for this NDA that has a PDUFA due date of September 19, 2008.

The Agency sent a revised package insert to GSK on September 8, 2008. GSK requested a teleconference with the Agency to discuss their comments regarding the revised labeling.

GSK had the following comments:

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The Agency stated that we will not meet the PDUFA due date of September 19, 2008, but that we are foreseeing of taking an action by the end of October, 2008 due to the currently ongoing labeling negotiations and REMS. Once the labeling is finalized and the revised REMS reviewed, we will issue an information request letter for REMS. Also, once the labeling is finalized, GSK should submit the promotional materials that they intend to disseminate to DDMAC for review (although, some portions of the promotional materials that would not be dependent on the final labeling could be submitted now).

The Agency stated that the other alternative of delaying the action date is to issue a complete response (CR) letter, and that currently, no final decisions are made.

GSK responded that they rather want to delay the action date than receiving a CR letter, and asked if the DRISK team would be up for a face to face meeting to discuss the REMS.

The Agency responded that we will check with the DRISK team.

The teleconference concluded.

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/s/

Hyon Z Lee
9/12/2008 10:57:04 AM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, September 08, 2008 4:43 PM
To: 'dennis.q.williams@GSK.com'
Subject: Promacta label
Attachments: FDA.clean.9.8.08.doc

Mr. Williams,

Please see attached FDA edits of the label and provide your comments by COB September 10, 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

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9/8/2008

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/s/

Hyon Z Lee
9/8/2008 05:00:21 PM
CSO

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 3, 2008

TO: Hyon-Zu Lee, Regulatory Project Manager
Andrew Dmytrijuk, Medical Officer

FROM: John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections, Addendum

NDA: 22-291

APPLICANT: GlaxoSmithKline, Inc.

DRUG: Eltrombopag (Promacta)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority review

INDICATIONS: Short-term treatment of thrombocytopenia associated with ITP

CONSULTATION REQUEST DATE: February 14, 2008

DIVISION ACTION GOAL DATE: August 27, 2008

PDUFA DATE: September 19, 2008

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I. BACKGROUND

This Clinical Inspection Summary Addendum amends the previous Summary to include the results of two inspections that had not been completed at time of the previous Summary. These two inspections (shaded items in table below) are: (1) clinical investigator site _____ and (2) sponsor (GlaxoSmithKline, Inc.), Collegeville, Pennsylvania. The results of all inspections performed in support of this NDA review are shown in the table below, followed by summaries of inspectional findings for the two inspections that were recently completed.

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II. INSPECTION RESULTS

	Name of CI or Sponsor City and State / Country	Protocol Subjects	Inspection Dates	Classification	
				Interim	Final
1	/ / /	TRA104603 16 subjects	5/19/08 - 5/28/08	NAI	NAI
		TRA105580 42 subjects			
2	f /	TRA100773A 12 subjects	5/26/08 - 5/30/08	VAI	VAI
		TRA100773B 6 subjects			
3	/ /	TRA100773A 3 subjects	6/2/08 - 6/6/08	VAI	VAI
4	/ /	TRA100773A 10 subjects	5/5/08 - 5/16/08	NAI	NAI
		TRA100773B 1 subject			
5	GlaxoSmithKline, Inc. Collegeville, Pennsylvania	NA	6/9/08 - 6/12/08	NAI	pending

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NAI = no action indicated / no deviations from regulations; VAI = voluntary action indicated / no significant deviations from regulations; OAI = official action indicated / significant deviations from regulations; NA = not applicable; pending = inspection completed and preliminary results available, full report not available as of 9/3/08.

3.

/ / /

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- a. What was inspected:
- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations.
 - Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
 - Subjects: 3 subjects were screened, 3 enrolled in the study, and 2 completed the study. Complete records were reviewed for 3 subjects.
- b. General observations and commentary: The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. Minor deficiencies in good clinical practice (GCP) consisted of not strictly adhering to the study protocol in that: (1) the subjects with non-platelet blood cell counts minimally outside the reference range were permitted to participate in the study, and (2) a non-serious adverse event of mild upper respiratory tract infection was not reported in the case report form.
- c. Assessment of data integrity: The data from this site appear to be reliable.
5. GlaxoSmithKline, Inc.
1250 South Collegeville Road
PO Box 5089
Collegeville, Pennsylvania 19426-0989
- a. What was inspected:
- Review of standard operating procedures (SOPs) for: study monitoring, compliance audits, software validation, data management (including statistics and programming), automated entry of clinical data, management of test article, and computer security.
 - Review of electronic and hard copies of CRFs used in the studies in Japan, and electronic CRFs for the studies conducted in Hong Kong and US.
- b. General observations/commentary: No FDA-483 was issued at the close of the inspection. The sponsor's records indicate adequate control over the various aspects of the audited studies.
- c. Assessment of data integrity: The inspectional findings indicate that the data reported by the sponsor in the NDA accurately reflect the data reported by the clinical sites.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five inspections performed in support of this NDA review consisted of three foreign clinical sites in East Asia _____, one US clinical site _____ and the sponsor inspection (GSK at Collegeville, Pennsylvania).

- The deficiencies noted at the clinical site in _____ were minor in nature and appeared to be isolated occurrences. However, the reliability of the data obtained at this site could not be verified at this inspection since source data were kept by the sponsor at GSK- _____ and no longer at this clinical site.

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- Significant GCP deficiencies noted at the two sites in _____ were similar and consisted of isolated instances of unreported non-serious adverse events. Efficacy data were not affected and appear reliable.
- No significant deficiencies were observed at the US clinical site, and data obtained at this site appear to be reliable for safety and efficacy evaluations.
- The results of the sponsor inspection (GSK-US) indicate that the data reported by the sponsor in the NDA accurately reflect the data reported by the clinical sites.

Overall, the inspectional findings indicate that the efficacy and safety data from all inspected clinical sites are reliable.

As of this addendum (September 3, 2008), the final inspection report from the sponsor inspection remains pending. After the final inspection report has been evaluated by DSI, a second clinical inspection summary addendum will be generated and forwarded to the review division if the final classification differs from the interim classification, or if any additional significant observations are noted.

{See appended electronic signature page}

John Lee, MD
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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/s/

John Lee
9/4/2008 03:51:50 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
9/4/2008 04:14:57 PM
MEDICAL OFFICER

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Friday, August 29, 2008 10:35 AM
To: 'dennis.q.williams@gsk.com'
Subject: Promacta label
Attachments: FDA to GSK 8.29.08 Promacta label.doc

Mr. Williams,

Please see attached FDA's edits on Dosage Forms and Strengths, Drug Interactions, Use in Specific Populations, Clinical Pharmacology and Patient Counseling Information sections.

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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8/29/2008

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/s/

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Hyon Z Lee  
8/29/2008 10:57:19 AM  
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,

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 acknowledge your August 19, 2008 email correspondence containing comments upon the draft package insert. We request responses to the items listed below by August 27, if possible. Responses to these questions are essential to development of the package insert, especially with respect to the warnings and precautions, dosage and administration and adverse reactions sections of the label.

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       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}

Rafel Dwaine Rieves, M.D.
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
8/25/2008 11:54:35 AM

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, August 25, 2008 11:01 AM
To: 'dennis.q.williams@gsk.com'
Subject: Promacta: FDA edited labeling
Attachments: FDA to GSK 8.25.08 Promacta label.doc

Mr. Williams,

We are providing edits on the following sections at this time: Overdosage, Description, Nonclinical Toxicology and How Supplied/Storage and Handling sections.

Please see attached and let me know GSK's comments.

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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/s/

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Hyon Z Lee  
8/25/2008 11:36:32 AM  
CSO

## MEMORANDUM OF TELECONFERENCE

**Date:** August 5, 2008

**Time:** 1:50-2 PM

**Location:** White Oak Bldg 22, Rm 2376

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

**Between**

**FDA Attendees:**

Rafel Rieves, M.D., Division Director

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

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader

Joseph Grillo, Pharm.D. Clinical Pharmacology Reviewer

Yaning Wang, Ph.D., Pharmacometrics Team Leader

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

And

**External Constituent Attendee and Title:**

GlaxoSmithKline

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

The Agency called Mr. Dennis Williams at GSK to discuss the  
to develop the Dosage and Administration section of the labeling.

dosing

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The Agency stated that we have two items to discuss:

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The teleconference ended.

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/s/

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Hyon Z Lee  
8/6/2008 09:54:53 AM  
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Q

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       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, August 25, 2008 9:38 AM
To: 'dennis.q.williams@gsk.com'
Subject: Promacra: FDA preliminary REMS comments
Attachments: Promacta REMS comments 8.25.08.doc

Mr. Williams,

Please see attached FDA preliminary REMS comments and let me know if you have any questions.

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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8/25/2008

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Friday, August 08, 2008 1:32 PM
To: 'dennis.q.williams@gsk.com'
Subject: Promacta: FDA edited labeling
Attachments: PI_FDA to GSK 8-8-08.doc

Mr. Williams,

Please see attached FDA edited labeling. We have added a Black Box Warning, and are providing edits on the Indications and Usage, Contraindications, Warnings and Precautions and Clinical Studies sections at this time. Please note that we will send you our edits on the other sections in the following weeks.

Please let me know if GSK's comments.

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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Hyon Z Lee
8/8/2008 04:02:04 PM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-291

Glaxo Smith Kline
Attention: Dennis Williams
1250 S. Collegeville Road
UP4110
Collegeville, PA 19426

Dear Mr. Williams:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Promacta® (eltrombopag olamine) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on July 29, 2008. The purpose of the meeting was to discuss the Divisions's information request sent via telefacsimile on July 23, 2008 regarding the dose adjustment schemes.

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) 796-1424.

Sincerely,

(See appended electronic signature page)

Diane Leaman
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: July 29, 2008
TIME: 2:00 PM – 2:30 PM
LOCATION: White Oak Campus, Building 22, room 2376
APPLICATION: NDA 22-291
DRUG NAME: Promacta
INDICATION: Idiopathic Thrombocytopenia Purpura (ITP)
TYPE OF MEETING: Type A Clinical Pharmacology
MEETING CHAIR: Dr. Young-Moon Choi

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP; HFD-160)

Diane Leaman, Regulatory Health Project Manager

Office of Clinical Pharmacology (OCP)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D. Clinical Pharmacology Reviewer
Yaning Wang, Ph.D., Pharmacometrics Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Glaxo Smith Kline

Debasish Roychowdhury, MD, Senior VP, Clinical Development
Michael Arning, MD, VP, Clinical Development
Manuel Aviado, MD, Clinical Development
Nicole Stone, PhD, Clinical Development
Dennis Williams, RPh, Assistant Director, Regulatory Affairs
Mary Wire, PharmD, Pharmacokinetics
Bin Peng, MD, PhD, Director, Clinical Pharmacology

BACKGROUND:

On December 18, 2007 (received December 19, 2007) GlaxoSmithKline (GSK) submitted NDA 22-291. On July 21, 2008, GSK submitted an amendment to the NDA. On July 23, 2008, the Division of Medical Imaging and Hematology Products (DMIHP) sent GSK a telefacsimile requesting additional information on the dose adjustment schemes (see July 23, 2008 telefacsimile by James Moore, RPM). On July 24, 2008, GSK requested a teleconference to clarify the information being requested. On July 25, 2008, Diane Leaman scheduled the teleconference for July 29, 2008.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Product labeling

ACTION ITEMS:

GSK will send DMIHP the safety information on Promacta by Thursday, July 31, 2008.

ATTACHMENTS/HANDOUTS:

none

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/s/

Diane V Leaman
7/30/2008 04:53:30 PM



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

FACSIMILE TRANSMITTAL SHEET

DATE: July 23, 2008

To: Dennis Williams	From: James Moore
Company: Glaxo Smith Kline	Division of Medical Imaging and Hematology Products
Fax number: 610-917-5772	Fax number: (301) 796-9849
Phone number: 610-917-6844	Phone number: (301) 796-2050
Subject: Fax of Clinical Pharmacology Request for N 22-291 (Promacta)	

Total no. of pages including cover: 2

Comments: These comments are draft and are subject to addition, deletion or revision.

Document to be mailed: ☐ YES ☒ NO

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July 23, 2008

Regarding your 7/21/08 submission for Promacta, NDA 22-291 the reviewing clinical pharmacologist is requesting additional information on the _____

b(4)

You should provide data/information that supports _____

Please submit all pertinent reports, models, parameters, and raw data associated with this analysis to the Agency for consideration and provide a timeline for submitting this information.

b(4)

You should respond to this request as soon as possible.

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

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

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/s/

James Moore
7/23/2008 05:48:29 PM
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Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Wednesday, July 09, 2008 2:31 PM
To: 'dennis.q.williams@gsk.com'
Subject: RE: July 8, 2008 meeting: REMS slides

Mr. Williams,

Please provide proposals for drug distribution that can be fully tracked, and we will review them.

Thank you,
Hyon-Zu

From: dennis.q.williams@gsk.com [mailto:dennis.q.williams@gsk.com]
Sent: Wednesday, July 09, 2008 1:28 PM
To: Lee, Hyon-Zu
Subject: Re: July 8, 2008 meeting: REMS slides

Hi Hyon-Zu,

I do have one quick clarification question about one of the FDA slides I did not think to ask yesterday. It is related to slide 6, last bullet point (distribution). Does the FDA agree with our proposal to _____

If you could check with Dr. Berkman, that would very helpful.

Thanks,
Dennis

"Lee, Hyon-Zu" <Hyon.Lee@fda.hhs.gov>

08-Jul-2008 13:10

To dennis.q.williams@gsk.com
cc

Subject July 8, 2008 meeting: REMS slides

b(4)

Hi,

Please see attached the REMS slides that were presented during the meeting.

Thanks,

7/9/2008

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/s/

Hyon Z Lee
7/9/2008 03:42:28 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 9, 2008
TIME: 12 PM – 1 PM (Eastern Standard Time)
LOCATION: White Oak Conference Room 2201
APPLICATION: NDA 22-291
DRUG NAME: Promacta™ (eltrombopag) Tablets
TYPE OF MEETING: Clinical Advice meeting

MEETING CHAIR: Rafael Rieves, M.D.

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

FDA ATTENDEES:

Office of Oncology Drug Products (OODP)
Richard Pazdur, M.D., Office Director

Division of Medical Imaging and Hematology Products (DMIHP):
Rafael Rieves, M.D., Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Qing Xu, Ph.D., Statistics Reviewer
Sue-Ching Lin, Ph.D., CMC Reviewer
Adebayo Lanionu, Ph.D., Pharmacology/Toxicology Team Leader
Yash Chopra, Ph.D., Pharmacology/Toxicology Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

Office of Surveillance and Epidemiology (OSE):
Claudia Karwoski, Pharm.D., Acting Director, DRISK
Suzanne Berkman, Pharm.D., Risk Management Analyst, DRISK
Timothy Lape, Pharm.D., Safety Reviewer, DAEA
Janet Anderson, Pharm.D., Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

GlaxoSmithKline
Debasish Roychowdhury, M.D., V.P. Clinical Development
Michael Arning, M.D., Group Director, Clinical Development
Julian Jenkins, Project Leader
Manuel Aviado, M.D., Clinical Development
Randy Batenhorst, Pharm.D., V.P., Regulatory Affairs
Nicole Stone, Ph.D., Clinical Development
Katie Dawson, M.D., Clinical Development
Sophia Goodison, M.P.H., Safety Evaluation and Risk Management
Rezvan Rafi, M.D., Director, Safety Evaluation and Risk Management
Isaac Hammond, M.D., V.P., Safety Evaluation and Risk Management
Dennis Williams, R.Ph., Regulatory Affairs

BACKGROUND AND MEETING OBJECTIVES:

NDA 22-291 Promacta was discussed at the Oncologic Drugs Advisory Committee (ODAC) on May 30, 2008 for the short-term treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP). The Agency arranged the teleconference to discuss the issues of this application and how to proceed from here.

DISCUSSION POINTS:

The Agency stated there are two potential patient populations that will be taking this drug: 1) the ITP population with low grade severity of thrombocytopenia who may use the drug on a short-term basis and continue or resume their usual ITP treatment after cessation of eltrombopag and 2) the refractory ITP patients who failed all prior therapies and who need an effective therapy for severe thrombocytopenia. The available data suggest that use of eltrombopag in a "short term" manner among the "refractory population" is associated with serious hemorrhage following discontinuation of the drug. The issues of this application among others is that the two major short-term studies conducted (773A, 773B) do not adequately address the needs for the "refractory population" and FDA is concerned that the proposed labeling raises important safety considerations for this population, since it _____

b(4)

Following extensive discussion of the risk and benefit considerations, the following conclusions were proposed:

- FDA will direct attention to review of the EXTEND study, with a special focus upon using data from this study to support an indication for use of the product in the treatment of thrombocytopenia among patients with chronic ITP (and potentially not refer to either "short term" or "long term" course descriptions); this is an on-going review item.
- The sponsor will supply revised labeling _____
/ / / /
- The sponsor will supply a detailed, annotated label _____

- The sponsor will work to develop a more thorough risk management plan that will be in a Risk Evaluation and Mitigation Strategy (REMS) format.

b(4)

b(4)

ACTION ITEMS:

The sponsor will submit the following:

1. Final study report of the REPEAT study. The sponsor noted this will be submitted many months later.

2. Revised labeling _____ and revised
Risk Management Plan (RMP) and other information as outlined above.

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3. _____

b(4)

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/s/

Hyon Z Lee
7/14/2008 09:19:00 AM
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,

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 EXTEND study report within your submission and have the following comments and information requests. We request a prompt written response within ten days of receipt of this letter in order to continue our evaluation of your NDA.

Comprehensive EXTEND efficacy data cut off (including dosing information) is apparently available only for the original NDA data cut off (August, 2007), a time point at which 117 subjects were enrolled and 109 included in the ITT analysis.

1. Please clarify exposure history of the 109 patients:

Table 1. Exposure:

Exposed for:	n, on med	n, withdrawn from med	Basis for withdrawal (n, reason)
3 months	74 (68%)	? between 0 and end of 3 months	
6 months	53 (49%)	? between 3 months and end of 6 months	
9 months	19 (17%)	? between 6 months and end of 9 months	
12 months	3 (3%)	? between 9 months and end of 12 months	

2. Clarify concomitant medication discontinuation effects: of the 109 patients, only 40 patients (37%) were receiving concomitant ITP medications; hence, the nominal utility of eltrombopag to support decrease in concomitant ITP medications can be estimated from the experience with these 40 patients. Within this subset of 40 patients:

- What was the exposure history? (Construct a table as in Table 1 to allow time point assessments using ITT approach; population of patients who had either withdrawn or continued on eltrombopag by each time point)
 - How many had all concomitant ITP medications discontinued and no rescue medications at each time point? (As in Table 1, to allow time point assessments; use the ITT population of patients who had either withdrawn or continued on eltrombopag by each time point)
3. Clarify platelet count responses by end of month six using the subset of patients who had either withdrawn by the end of six months or completed 6 months exposure:
- How many (n, %) achieved a platelet count of ≥ 50 K at any time?
 - How many (n, %) achieved a platelet count of ≥ 50 K at the time of last measurement (6 month time point)?
 - How many (n, %) achieved and maintained a platelet count ≥ 50 K during all assessments after the first month of exposure?
 - How many did not achieve any platelet count ≥ 50 K?
4. In Figure 2 of the EXTEND study report (original submission) the week 24 (nominal end of 6 months), provides platelet count response data for only 30 subjects; however, 53 subjects were supposedly still receiving eltrombopag. Please clarify why platelet count data are not presented for the 23 patients who were still receiving eltrombopag (please note that the sample sizes for platelet count responses appear to decrease after week 24, even though higher exposure is reported). Please present a summary of platelet count responses using all available platelet data for each time point (i.e., clarify figure 2).
5. Regarding safety: please clarify by the end of six months, how many patients (n, % using ITT population of patients continued on medication or withdrawn) had received at least one rescue medication?
6. Regarding safety: please clarify by the end of six months, how many patients (n, % using ITT population of patients continued on medication or withdrawn) had experienced:
- Any SAE?
 - Any bleeding SAE?
 - Please identify the specific patients/events.
7. Regarding dosing: please clarify by the end of six months, how many patients (n, % using ITT population of patients continued on medication or withdrawn) had:
- Eltrombopag discontinued for more than one day as part of dose adjustment. Clarify, what was the reason for the drug discontinuation?
 - Eltrombopag changed to any regimen other than once daily (clarify the alternate regimen).

- Were receiving eltrombopag on any regimen other than daily at the end of the six month period?
- Construct a tabular distribution of the final drug regimen at the end of six months of therapy (ITT), e.g.,

Number of subjects:	n (%)
Withdrawn from eltrombopag by 6 months	
Receiving 50 mg daily	
Receiving 75 mg daily	
Receiving 25 mg daily	
Receiving 25 mg QOD	
etc	

8. Clarify dosing regimen as it relates to platelet response using the tabular presentation format (above), summarize the platelet count response outcome to the specific dose regimen (with columns identifying the duration of the specific regimen; the n (%) with platelet counts ≥ 50 K (for duration of the regimen exposure and other permutations of response). We need to know the platelet outcomes for each permutation of the dose regimen.

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

Sincerely,

(See appended electronic signature page.)

Rafel Dwaine Rieves, M.D.
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
7/9/2008 11:26:45 AM

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, July 08, 2008 1:11 PM
To: 'dennis.q.williams@gsk.com'
Subject: July 8, 2008 meeting: REMS slides
Attachments: Eltrombopag draft REMS 7 8 08 cleared.ppt

Hi,

Please see attached the REMS slides that were presented during the meeting.

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

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7/8/2008

3

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✓ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

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Hyon Z Lee  
7/8/2008 03:44:55 PM  
CSO

**Lee, Hyon-Zu**

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**From:** Lee, Hyon-Zu  
**Sent:** Friday, June 20, 2008 8:27 AM  
**To:** 'dennis.q.williams@gsk.com'  
**Cc:** Lee, Hyon-Zu  
**Subject:** Promacta: information request  
**Follow Up Flag:** Follow up  
**Flag Status:** Blue

Mr. Williams,

Please submit the patient listings for the EXTEND study that you have indicated in your initial NDA submission that you have on file (Attachment 3 in the Abbreviated Clinical Study Report for TRA105325). Please let me know when you will be submitting this information.

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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6/23/2008

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/s/

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Hyon Z Lee  
6/23/2008 09:57:01 AM  
CSO



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-291

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.

On April 17, 2008, we received your April 16, 2008 amendment to this application. This amendment contained the 120 day safety update to the application, including information from the on-going clinical studies. We have determined that this supplied information from the on-going clinical studies is essential to completion of our review, especially with respect to consideration of use of eltrombopag outside of a "short-term" period. Consequently, we regard the April 16, 2008 amendment as containing significant new clinical data from on-going clinical studies and we have classified this submission as a major amendment. The receipt date for the April 16, 2008 information is within 3 months of the user fee goal date. Therefore, we are extending the user fee goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 19, 2008.

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

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/s/

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Hyon Z Lee  
6/16/2008 03:10:16 PM

**Lee, Hyon-Zu**

**From:** Lee, Hyon-Zu  
**Sent:** Wednesday, June 11, 2008 9:44 AM  
**To:** 'bekki.e.komas@gsk.com'  
**Cc:** 'dennis.q.williams@gsk.com'  
**Subject:** NDA 22-291: Promacta

Ms. Komaz,

We have the following CMC comment for Promacta:

Revise the drug substance specification sheet to include the following footnote and submit the revision to the NDA.

"Genotoxic impurity \_\_\_\_\_ is controlled \_\_\_\_\_ such that it is below the Threshold for Toxicological Concern (TTC) in the drug substance." **b(4)**

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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6/11/2008

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/s/

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Hyon Z Lee  
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CSO

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** June 5, 2008

**TO:** Hyon-Zu Lee, Regulatory Project Manager  
Andrew Dmytrijuk, Medical Officer

**FROM:** John Lee, Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

**THROUGH:** Tejashri Purohit-Sheth, MD  
Acting Branch Chief, Good Clinical Practice Branch II  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 22-291

**APPLICANT:** GlaxoSmithKline, Inc.

**DRUG:** Eltrombopag (Promacta)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Priority review

**INDICATIONS:** Short-term treatment of thrombocytopenia associated with ITP

**CONSULTATION REQUEST DATE:** February 14, 2008

**DIVISION ACTION GOAL DATE:** May 27, 2008

**PDUFA DATE:** June 19, 2008

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Page 3 CLINICAL INSPECTION SUMMARY; NDA 22-291, Promacta

## I. BACKGROUND

Eltrombopag, developed by GlaxoSmithKline (UK), is an orally active small-molecule (thrombopoietin-receptor agonist) which stimulates platelet production and increases peripheral platelet counts. Eltrombopag may be effective in treating immune thrombocytopenic purpura (ITP), a disorder in which auto-antibodies directed against platelets and platelet precursors cause severe thrombocytopenia, including life-threatening thrombocytopenia.

### Study Synopses

#### TRA104603

- This was a phase 1, single-center, placebo-controlled, double-blind, randomized, dose escalation, 4-period crossover, single oral dose study in 16 healthy Japanese men. The major study objectives were: (1) to investigate the safety and tolerability of eltrombopag following single oral doses in healthy Japanese men, and (2) to investigate the pharmacokinetics (PK) of eltrombopag following single oral doses in healthy Japanese men.
- 16 subjects were randomized to one of four treatment sequences and received placebo and three of the 4 eltrombopag doses (30, 50, 75, and 100 mg) in 4 dosing periods. Each treatment was separated by 12 days. Investigational products were administered as single oral doses after fasting according to the treatment sequences shown below:

| Group                | Period 1                                        | Period 2                         | Period 3                           | Period 4                          |
|----------------------|-------------------------------------------------|----------------------------------|------------------------------------|-----------------------------------|
| A (n=4)              | Placebo<br>(Two placebo tablets)                | 50mg<br>(Two 25mg tablets)       | 75mg<br>(Three 25mg tablets)       | 100mg<br>(Four 25mg tablets)      |
| B (n=4)              | 30mg<br>(One 25mg tablet<br>and one 5mg tablet) | Placebo<br>(Two placebo tablets) | 75mg<br>(Three 25mg tablets)       | 100mg<br>(Four 25mg tablets)      |
| C (n=4)              | 30mg<br>(One 25mg tablet<br>and one 5mg tablet) | 50mg<br>(Two 25mg tablets)       | Placebo<br>(Three placebo tablets) | 100mg<br>(Four 25mg tablets)      |
| D (n=4)              | 30mg<br>(One 25mg tablet<br>and one 5mg tablet) | 50mg<br>(Two 25mg tablets)       | 75mg<br>(Three 25mg tablets)       | Placebo<br>(Four placebo tablets) |
| No. of tablets taken | 2 tablets                                       | 2 tablets                        | 3 tablets                          | 4 tablets                         |

- Post-study screen was performed 12 days after the final dose in Period 4 (ophthalmologic examination performed 6 months after the final dose). Monitoring consisted of the following evaluations: platelet counts, pharmacokinetic parameters, adverse events, changes in clinical laboratory tests, body weight, vital signs, 12-lead ECG, and ophthalmologic examinations.
- Eltrombopag was well tolerated. Following single oral doses, maximum plasma concentrations of eltrombopag (free acid) were observed at 3 to 4 hours (median) post-dose and then declined with a mean elimination half-life of about 23 to 28 hours. C<sub>max</sub> and AUC increased approximately linearly with increasing dose over the dose range examined. The urinary excretion of eltrombopag was 0.032% (maximum). No clinically significant changes in platelet counts were observed at either dose level.

#### TRA 105580

- This was a phase 1, single-center, placebo-controlled, single-blind, randomized, dose escalation, three-dose, parallel group, single and multiple oral dose study in 42 healthy Japanese men. The major study objectives were: (1) to investigate the safety and

tolerability of eltrombopag following single and multiple oral doses in healthy Japanese men, and (2) to investigate the PK of eltrombopag following single and multiple oral doses in healthy Japanese men.

- 42 subjects (14 per dose group) were randomized to receive the active drug at three dose levels (n = 10 per group/level) or placebo (n = 4). Initially, the subjects received a single dose; after a washout period of 5 days, the subjects received once daily dosing for 10 days. Study drug was orally administered after fasting according to the following scheme:

| Treatment Group         | SB-497115-GR group<br>(n=10)                                    | Placebo<br>(n=4)      |
|-------------------------|-----------------------------------------------------------------|-----------------------|
| Dose                    |                                                                 |                       |
| SB-497115-GR 25mg group | 25mg tablet×1/time                                              | Placebo tablet×1/time |
| SB-497115-GR 50mg group | 25mg tablet×2/time                                              | Placebo tablet×2/time |
| SB-497115-GR 75mg group | 25mg tablet×3/time                                              | Placebo tablet×3/time |
| Total number of dosing  | 11 times (single dose + once daily dosing for 10 days) /subject |                       |

- Platelet counts and safety data were reviewed (12 days after the final dose, day 22) prior to dose escalation to the next level. Post-study screen was performed 16 days after the final dose (day 26). Ophthalmologic examination was performed 28 days after the final dose (day 38). Monitoring consisted of the following evaluations: platelet counts, pharmacokinetic parameters, adverse events, changes in clinical laboratory tests, body weight, vital signs, 12-lead ECG, and ophthalmologic examinations.
- Eltrombopag was well tolerated. Following single and multiple oral dosing, maximum plasma concentrations (free acid) were reached at 3 to 4 hours (median) post-dose. Mean elimination half-life was 30 - 32 hours after a single dose, and 40 - 51 hours on day 10 of multiple dosing. Systemic exposure (C<sub>max</sub> and AUC) increased approximately linearly with increasing dose following single and multiple dosing. Based on changes in the trough concentration of SB-497115 over 10 days of multiple dosing, the steady state was achieved by about 7 days after starting multiple dosing.
- There were no clinically significant changes in the platelet count following a single dose. However, following 10 days of multiple doses, maximum platelet counts were reached 4 to 6 days after the final dose (days 14-16 of multiple dosing) at all doses and returned to within the reference range by 16 days after the final dose (day 26 of multiple dosing) in nearly all subjects. At 25, 50 and 75mg dose levels over 10 days, mean maximum change in platelet counts were 1.5, 1.7 and 1.9 times the baseline level, respectively.

#### TRA100773

Two double-blind, randomized, placebo-controlled, parallel group studies were conducted under a sequential adaptive study design to investigate the efficacy, safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of eltrombopag, a thrombopoietin receptor agonist, administered orally once daily for 6 weeks in adult patients with refractory (platelet count < 30 x 10<sup>9</sup>/L on standard therapy) immune thrombocytopenic purpura (ITP).

- The primary efficacy assessment was the platelet count, and the primary endpoint was the proportion of subjects with a platelet count of ≥ 50 after up to 42 days of dosing. Other efficacy assessments included incidence and severity of bleeding and health-related quality of life (HR-QoL). Safety assessments included adverse events (AEs), clinical laboratory

evaluations, physical examination, 12-lead ECG, spleen size (ultrasound), and ocular examination.

- Subjects were classified as responders if they achieved a platelet count of  $\geq 50$  at Day 43, or if the platelet count exceeded 200. Subjects were classified as non-responders if they discontinued treatment with study medication prior to Day 43 for any other reason. Subjects who attained a platelet count  $>200$  discontinued treatment but continued in the study with their follow-up visits. After the dosing period, subjects were assessed every 2 weeks for up to 6 weeks to evaluate the durability of the platelet response.

#### TRA100773A

This study A was a dose-finding phase 2 study involving 118 subjects randomized equally to one of four treatment groups (30 mg, 50 mg, 75 mg, and placebo) to determine the optimal starting dose.

- Eltrombopag treatment increased the platelet count in a dose-dependent manner. Both 50 and 75mg treatment groups achieved a statistical significant treatment effect compared with placebo ( $p < 0.001$ ). A decreased incidence of on-therapy bleeding (relative to baseline) was observed in the eltrombopag 30mg, 50mg and 75mg groups. No major differences were observed among treatment groups for pharmacodynamic or HR-QoL assessments.
- The incidence of AEs was similar across all treatment groups. Headache was the most frequent AE in each treatment group. A total of 7 on-therapy serious adverse events (SAEs) occurred in 4 subjects. One death was reported in the 50 mg treatment group (hepatitis, renal failure, embolism including pulmonary embolism).

#### TRA100773B

This study B was a pivotal phase 3 study conducted in follow up of study A in 114 subjects randomized in a 2:1 ratio to eltrombopag (50 mg) or placebo, respectively.

- 59% of subjects on eltrombopag achieved platelet counts to  $\geq 50$ , compared to 16% of subjects on placebo ( $p < 0.001$ ). Platelet counts  $> 200$  dropped to  $< 200$  within 2 weeks after stopping the study medication. Odds of bleeding at Day 43 were significantly lower for eltrombopag than for placebo (OR = 0.27,  $p = 0.029$ , logistic regression adjusted for concomitant medication at randomization, splenectomy, baseline platelet count, and baseline bleeding). An analysis of bleeding (WHO Grades 1-4) through Weeks 2-6 confirmed a statistically significant decrease in bleeding during treatment (OR = 0.49,  $p = 0.021$ ).
- The incidence of AEs was greater for eltrombopag than for placebo. The incidence of SAEs and AEs leading to withdrawal were similar for the two treatment groups. Headache was the most commonly reported AE in the study and was evenly distributed across the two treatment groups. Mild to moderate, self-limited gastrointestinal AEs (nausea, vomiting, and diarrhea) were reported more frequently for eltrombopag. On-therapy SAEs occurred in 2 subjects for both groups (2 events for eltrombopag and 4 events for placebo). No deaths were reported.

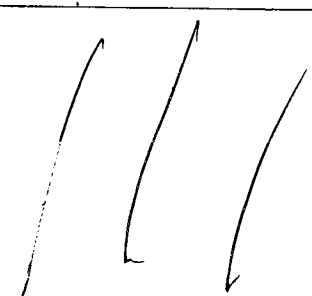
#### Site Selection

Drug levels of eltrombopag appeared to be higher in healthy volunteers of East Asian ancestry than in other volunteers (Central and South Asia, Europe), and ITP patients of East Asian

ancestry appeared to require smaller doses of eltrombopag than other ITP patients. Clinical sites were selected based on study enrollment (among US sites, largest site) with the special aim of addressing the curious dosing observation (among foreign sites, as many of the East Asian sites as feasible, beginning with the largest sites).

- TRA104603 and TRA105580: The primary goal was to verify the integrity of the pharmacokinetic data that support this observation. The two studies involving a total of 58 patients were conducted at Dr \_\_\_\_\_ site in Japan. Patients in Japan were not represented in the pivotal studies. **b(4)**
- TRA100773: In addition to evaluating good clinical practice (GCP), two additional major goals of this inspection were to: (1) verify the integrity of the data that support the sponsor's dosing recommendation (relationship between dosing data and platelet response data) for patients of East Asian ancestry, and (2) to examine source data to identify potential regional differences in good clinical practice (GCP) that may explain the apparently higher drug exposure and pharmacodynamic response in East Asians. The identification of any regional difference in GCP has implications important also to non-East Asian patients: the proposed dosing regimen may result in excessive platelet response and unwarranted adverse events.
- Limited pivotal data support this dosing recommendation: Of a total of 27 patients of East Asian ancestry in the pivotal studies, 21 (78%) were in \_\_\_\_\_ and 6 (22%) were in \_\_\_\_\_. Per discussion between DSI and DMIHP, CDER attempted to audit as much of the East Asian data as feasible under the pilot GRMP timeframe (to audit approximately 25% of all pivotal data, including 100% of the limited data at East Asian sites). **b(6)**

## II. INSPECTION RESULTS

|   | Name of CI or Sponsor<br>City and State/Country                                     | Protocol<br>Subjects      | Inspection<br>Dates             | Classification            |         |
|---|-------------------------------------------------------------------------------------|---------------------------|---------------------------------|---------------------------|---------|
|   |                                                                                     |                           |                                 | Interim                   | Final   |
| 1 |  | TRA104603<br>16 subjects  | completed:<br>5/19/08 - 5/30/08 | pending,<br>likely<br>NAI | pending |
|   |                                                                                     | TRA105580<br>42 subjects  |                                 |                           |         |
| 2 |                                                                                     | TRA100773A<br>12 subjects | completed:<br>5/26/08 - 5/30/08 | pending,<br>likely<br>OAI | pending |
|   |                                                                                     | TRA100773B<br>6 subjects  |                                 |                           |         |
| 3 |                                                                                     | TRA100773A<br>3 subjects  | pending:<br>6/2/08 - 6/6/08     | pending                   | pending |
| 4 |                                                                                     | TRA100773A<br>10 subjects | completed:<br>5/5/08 - 5/16/08  | pending,<br>likely<br>NAI | pending |
|   |                                                                                     | TRA100773B<br>1 subject   |                                 |                           |         |
| 5 | GlaxoSmithKline, Inc.<br>Collegeville, Pennsylvania                                 | NA                        | pending:<br>6/9/08 - 6/12/08    | pending                   | pending |

NAI = no action indicated / no deviations from regulations; VAI = voluntary action indicated / no significant deviations from regulations; OAI = official action indicated / significant deviations from regulations; NA = not applicable

1. \_\_\_\_\_

b(4)

- No major deficiencies were noted and no FDA 483 was issued. However, for PK data, all data were handled (collection, analysis, storage) by GSK-Japan and the clinical site had no access to the database.

b(5)

- Minor deviations observed included a brief excursion in sample storage temperature. In storing clinical samples for laboratory testing, the temperature recording for the -80 C freezer showed an excursion to -70 C for a time period not exceeding one hour.
- Periodic monitoring of study conduct was not adequately documented. Formal monitoring reports and monitoring visit log were not available and apparently were not maintained. This deficiency is significant. The sponsor, and not the clinical investigator, bears the bulk of the responsibility for this deficiency.

Recommendation: The integrity of the phase 1 data (including PK data) collected at this site cannot be verified at this inspection. DSI recommends not relying on the PK data obtained at this site as substantial support for the sponsor's proposed dosing recommendation in East Asian patients.

2. \_\_\_\_\_

b(6)

- In general, documentation of subject records was inadequate. Case histories were often insufficient and progress notes were typically sparse. Inadequate documentation included obliteration (or otherwise making unreadable) of original information when corrected with new information. Infrequently (noted on two occasions), source data were recorded in pencil. Primary efficacy endpoint data, however, appeared not to be affected.
- An FDA Form 483 was issued for the following two major deficiencies:
  - The use of an inadequate consent form in obtaining informed consent
  - Enrollment of subjects who should have been excluded based on screening laboratory values (including positive serology for hepatitis B)

Recommendation: Data from this site relevant to the primary efficacy endpoint (change in platelet count) appear to be reliable. However, the overall poor state of subject records and evidence of inappropriate subject enrollment suggest that the data obtained at this site may not be reliable with respect to: (1) the assessment of treatment-related adverse events, and (2) the confirmation of the need for decreased initial dosing among East Asian patients, as presumably suggested by the phase 1 PK data.

b(6)

3. \_\_\_\_\_

This inspection has not been completed and the results are pending.

4. \_\_\_\_\_

b(6)

- Of the 13 subjects screened at this site (12 in study A, one in study B), 11 enrolled

(10 in study A, one in study B) and 9 completed the studies. Two subjects were withdrawn from the study (due to the platelet count rising above  $200 \times 10^6 / \text{mL}$ ).

- No significant deviations were observed and no FDA 483 was issued.
  - Subject records for all 11 subjects completing the study were reviewed. There was no evidence of underreporting of adverse events and data submitted under the NDA matched source documentation.
  - The study was conducted at three different sites and study monitors visited all three sites. No deficiencies were noted with respect to drug accountability, subject compliance in taking the study medication, and the maintenance of proper IRB approval during the studies.

Recommendation: Data from this site are reliable.

**5. GlaxoSmithKline, Inc., Collegeville, Pennsylvania**

This inspection has not been completed and the results are pending.

**III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Five inspections were scheduled for this NDA consisting of 3 foreign clinical sites in East Asia and one US clinical site in addition to the sponsor inspection. As of this clinical inspection summary (June 4, 2008), 3 inspections were completed (major clinical sites in \_\_\_\_\_, \_\_\_\_\_, and US) and two remain pending (minor clinical site in \_\_\_\_\_ and sponsor inspection).

- The deficiencies noted at the clinical site in \_\_\_\_\_ were minor in nature and appeared to be isolated occurrences. However, the reliability of the data obtained at this site could not be verified at this inspection since source data were kept by the sponsor at GSK-\_\_\_\_\_ and no longer at this clinical site. b(6)
- The deficiencies noted at the major clinical site in \_\_\_\_\_, were significant. The impact of the deficiencies appears to be limited to safety assessment; efficacy assessment appears to be largely unaffected by the observed deficiencies. Results at the minor (second of two) clinical site in \_\_\_\_\_ remain pending as of June 4, 2008. b(6)
- No significant deficiencies were observed at the US clinical site, and data obtained at this site are reliable for safety and efficacy evaluations. Results of the sponsor inspection (GSK-US) remain pending as of June 4, 2008.

The inspectional findings to date based on preliminary communication with the field investigator: (1) indicate that the primary efficacy endpoint data (treatment-related rise in platelet count) are reliable, (2) suggest that the safety data from the major (first of two) clinical site in \_\_\_\_\_ may not be reliable, and (3) do not support the sponsor's proposal to use a reduced dose in initiating treatment in East Asian patients. As of June 4, 2008 (date of this summary), the results from the minor clinical site in \_\_\_\_\_ and the sponsor inspection are pending, as are the final inspection reports from all inspections. b(6)

Follow-Up Action: A clinical inspection summary addendum will be generated after the inspections have been completed and the results have been evaluated by DSI.

{See appended electronic signature page}

John Lee, MD  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.  
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Office of Compliance

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John Lee  
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Tejashri Purohit-Sheth  
6/5/2008 04:56:37 PM  
MEDICAL OFFICER

NDA 22-291  
Promacta (eltrombopag olamine)

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**Microbiology Review**

This section of the action package is not applicable.

Hyon-Zu Lee 6/8/08  
Hyon-Zu Lee

NDA 22-291  
Promacta (eltrombopag olamine)

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**Clinical Microbiology**

This section of the action package is not applicable.

Hyon-Zu Lee 8/8/06  
Hyon-Zu Lee

NDA 22-291  
Promacta (eltrombopag olamine)

**DSI Nonclinical Inspection**

This section of the action package is not applicable.

Hyon-Zu Lee 6/8/08  
Hyon-Zu Lee

NDA 22-291

Promacta (eltrombopag olamine)

**Controlled Substance Staff review**

This section of the action package is not applicable.

Hyon-Zu Lee 6/8/08  
Hyon-Zu Lee

NDA 22-291

Promacta (eltrombopag olamine)

**Postmarketing Commitment (PMC) Studies**

This section of the action package is not applicable.

*Hyon-Zu Lee 6/4/08*

Hyon-Zu Lee

NDA 22-291

Promacta (eltrombopag olamine)

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**AIP related documents**

This section of the action package is not applicable.

Hyon-Zu Lee 6/6/08  
Hyon-Zu Lee

*In several places within the OSE review, it states certain risks (e.g. cataract) are not addressed in the label. To clarify, these risks are identified in the label. Currently, the only risk not identified in the label is \_\_\_\_\_ . This item can be discussed between GSK and the FDA during the labeling negotiations."*

**b(4)**

The following questions were emailed to GSK on May 19, 2008:

*"1. Describe the extent to which the EXTEND and REPEAT clinical study data have been audited--were the 120 day safety update datasets comprehensively audited (e.g., for transcription errors from case report forms/as well as on-site audit for verification of accurate transcription from medical records to case report forms)?*

*2. The study protocol and report appear to indicate that differentials were obtained with CBC's but peripheral smear results do not appear to have been actively solicited for cellular abnormalities (e.g., blasts) during the study 773A and 773b...or, if they were, they supposed to have been they apparently were not captured on the case report forms (our exam of the case report form--electronic--does not indicate a space or active query for the detection of peripheral blood smear abnormalities/instead, peripheral smear abnormalities would apparently have to have been reported as adverse events (if reported at all)....is this true?*

*3. Apparently in 773A and 773b, investigators were not blinded to platelet count results and these same investigators were also performing the WHO scale assignments; given this consideration, could investigators been aware of patient platelet count results at the time of assignment of WHO bleeding scale results? Or, were procedures in place (we can find no verification of such procedures) to require WHO scale completion by an independent evaluator who had no access to platelet count data?*

*4. In 773A, subjects who withdrew from the drug because of platelet counts  $\geq 200K$ , were followed up on day 57...is this "day 57" two weeks after the date of drug withdrawal? In effect, is it true that the date of study withdrawal is denoted as "day 43" for any subject who prematurely withdraws because of platelet counts  $\geq 200K$  and the next date of follow-up (for example, the next platelet count) is obtained two weeks later, on the "new" day 57?*

*In 773B, subjects who withdrew from the drug because of platelet counts  $\geq 200K$ , were followed upon on day 50...is this nominal "day 50," one week after the date of drug withdrawal? Similar to the procedure mentioned above, is it true that the date of study withdrawal is denoted as "day 43" for any subject who prematurely withdraws because of platelet counts  $\geq 200K$  and the next date of follow-up (for example, the next platelet count) is obtained one week later, on the "new" day 50?*

*5. In 773A, the "primary dataset" (for description of platelet count/responses) consists of imputation (LOCF) for subjects who withdrew before day 43...correct? However, the "observed dataset" does not include imputation...correct? For example, Figure 4 ("Median Platelet Counts (Efficacy Population, Observed Dataset)") from the 773A study report contains all available platelet count data with no imputation...is that correct?*

*6. Please confirm that, in the Study 773A report, Figure 7 ("Subjects with bleeding grad 1-4 by visit (Efficacy Population)") includes no imputation/only observed data...correct?*

7. Is it true that the extent of "worsened thrombocytopenia" after discontinuation of eltrombopag in Study 773A could only be assessed based upon a platelet count obtained 2 weeks after study drug discontinuation/while data from 1 week after study drug discontinuation are available for Study 773B?"

The following questions were emailed to GSK on May 20, 2008:

"GSK, please clarify the following laboratory data for Subject 144 who was enrolled in Study 773A.

This 66 year old male had undergone a right pneumonectomy for lung cancer five years before study enrollment. His baseline laboratory data were unremarkable. However, 14 days after starting Eltrombopag at 50 mg daily, he was hospitalized with a COPD exacerbation that was accompanied with liver test and renal abnormalities. The subject died eleven days after hospitalization with a death reported by the investigator as due to cardiac failure caused by pulmonary failure. The initial (site) autopsy reported thromboemboli in peripheral vessels of lung and liver, left and right ventricular hypertrophy with "terminal ischemia" and evidence of prior myocardial infarction.

Two "external" reviews of the pathology were performed and one physician regarded the cause of death as due to "multiple pulmonary emboli" and the other physician regarded the cause of death as due to "cardiac failure caused by pulmonary failure" (similar to the site investigator assessment of death causality).

The laboratory data are unclear between the narrative and dataset. Please explain the discordance between the dataset "day 15" data and the dataset "day 43" (withdrawal) data. Address the following questions:

Were the day 15 data obtained one day prior to the day 43 data? Were the day 15 data obtained on a routine follow-up visit when the patient was apparently well? Were the day 43 data obtained at the local hospital/at the time of hospitalization (one day after the day 15 visit)? Please correct any inaccuracies."

| Lab        | Baseline                    | Day 8     | Day 15    | Day 43                                        |
|------------|-----------------------------|-----------|-----------|-----------------------------------------------|
| Platelet   | 17/5 K                      | 10 K      | 44 K      | 108 K                                         |
| ALT        | 21 U/L<br>(nl up to 45)     | 15 U/L    | 274 U/L   | 1897 U/L                                      |
| AST        | 15 U/L<br>(nl up to 40)     | 12 U/L    | 186 U/L   | 755 U/L                                       |
| Bilirubin  | 9 mcml/L<br>(nl up to 40)   | 11 mcml/L | 14 mcml/L | 53                                            |
| Alk Phos   | NA                          | NA        | NA        | NA<br>(narrative reports 413<br>U/L; nl < 40) |
| Creatinine | 77 mcml/L<br>(nl up to 110) | 84 mcml/L | 97 mcml/L | 128 mcml/L                                    |
| BUN        | NA                          | NA        | NA        | 22 millimol/L (nl up to 7<br>millimol/L)      |

## DISCUSSION POINTS:

The following agreements were reached after the discussion. The format provides the firm's comments in italics followed by DMIHP responses in regular font.

*The sponsor started the discussion with the* \_\_\_\_\_

b(4)

*The sponsor then stated that they have some general questions about the ODAC such as FDA questions to the advisory committee and the indication statements whether it will be for the short-term or the long-term/broader indication.*

b(4)

The Agency responded that the FDA presentation will be brief and focused only on the clinical data. We will not have non-clinical or clinical pharmacology presentations. The Agency's clinical presentation will be the overview of the original NDA submission, and will be focused on the short-term indication. We will present a summary of the robustness of the data and highlights of the major aspects of the safety findings, including information from the ongoing clinical studies. The Agency stated that we are working on the questions and presentation, and might have some information requests before the AC regarding the accuracy of specific numbers.

*The sponsor commented that they have questions regarding FDA's briefing package. They indicated that the second bullet on page 2 states "FDA had informed the sponsor during the clinical development of eltrombopag that a "short-term" indication may be reasonable in specified circumstances. For example, a reasonable short-term use may relate to the use of the product prior to and during a surgical (or other invasive) procedure. However, FDA repeatedly stressed the critical need to evaluate eltrombopag's longer term safety and efficacy data given the likelihood of chronic use regardless if data are only available for short-term use."*

*Regarding the above, they stated that will present the efficacy data from the EXTEND study.*

The Agency responded that the above statement (extracted from the briefing document) reflects FDA concerns and stated that the Agency had not objected to submission of a solid short term proposal with the NDA submission.

*The sponsor commented that they will present the short term usage and that* \_\_\_\_\_  
\_\_\_\_\_ *in the revised labeling* \_\_\_\_\_

b(4)

*They asked if the REPEAT data is considered short term or long term data as the indication now is focused on the short term.*

The Agency responded that the REPEAT study is ongoing and that more doses are given than the pivotal/proposed short term use. Although the REPEAT data has indications for short term treatment cycle, it has implications for repetitive use of the drug (which is a form of "long term" usage).

*The sponsor then commented that the FDA briefing package on page 2, second bullet states "The sponsor did not specifically design studies to evaluate the clinical utility of eltrombopag in specific circumstances where short-term therapy was necessary."*

*Regarding the above, they stated that they had limitations with the study and that it was designed for surgical procedures.*

The Agency stated that the FDA presentation will focus on the data and that we expressed concerns regarding the short-term studies since the bleeding scale used in these studies appeared to focus upon assessment of changes in chronic/baseline bleeding (not bleeding that occurs during a surgical/invasive procedure).

The Agency indicated that the WHO bleeding outcomes were not classified as secondary endpoint, but classified as "other" on both 773A and 773B protocols and asked to provide specific pages that state the primary and the secondary endpoints under statistical analyses and the pre-specified single statistical methodology for bleeding scores for both protocols. FDA emphasized that the "other" aspects was extracted from the statistical analytical plan and the text within this plan appeared inconsistent with other parts of the protocol.

*The sponsor responded that for the 773B protocol, the bleeding is classified as secondary endpoint on page 29 and it was pre-specified on page 20.*

The discussion then shifted towards the sponsor's "Questions regarding the FDA backgrounder for ODAC" sent to FDA on May 16, 2008. It was decided that a face to face meeting be scheduled to discuss the statistics and that the Agency and sponsor will exchange the datasets used for the analyses. For the sponsor's questions regarding the Clinical Pharmacology, the Agency stated that we will email the responses. Regarding the risk management plan, the Agency stated that we expect Risk Evaluation and Mitigation Strategy (REMS) and that the details will be contingent on the indications, labeling and the feedback of the ODAC.

*The sponsor stated that they will send the responses to the questions emailed to the sponsor on May 19, 2008 and will send the narratives and the autopsy report requested for subject 144.*

The Agency indicated that the sponsor's response dated April 14, 2008 regarding the pharmacokinetic data related to ethnicity is not sufficient and that the sponsor needs to send additional information.

#### **ACTION ITEMS:**

- The Agency will arrange for a face to face meeting to discuss the statistical analyses.
- The Agency will send the responses to the Clinical Pharmacology questions that were emailed on May 16, 2008.
- The sponsor will submit the responses to the questions emailed on May 19, 2008 and May 20, 2008.

#### **POST ADDENDUM:**

The following Clinical Pharmacology responses were sent to the sponsor on May 21, 2008. The questions are restated followed by FDA responses in bolded font:

We have a question regarding the following statement on Page 23 of the FDA Advisory Committee Briefing Document for the May 30, 2008 meeting regarding eltrombopag: "The true magnitude of this difference the healthy East Asian population is difficult to confirm given the high variability and possible systematic errors found in some of the trials conducted in Japan."

1. Please clarify what is meant by "...possible systematic errors found in some of the trials conducted in Japan."

**Please refer to the April 8, 2008, teleconference where we discussed our specific concerns regarding the studies conducted in Japan. FDA 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. Given these concerns are still unresolved, FDA conducted an analysis using your pop-PK model looking at the effect of including and excluding study 105580 data. FDA found the exposure difference to be approximately 60-70% based on this analysis.**

We have a question regarding the following statement on Page 23 of the FDA Advisory Committee Briefing Document for the May 30, 2008 meeting regarding eltrombopag: "The glutathione conjugation pathway has yet to be fully characterized."

2. What additional work do you consider necessary to fully characterize the glutathione conjugation pathway?

**The report for protocol O5DMM155 "Identification and Quantification of the Major Metabolites of SB-497115 Following a Single Oral Administration (75 mg 100 pCi) of [<sup>14</sup>C]SB-497115-GR to Healthy Adult Male Subjects" identifies metabolites M9, F, & G as glutathione and cysteine conjugates. These fecal metabolites were lower in the two African American subjects in this study compared to the other subjects. In addition, study TRA102861 reports one of these subjects (#2) had the highest screening bilirubin, lowest fecal concentration of these metabolites, and the highest AUC<sub>inf</sub> of the group (~1.5 times Caucasian). Information regarding the enzymes/transferases associated with these metabolic pathways would provide additional characterization. This information was not provided in the application. If this information is available please submit it for review.**

We have a question regarding the following statement on Page 24 of the FDA Advisory Committee Briefing Document for the May 30, 2008 meeting regarding eltrombopag: "FDA also noted a trend suggesting approximately 40% higher eltrombopag exposure in some healthy African-American subjects in several clinical pharmacology studies. This issue was not fully explored by the sponsor."

3. What additional analysis has the FDA completed to conclude that exposures in African American subjects are approximately 40% higher and what is meant by "several" clinical pharmacology studies?

**Please refer to the April 8, 2008, teleconference where we discussed our specific concerns regarding increased eltrombopag exposure in African American subjects in some of your clinical studies.**

**Given the small number of African American subjects represented in your clinical studies, an inferential or pop-PK analysis was not possible. Therefore, FDA looked at differences descriptively. The studies FDA noted exposure differences were studies**

1029861, TRA105122, 497115/002, TRA 102860 (cohorts 100 mg and 200 mg), 102863 (cohort 75 mg) and TRA105120.”

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