FDA Advisory Committee Briefing Document

Oncologic Drugs Advisory Committee
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Prepared by the Division of Medical Imaging and Hematology Products/Office of Oncology Drug Products/Office of New Drugs
Consultative assistance from the Office of Clinical Pharmacology, Office of Biostatistics and Office of Surveillance and Epidemiology (OSE)

New Drug Application (NDA) 22-291: Eltrombopag
for the short-term treatment of previously-treated patients
with chronic idiopathic thrombocytopenic purpura

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Topics for Questions
and Major Background Points

FDA anticipates questions and discussions pertaining to the topics outlined below. Each topic is followed by a summary of the major background points.

1. The appropriateness of "short-term" use of an oral product in the treatment of patients with a chronic condition, especially patients with platelet counts < 30,000/mcL despite prior therapy.

- 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.

- The sponsor did not specifically design studies to evaluate the clinical utility of eltrombopag in specific circumstances where short-term therapy was necessary.

- The sponsor's proposed indication does not identify the specific circumstances for short-term use of eltrombopag (for example, prior to a surgical or invasive procedure).

- Based upon the proposed label and drug distribution plan, the proposed market approval for short-term use may, in fact, result in long term use of eltrombopag. The sponsor's major investigational clinical study to support long term use is on-going.

2. The strengths and limitations of the short-term efficacy data, especially with respect to the proposed claim that eltrombopag reduces or prevents bleeding. In the short-term studies:

- patients were enrolled even though they apparently did not have a specific need for the short-term use of Eltrombopag. Instead, the studies enrolled patients with chronic ITP who appeared to have low-grade, chronic bleeding at baseline with platelet counts < 30,000/mcL. In these studies, 60 to 70% of patients receiving Eltrombopag experienced an increase in platelet counts to ≥ 50,000/mcL while the placebo group response rate was 11 to 16%.

- the sponsor reports that patients who had bleeding at baseline generally had lesser bleeding while receiving eltrombopag but resumed the baseline level of bleeding following discontinuation of eltrombopag.

- bleeding was mainly assessed with the WHO scale in which subjects were subjectively categorized into one of five categories: no bleeding (grade 0); petechiae (grade 1); "mild blood loss" (grade 2); "gross blood loss" (grade 3) or "debilitating blood loss" (grade 4).

- the clinical meaningfulness of a change from a WHO category of "mild blood loss (grade 2)" to a lower grade, such as petechiae (grade 1) is unclear. Almost all nominal improvement in bleeding was for the lessening of bleeding among patients with grade 2 or less severe bleeding. Statistical analyses of these data are not robust (due to missing data and biased analytical methodology) and inconsistency with the "ITP Bleeding Scale" results, another measure of bleeding.

- anecdotal hemostatic challenge (e.g., invasive procedures) outcomes were reported in four eltrombopag group patients and three placebo group patients; only one patient (placebo) received red blood cells or platelet transfusions. Hence, the response to hemostatic challenges was assessed in only seven of the 231 chronic ITP patients randomized and treated in these studies.

3. The strengths and limitations of the short-term safety data, especially in the context of potential long term use of eltrombopag.

- One of the considerations in the use of thrombopoetic products is the possibility of worsened thrombocytopenia following discontinuation of the product (perhaps due to suppression of intrinsic thrombopoietin).

- In combined analyses of the short-term studies, a slight imbalance was evident in the occurrence of worsened thrombocytopenia, compared to baseline, following study drug discontinuation, (10% in the 50 mg eltrombopag group and 6% in the placebo group).

- Eltrombopag is metabolized in the liver and preclinical studies signaled potential liver toxicity. Liver test abnormalities were predominantly CTC grade 2 or less severity in the short-term studies, however, the overall pattern indicated a slight excess of liver test abnormalities within the eltrombopag group. For example, the rate of CTC grade 2-4 ALT elevations was 8% in the 50 mg eltrombopag group and 3% in the placebo group. Comparative data for liver tests with longer duration of eltrombopag treatment are not available at this time.

- Safety findings in the preliminary report from the REPEAT study (repetitive "six week cycles" separated by 30 days off drug), suggested that eltrombopag was tolerated in a manner similar to the initial "six week cycle." For example, transient worsening of thrombocytopenia (compared to baseline) following eltrombopag was also observed in this study. Of the 66 enrolled patients, thrombocytopenia transiently worsened (compared to baseline) following eltrombopag discontinuation in 24 (41%) subjects; rescue medication was administered during the "off therapy" period to 11 (17%) subjects.

4. The strengths and limitations of the available "long term" data:

    - The phase 3, six month, placebo-controlled study (RAISE) is on-going and the results remain blinded; RAISE was proposed by the sponsor as the main clinical study to assess the safety and efficacy of long-term eltrombopag therapy. The use of a control group in this study is especially important to help assess the potential risks for thromboses and marrow toxicity (e.g., fibrosis), events not readily assessable from the short term studies or the long term, uncontrolled studies.

    - All long term clinical data are from uncontrolled clinical studies or limited to the blinded data from RAISE. Notably, approximately half of the patients who participated in the short-term studies had not enrolled in the long term extension studies as of the data cut-off point, a loss exemplary of the selection bias inherent in the uncontrolled data.

    - To date, only 39 patients have been exposed to eltrombopag for a year and no patients have been exposed for two years.

    - The overall (short term and long term) incidence of notable hepatobiliary abnormalities was 9% (predominantly ≤ grade 3 bilirubin elevation and liver enzyme elevation); eltrombopag was discontinued in the extension study in two patients because of elevated liver tests.

    - Preclinical data are of limited usefulness since eltrombopag does not stimulate platelet production in most animal species. However, chronic exposure animal studies signaled renal, hepatic and ocular toxicity, events that underscore the importance of the RAISE study and supportive long term clinical data.

5. The major aspects of the proposed risk management plan (RiskMAP):

    - The proposed plan includes efforts to educate patients (leaflet and booklet) and physicians regarding the risks and benefits of short-term eltrombopag use, including reminder systems.

    - The plan does not restrict use of eltrombopag to a short-term or particularly emphasize the role and importance of short-term eltrombopag use. Instead, the plan appears to anticipate long term use of the drug. For example, the plan allows the dispensation of a 42 day supply of eltrombopag at any one time, although the plan does not preclude sequential, regular dispensations of a 42 day supplies to any one patient. Further, the plan includes a safety questionnaire to be completed for each patient at six month intervals for the first two year of therapy.

    - All patients and prescribers are expected to enroll in the program which will allow for active pharmacovigilance over two years (for each patient). During this time, prescribers will be asked, every six months, to fill out a safety questionnaire

regarding the occurrence of liver abnormalities, thromboembolic events, bone marrow reticulin events and malignancies.

- "Off label" use of eltrombopag is to be determined from review of ICD-9 codes, although the extent of long-term eltrombopag use is not targeted for tracking.

- Distribution is controlled to the extent that only "authorized" pharmacies and clinics will distribute eltrombopag.

Executive Summary

1. Product Background:

Eltrombopag (GlaxoSmithKline) is the subject of a New Drug Application (NDA) for marketing the product with the following clinical indication:

"Eltrombopag (Promacta™) is indicated for the short-term treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding."

Eltrombopag is a chemically synthesized, small molecular weight compound which binds to the transmembrane portion of the thrombopoietin (TPO) receptor on blood and bone marrow cells, including megakaryocytes. Eltrombopag is administered orally with a proposed dose of 50 mg daily, which may be increased to 75 mg daily if the platelet count remains below 50,000/mcL after three weeks of therapy. Treatment targets a platelet count in excess of 50,000/mcL and cessation of dosing is recommended if the platelet count exceeds 200,000/mcL (with no proposal for resumption of dosing since the treatment period is limited to six weeks).

Of the species studied in animal testing, eltrombopag stimulated platelet production only in chimpanzees. However, toxicity testing was performed in mice, dogs, rats and monkeys. Repetitive dose studies (at dosages in excess of the clinically applicable) resulted in chronic progressive nephropathy, cataracts and liver abnormalities.

The clinical pharmacology of eltrombopag is notable for extensive metabolism in the liver; most of the product (~ 60%) is eliminated through the feces and the remainder eliminated in urine. The plasma half-life for eltrombopag elimination is approximately 21 to 32 hours. Limited pharmacology data suggest that patients of East-Asian ethnicity (e.g., Japanese, Chinese, Korean, etc) may have greater exposure to eltrombopag compared to non-East-Asians. The sponsor proposes a lower initial dose (25 mg daily) for patients who identify themselves as East-Asian.

The clinical development program has focused upon use of eltrombopag in the treatment of chronic ITP, but additional studies are planned or ongoing for use of eltrombopag in the treatment of thrombocytopenia among patients with hepatitis C as well as patients with cancer (solid tumors) who were undergoing chemotherapy. Preliminary data from these studies provide no unique safety and bioactivity findings with respect to the use of eltrombopag among patients with chronic ITP.

2. Clinical Background

Chronic ITP is generally regarded as an immunologically-mediated condition in which antibody development to platelet epitopes results in platelet destruction and thrombocytopenia, the laboratory hallmark of the condition. ITP occurs in adults and pediatric patients although the manifestations importantly differ between these two groups. In pediatric patients, thrombocytopenia frequently resolves spontaneously. In

adults, ITP frequently results in chronic thrombocytopenia and a risk for life-threatening hemorrhage. Throughout this document chronic ITP will refer to the condition among adults.

The treatment for chronic ITP consists of various medications and, in some situations, splenectomy. The major goal of chronic ITP therapy is to reduce the risk for hemorrhage. In general, the risk for bleeding correlates with the severity of thrombocytopenia and a response to most therapy is indicated by improvement in platelet counts. Medications for chronic ITP consist of corticosteroids, intravenous gamma globulin (IVIG), anti-D immunoglobulin and, in more refractory situations, a variety of immunomodulatory medications (such as rituximab or azathioprine).

Thrombocytopenia in chronic ITP is thought to result primarily from enhanced platelet destruction. However, inappropriately reduced platelet formation is also proposed as a contributor to the thrombocytopenia, as evidenced by "inappropriately low" blood levels of thrombopoietin (TPO) among thrombocytopenic patients with chronic ITP. Conceivably, eltrombopag functions to stimulate the formation of platelets in the setting of "inappropriately low" blood TPO levels among patients with chronic ITP.

3. Regulatory Background:

The sponsor submitted the eltrombopag NDA with a proposal for short-term (six weeks) use of the product. Data from two randomized, double-blinded, short-term clinical studies were submitted in support of this indication. Supplemental information was provided from a study (REPEAT) in which patients received repetitive "six week cycles" of eltrombopag; each cycle was separated by a 30 day off-drug period.

The sponsor's proposed drug distribution and risk management plan are conducive to long term use of eltrombopag. However, the long term clinical development program remains on-going. This program, intended to provide a thorough evaluation of safety and efficacy, consists of a randomized, double-blind, placebo-controlled study of six months duration (RAISE) and accumulating data from an open label, extension study (EXTEND).

Updated, preliminary data from the ongoing clinical studies (REPEAT, EXTEND and RAISE) were recently submitted to the FDA as a component of the expected safety update for the application. The results from RAISE remain blinded to treatment assignment and the data from REPEAT and EXTEND are all uncontrolled. Hence, these long term exposure data provide useful but limited safety and bioactivity information and FDA review of these data are ongoing. This document will focus upon the sponsor's proposed short-term usage of eltrombopag, with a summary of the longer exposure data.

4. Efficacy:

The safety and efficacy of short term use of eltrombopag were evaluated in two randomized, double-blinded clinical studies, Study 100773 A ("Study A") and Study 100773 B ("Study B"). Both studies enrolled patients with chronic ITP who had either not responded to one or more prior therapies (including splenectomy), or who had

relapsed within three months of prior therapy and who had a baseline platelet count of < 30,000/mcL. Patients were allowed to receive concomitant ITP medications, provided the dose had been stable for at least one month.

Major study design features were similar for both studies. Randomization was stratified based upon use or non-use of ITP medications at baseline, splenectomy status and baseline platelet count (≤ 15,000/mcL or > 15,000/mcL). Study medication was administered daily for six weeks, followed by a six week follow-up, off-drug observation period. An ocular examination was performed at baseline and six months following the final dose of study drug. Subjects who attained a platelet count > 200,000/mcL had study drug discontinued but continued to be evaluated over the subsequent six weeks.

In both studies, the primary endpoint was a comparison of "responders" among the groups, where a response was defined as a platelet count of ≥ 50,000/mcL by the end of the active treatment period (which included patients who had study drug discontinued because platelet counts exceeded 200,000/mcL before the six week end of the study's active treatment period). Secondary endpoints included various explorations of the platelet count responses and descriptive statistics were to be applied to "other efficacy" analyses (which included bleeding scale assessments and changes in "quality of life" (SF-36) outcomes.

Study A was an initial, dose-determination study and randomized patients among four groups (1:1:1:1), placebo or one of three eltrombopag dose regimens (30 mg, 50 mg or 75 mg). This study's results suggested that the 50 mg dose was optimal for subsequent testing in Study B.

Study B randomized patients (1:2) between placebo and eltrombopag 50 mg. Patients who had platelet counts < 50,000/mcL on day 22 (or later) could have had their study drug doses increased to 75 mg eltrombopag (or matching placebo).

a. Platelet responses:

Study A and B primary endpoint results are shown in Table 1. Both studies enrolled patients who generally had received multiple prior ITP therapies and approximately 40% of the patients had undergone splenectomy.

Table 1. Study A and B primary endpoint results (responders)*

Study A	Placebo n = 27	Eltrombopag		
		30 mg, n = 29	50 mg, n = 27	75 mg, n = 26
Responders	3 (11%)	8 (28%)	19 (70%)	21 (81%)
Study B	Placebo n = 38	Eltrombopag 50 mg n = 74		
Responders	6 (16%)	43 (59%)		

*$p < 0.05$ for comparisons of 50 mg eltrombopag groups to placebo groups

The time course for the platelet response is shown in Figure 1 (below) with pooling of Study A and B results for the 50 mg eltrombopag dose groups (shown are median platelet counts and 25th-, 75th- percentiles). Exploratory analyses generally showed a similar pattern of response between patients who had not undergone splenectomy and patients who had splenectomy.

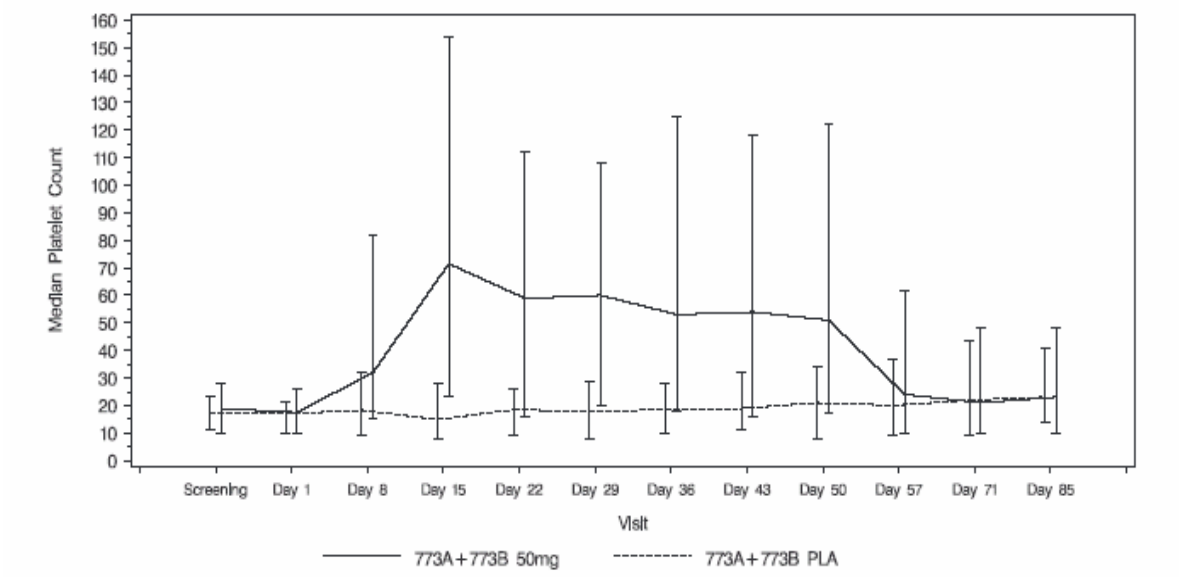


Figure 1. Median platelet counts for placebo and 50 mg Eltrombopag groups.

b. Bleeding:

The sponsor has proposed a specific text statement that indicates Eltrombopag will "reduce or prevent bleeding." Controlled clinical data evaluating bleeding outcomes are available only from Studies A and B and these outcomes were prospectively identified as analyses to be compared using descriptive statistics as a form of "other efficacy."

Notably, Studies A and B were not specifically designed to study the effects of Eltrombopag among patients who were undergoing a hemostatic challenge, as may occur with surgery. Instead, the collection of outcomes from patients who happened to undergo a hemostatic challenge was based upon survey of the available case report forms for tabulation of anecdotal information.

Bleeding at baseline and at specific follow-up time points was assessed using a "WHO Bleeding Scale" and an "ITP Bleeding Scale." Computation of the WHO bleeding scale results was relatively simple, even though the analytical plan did not provide a detailed plan for the statistical methodology, since the WHO bleeding scale is a relatively simple outcome measure (see Table 2). However, the ITP Bleeding Scale was a much more complex bleeding scale (for example, various "body areas" are to be graded as 0 for "none" to 2 for extensive bleeding) and the lack of detailed statistical methodology severely limits interpretation of these data (especially for Study A). The statistical reviewer provides a detailed summary of the major bleeding data (see attachment).

Table 2. WHO bleeding scale

Grade 0	No bleeding
Grade 1	Petechiae
Grade 2	Mild blood loss
Grade 3	Gross blood loss
Grade 4	Debilitating blood loss

As shown in the attached statistical summary, the overwhelming preponderance of bleeding was assessed as grade 2 or less severity; the multiplicity of data assessment time points and missing data complicate any attempt at more than descriptive statistical assessment. Nevertheless, the following points are notable:

- Within the eltrombopag groups, approximately 60% of patients were bleeding at baseline and, after receiving eltrombopag, approximately 35% of patients were bleeding; following eltrombopag discontinuation, the bleeding rate returned to the baseline level.

- The WHO bleeding scale does not provide specific criteria for defining "mild, gross or debilitating" bleeding and the clinical meaningfulness of transitions among the lowest grades (0 to 2) is unclear.

- The nominal improvement in bleeding was for transitions among the lowest WHO bleeding grades (2 or less).

Another potential measure of bleeding relates to the handling of hemostatic challenges. Within the two studies, only seven patients experienced hemostatic challenges (4 eltrombopag, 3 placebo) and only one patient received platelets and/or a blood transfusion (a placebo patient).

5. Safety:

Overall, 330 patients with chronic ITP have been exposed to eltrombopag, including 164 patients exposed in the two controlled, short term clinical studies. As summarized below, the short term clinical study data are supplemented with data from the ongoing clinical studies. Overall, 155 subjects have been exposed to eltrombopag for six months or more and 39 subjects have been exposed to eltrombopag for at least a year. No subjects have been exposed for two years or more.

In addition to the short term, controlled clinical studies, the following studies provide useful safety data, including longer term exposure data:

REPEAT: this is an on-going study designed to help assess the safety of repeat "cycles" of short term (six week) eltrombopag therapy to responsive subjects. In this open label study, previously treated subjects with baseline platelet counts $\geq$ 20,000/mcL and $\leq$ 50,000/mcL received up to three cycles of eltrombopag, separated by 30 day off-drug

intervals. Subjects who responded to the first cycle were eligible for treatment in the subsequent cycles. A "response" was defined as a platelet count ≥ 2 times baseline and at least 50,000/mcL. As of the data cut-off point, 66 subjects were enrolled and 51 (78%) responded in cycle 1; 88% of subjects who responded in cycle 1 responded again in cycle 2 or 3. Safety findings were generally similar to those detected in the short term, controlled studies.

RAISE: this is the on-going study designed to more thoroughly assess the long term safety and efficacy of eltrombopag. The study uses a randomized, placebo-controlled, double blind design and exposes subjects to study drug over a six month period. The study data remain blinded.

EXTEND: this is the ongoing extension study that allows continued eltrombopag administration to subjects who enrolled in a prior eltrombopag study. As of the data cut-off point, 117 subjects had been enrolled and, to date, 11% of these subjects have withdrawn because of lack of efficacy. However, 80% of the evaluable subjects (86/108) had achieved a platelet count ≥ 50,000/mcL at least once during the study and generally sustained the increase. To date, the safety findings from EXTEND are generally similar to those from the short term, controlled studies except for a safety signal related to the occurrence of bone marrow fibrosis (see below).

The two controlled, short term studies provide the most readily interpretable safety data, and comparisons between the 50 mg eltrombopag groups and placebo groups are especially pertinent. Within the studies, the pattern and rate of serious adverse events was similar between the eltrombopag and placebo groups (5% vs 4%, respectively) with bleeding events as the most common (all reported among patients receiving placebo or patients who did not respond to eltrombopag). "Hepatitis" as a serious adverse event was reported among one placebo group patient and also one eltrombopag group patients (in the setting of suspected sepsis/cardiopulmonary failure; this was also the only death in the controlled studies).

The most common adverse events in the controlled, short term studies are shown in Table 3.

Table 3. Adverse reactions occuring in ≥ 5% of patients treated with eltrombopag 50 mg, 75 mg or placebo

Reaction	Eltrombopag 50 mg n = 106 (%)	Eltrombopag 75 mg* n = 63 (%)	Placebo n = 67 (%)
Headache	8	13	15
Nasopharyngitis	6	3	4
Nausea	6	3	0
Fatigue	4	3	7
Arthralgia	2	0	6
AST increase	2	6	0
ALT increase	2	5	0

*includes patients who received 75 mg either as a starting dose or patients (also counted in the 50 mg group) who received 75 mg in escalation from a starting dose of 50 mg.

The pattern of elevated liver test abnormalities evident in Table 3 was also shown in analyses of other laboratory results. In general, liver test abnormalities consisted of CTC grade 2 or lower severity scores for bilirubin, ALT and AST elevations with slightly higher rates (for certain grades) in the eltrombopag groups compared to placebo.

Table 4. Liver tests by maximum toxicity grade in Studies A and B

Outcome	Placebo n = 67	E 50 mg groups n = 106
ALT grade		
1	17 (26%)	22 (21%)
2	1 (2%)	5 (5%)
3	1 (2%)	2 (2%)
4	0	1 (1%)
AST grade		
1	12 (18%)	27 (26%)
2	0	1 (1%)
3	1 (2%)	2 (2%)
4	0	0
Total bilirubin		
1	5 (8%)	15 (14%)
2	2 (3%)	3 (3%)
3	1 (2%)	1 (1%)
4	0	0

Using FDA guidance document criteria for assessment of potential drug-induced liver injury, the rate of hepatobiliary abnormalities in the short term, controlled studies was 16/164 (10%) for the Eltrombopag group and 5/67 (8%) for the placebo group.

In general, the following items pose special safety considerations for eltrombopag:

a. Hepatic toxicity:

As noted above, liver test abnormalities were evidenced in the short term, controlled studies. Liver tests are monitored regularly in EXTEND and, to date, two subjects have been withdrawn from this study because of liver test abnormalities.

b. Worsening thrombocytopenia following discontinuation of eltrombopag:

One of the hypothetical considerations for a thrombopoietic product is the potential suppression of endogenous thrombopoietin (or other reactions) resulting in worse thrombocytopenia following discontinuation of the drug, compared to baseline. In the short-term, controlled studies, worsened thrombocytopenia was observed following study drug discontinuation in 10% eltrombopag subjects and 6% placebo subjects.

To date, of the 66 patients enrolled in REPEAT, 20 (30%) have experienced worsened thrombocytopenia following discontinuation of the study drug.

In general, the worsened thrombocytopenia has not been associated with adverse bleeding events but has required treatment with rescue medications in some patients.

c. Bone marrow fibrosis:

Additional hypothetical considerations for a thrombopoietic product are the development of bone marrow reticulin deposition and collagen fibrosis. Animal studies of certain thrombopoietic products have shown the development of bone marrow fibrosis. Unfortunately, eltrombopag is not bioactive in most tested animal models. Hence, long term clinical data are necessary to estimate the magnitude for bone marrow toxicity, if any, associated with eltrombopag. No bone marrow fibrosis/toxicity was assessed nor reported in the short term, controlled clinical studies.

The interim data from EXTEND provide some bone marrow outcome data. To date, 19 patients (median exposure 13 months) have undergone a bone marrow examination and recently supplied data indicates that 7/19 had either reticulin (5) and/or collagen (2) deposition detected.

d. Thromboembolic events:

Conceivably, a thrombopoeitic product may increase the risk for thromboses. In the short term, controlled studies, only one thrombotic event was detected (a fatality as previously noted/patient had cardiopulmonary failure and multiple organ failure with suspected sepsis).

To date, seven patients have experienced thromboembolic events in EXTEND, the uncontrolled, longer exposure study.

e. Cataracts:

Preclinical testing signaled a risk for cataract formation during Eltrombopag therapy. The detection of the risk for cataracts is difficult based upon the limited controlled data (only short term exposure) and the background rate of corticosteroid use. Nevertheless, ocular exams at six months following initial drug exposure was a component of the short term study evaluations. Of the 231 subjects in the short term studies, 8 subjects had cataracts reported (2 in the placebo groups; 5 in the 50 mg Eltrombopag group and 1 in the 75 mg Eltrombopag group). The ongoing RAISE study should importantly inform the estimate of cataract risk.

f. Other hypothetical risks or risks signaled by preclinical data:

Thrombopoietic products conceivably increase the risk for hematologic malignancies. The short term clinical studies did not provide evidence of a safety signal for malignancy and, within the available data from RAISE, REPEAT and EXTEND, only isolated occurrences of elevated peripheral blast counts have been reported.

Preclinical data signaled risks for renal toxicity as well as phototoxicity (for example, sensitivity to sunlight). However, the limited available clinical data (predominantly short term) have not provided evidence of renal or phototoxicity.

6. Risk Management Plan

The sponsor has proposed a risk assessment and management plan with the following objectives:

- to enroll all patients and prescribers into the program
- to educate patients and prescribers
- to provide a mechanism for long term monitoring and surveillance for detection of important reactions
- to obtain quantitative data on the identified, potential and theoretical risks of eltrombopag
- to monitor and assess off-label eltrombopag use

Major points regarding the Plan:

- The sponsor has proposed a Patient Information Leaflet and Patient Education Booklet to assist in education. Outreach training is proposed for physician prescribers.
- Distribution will be "controlled", primarily to the extent that "only authorized pharmacies will be able to dispense PROMACTA" as well as authorized clinics and hospital pharmacies. The sponsor does not plan to distribute eltrombopag through the usual, retail pharmacy process.
- All patients and prescribers are required to enroll in the program in order to prescribe/receive eltrombopag.
- The plan does not limit eltrombopag to short term use (a six week cycle). Instead, eltrombopag will be available as a 42 day supply at any single time, with repeat dispensation permissible (including the day following completion of a short term cycle). Refills are apparently permitted.
- Periodically (every six months for two years) the prescriber will be asked to fill out a safety questionnaire. The purpose of the questionnaire is to obtain long term

eltrombopag safety data. Plans for ensuring and monitoring compliance with the questionnaire are pending.

Details pertaining to the Risk Management Plan are, in part, contingent upon finalization of the product label. Hence, development of this plan is on-going.

Statistical review and assessment of incidence of Bleeding for NDA 022291

This section provides the statistical reviewer's analyses of the data on bleeding events submitted by the sponsor in their NDA 022291. These analyses were conducted to assess if the data presented in this NDA at the time of initial submission provide statistically significant evidence to support a proposed labeling claim that eltrombopag in the treatment of ITP patients significantly decreases the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP.

The overall conclusion of the statistical reviewer's analyses is that although a trend toward reduced incidence of bleeding is observed in the eltrombopag group compared to placebo, this trend is not statistically significant and does not provide robust evidence to support the proposed labeling claim of a decrease in the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP when treated with eltrombopag.

To capture the full picture of bleeding events for two pivotal studies (Phase II 773A and Phase III 773B), the protocol-specified assessment included incidence and severity of bleeding using the WHO Bleeding Scale and ITP Bleeding Scale (Study 773B only)

WHO Bleeding Scale has 5 grades:

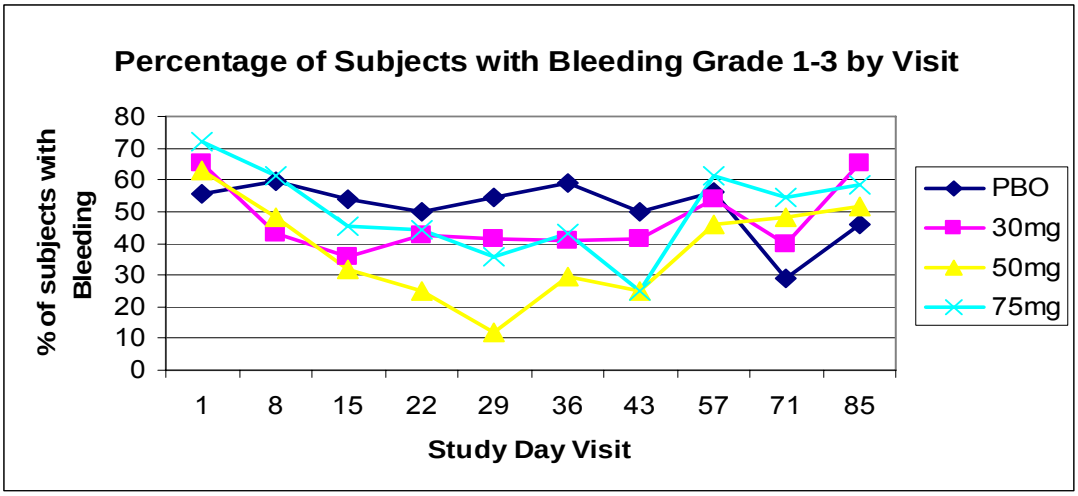
- Grade 0-no bleeding
- Grade 1- mild blood loss
- Grade 2- mild blood loss
- Grade 3- gross blood loss
- Grade 4- debilitating blood

ITP Bleeding Score is an assessment of the bleeding severity in each of the following anatomical locations: Skin: Petechiae, Skin: ecchymosis, Oral, Epistaxis, Ocular, Gastrointestinal, Genitourinary, Gynecological, Pulmonary and intracerebral Hemorrhage. Severity was graded using scores 0, 1 and 2.

Assessment of WHO Bleeding Scale

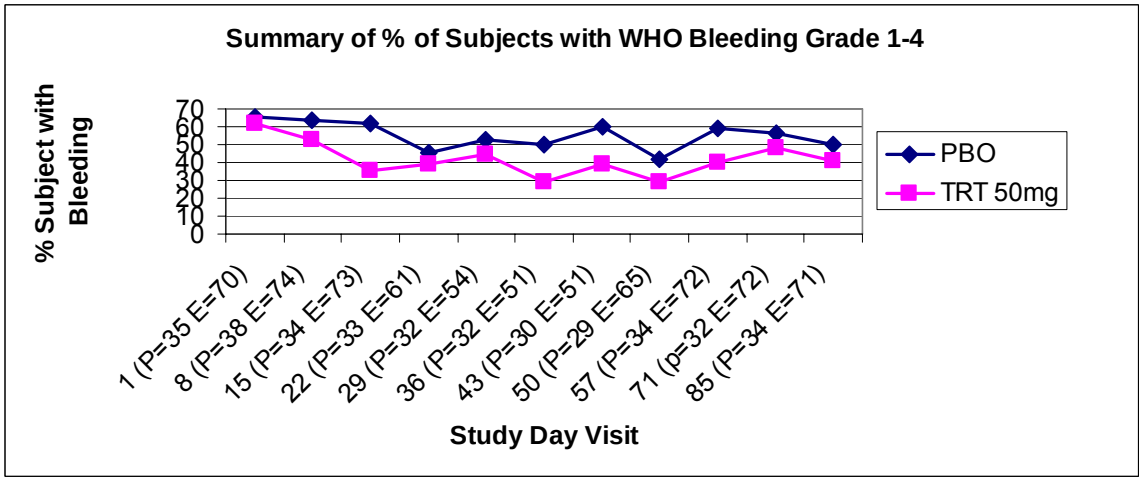
Study 773A

The following plot shows the observed proportion of subjects with bleeding (WHO Grade 1 to Grade 3, no subject on Grade 4) during the on-therapy as well as post-therapy period. A decrease was observed in the proportion of subjects with bleeding for the 30mg, 50mg and 75mg treatment groups compared to baseline. The proportion of subjects with bleeding was observed to be lower in all the eltrombopag treatment groups compared to placebo (PBO) for the Day 15 to Day 43 Visits. However, the sample-sizes in this study are not large enough to conduct a formal statistical hypotheses testing procedure to assess the significance of the observed decrease. At the first post-therapy assessment, within 2-weeks after discontinuation of study medication (Day 57 Visit), the proportion of subjects with bleeding in the 50mg and 75mg treatment groups increased to near baseline values and remained similar for the remainder of the post therapy assessments.



Study 773B

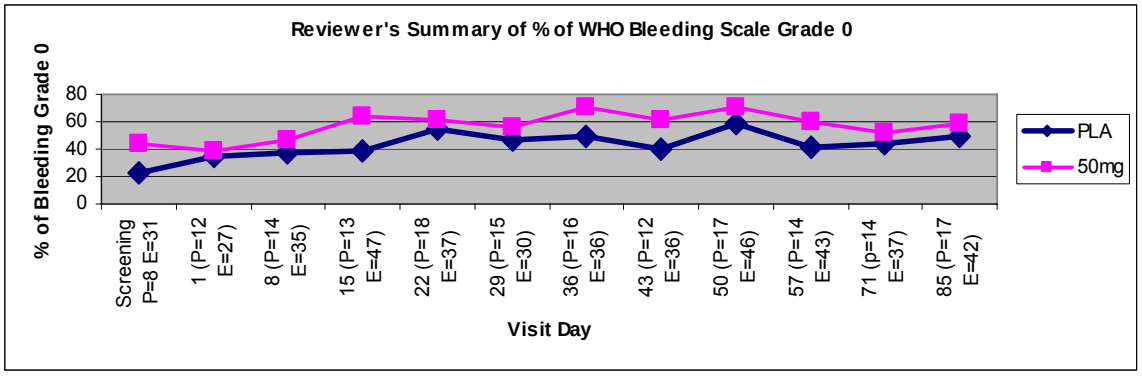
The following plot shows the observed proportion of subjects with bleeding (WHO Grade 1 to Grade 4) during the on-therapy as well as post-therapy period. As in Study 773A, a decreased incidence of bleeding on treatment relative to baseline in subjects who received eltrombopag was observed. At the baseline visit, 61% of the subjects in the eltrombopag treatment group and 66% of subjects in the PBO group reported any bleeding (Grade 1-4). At the Day 43 Visit, 39% of subjects in the eltrombopag treatment group had bleeding compared with 60% in the PBO group.

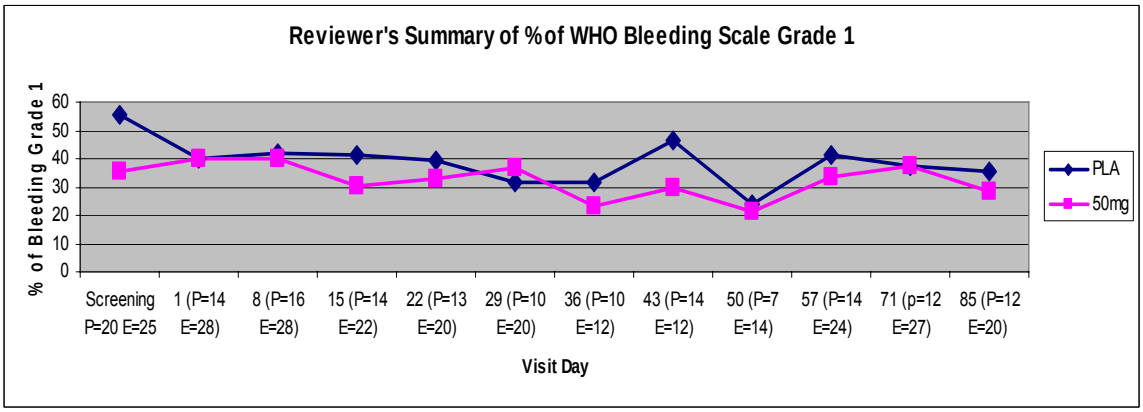


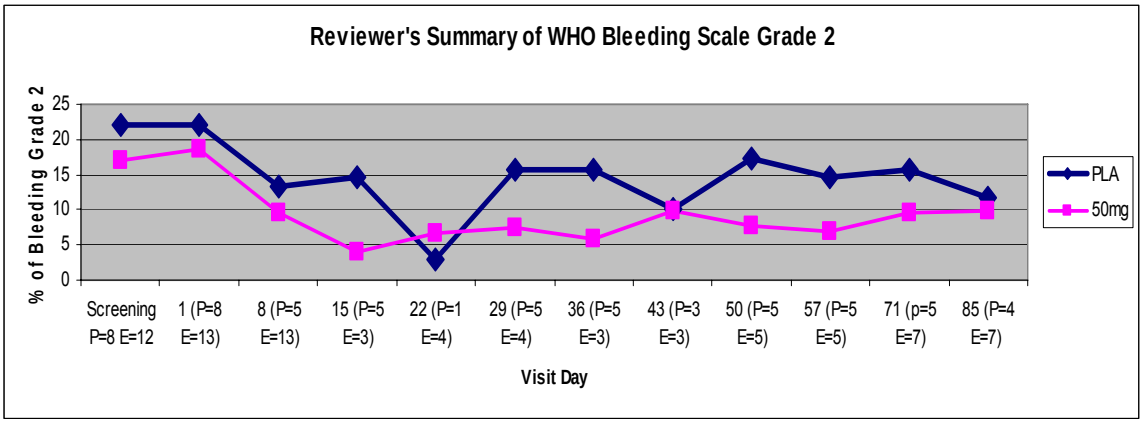
The sponsor conducted the logistic regression analysis, adjusting for the covariates of using concomitant medication at randomization, splenectomy and dichotomized baseline platelets. Results indicated that the odds of any bleeding in the eltrombopag were significantly lower than that of PBO at Day 43 (OR=0.27, 95% CI= [0.09, 0.88], p=0.029). However, the sponsor's analysis does not account for the time-dependent nature of bleeding and is subject to erroneous conclusion. Since, for the patient population in this study, the bleeding event is time dependent with multiple observations per subject, it is more appropriate to use survival analysis models based on time-to-event in multiple event setting. This statistical reviewer used the Andersen-Gill (AG) proportional hazards model and the results showed that the decrease in the incidence of bleeding for the eltrombopag group is not statistically significant (hazard ratio =0.781, p-value = 0.067).

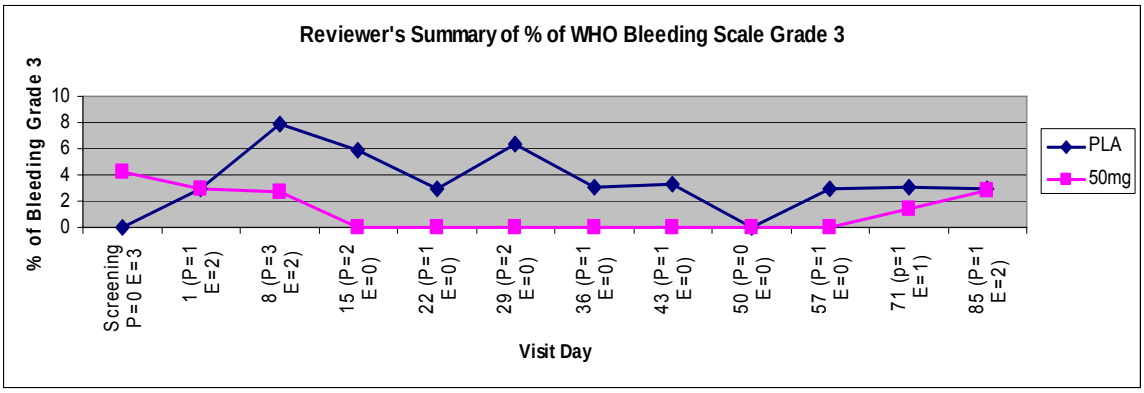
The following table and figures show the observed % of patients with bleeding at Grade 0, 1, 2, and 3

Visit Day	WHO Bleeding	PLA N=38	50mg N=74
Day 1	**n** **Grade 0** **Grade 1** **Grade 2** **Grade 3**	**35** **34.3% (12)** **40% (14)** **22.9% (8)** **2.9% (1)**	**70** **38.6% (27)** **40.0% (28)** **18.6% (13)** **2.9% (2)**
Day 15	n Grade 0 Grade 1 Grade 2 Grade 3 Grade 4	34 38.2% (13) 41.2% (14) 14.7% (5) 5.9% (2)	73 64.4% (47) 30.1% (22) 4.1% (3) 0 1.4% (1)
Day 43	**n** **Grade 0** **Grade 1** **Grade 2** **Grade 3**	**30** **40% (12)** **46.7% (14)** **10% (3)** **3.3% (1)**	**51** **70.6% (36)** **23.5% (12)** **5.9% (3)** **0**
Day 85	n Grade 0 Grade 1 Grade 2 Grade 3	34 50% 35.3% (12) 11.8% (4) 2.9% (1)	71 59.2% (42) 28.2% (20) 9.9% (7) 2.8% (2)









Assessment of ITP Bleeding Scale

Study 773B

The following table shows the summary of results using ITP Bleeding Score Assessment. Note that in 4 of the 10 categories, no or very few patients reported bleeding at baseline in both placebo and eltrombopag groups. A review of subjects with Grade 1-2 on ITP Bleeding Scale in the 6 categories in which the bleeding was reported, shows that in the skin ecchymosis and gynecologic categories, the observed decreases from baseline were greater for eltrombopag compared to placebo and for the remaining four categories, the observed decreases from baseline were similar between eltrombopag and placebo.

Assements	PBO N=38		EltrombopagN=74	
	Day1	Day43	Day1	Day43
Skin, petechiae,n	37	30	73	51
Grade 0	17(46)	21(70)	48(66)	42(82)
Grade 1	16(43)	8 (27)	20(27)	7 (14)
Grade 2	3 (8)	1 (3)	5 (7)	2 (4)
Skin,ecchymosis,n	37	30	73	51
Grade 0	18(49)	14(47)	29(40)	33(65)
Grade 1	13(35)	12(40)	35 (48)	14 (27)
Grade 2	5 (14)	4 (13)	9 (12)	4 (8)
Oral n	37	30	73	51
Grade 0	28(76)	27(90)	63(86)	47 92)
Grade 1	7 (19)	3 (10)	9 (12)	4 (8)
Grade 2	1 (3)	0	1 (1)	0
Epistaxis, n	37	30	73	51
Grade 0	32 86)	30(100)	63 86)	49(96)
Grade 1	4 (11)	0	9 (12)	1 (2)
Grade 2	0	0	1 (1)	1 (2)
Ocular ,n	37	30	73	51
Grade 0	36(97)	30(100)	73(100)	51(100)
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Gastrointestinal, n	37	30	73	51
Grade 0	36(97)	30(100)	71 (97)	50 (98)
Grade 1	0	0	2 (3)	1 (2)
Grade 2	0	0	0	0
Genitourinary, n	37	30	73	51
Grade 0	34(92)	29 (97)	69 (95)	51(100)
Grade 1	2 (5)	1 (3)	3 (4)	0
Grade 2	0	0	(1)	0
Gynecologic, n	26	23	41	24
Grade 0	8 (31)	7 (30)	11 (27)	10 (42)
Grade 1	0	0	2 (5)	1 (4)
Grade 2	1 (4)	0	5 (12)	0
Pulmonary, n	37	30	73	51
Grade 0	36(97)	30(100)	71 (97)	51(100)
Grade 1	0	0	2 (3)	0
Grade 2	0	0	0	0
Intracerebralhemorrhage,n	37	30	73	51
Grade 0	36(97)	30(100)	73(100)	51(100)
Grade 1	0	0	0	0

Conclusion

The data provided in this NDA do not demonstrate statistically significant, robust eltrombopag treatment effect in decreasing bleeding events based on the results from using WHO Bleeding Scale. The results based on the ITP Bleeding Score for

various anatomical regions suggest that the decrease in bleeding events from baseline is generally similar between eltrombopag and placebo.

Division of Clinical Pharmacology-5
Office of Clinical Pharmacology
Center for Drug Evaluation & Research

Memo

To: Hyon-Zu Lee, Project Manager
From: Joseph A. Grillo, Pharm.D. & Young Moon Choi, Ph.D.
CC: Andrew Dmytrijuk, Medical Officer
Date: 4/17/2008
Re: ODAC Briefing information for NDA # 22-291 Promacta (eltrombopag)

Eltrombopag is an orally bioavailable, small-molecule thrombopoietin receptor agonist that interacts with the transmembrane domain of the human TPO-R and initiates signaling cascades that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. Eltrombopag is being developed for the short-term treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding.

Eltrombopag tablets, 25 and 50 mg (each as the free acid) are film-coated immediate release debossed tablets proposed for commercialization. Early manufacturing experience of Eltrombopag tablets, 25 mg and 50 mg demonstrated that granulation is the critical manufacturing step that determines the physical properties of the granules and dissolution of the final product. An initial study of the relative bioequivalence of the 50 mg “phase 3” (commercial) tablet formulation compared to the “phase 2” tablet formulation showed a 15% reduction in exposure. A follow up study using a “Phase 2” tablet formulation made from a different substance batch demonstrated relative bioequivalence between the 50 mg tablets from the “phase 3” tablet formulation compared to the “phase 2” tablet formulation. Dose proportionality was not demonstrated between 25 mg and 50 mg commercial tablets. These difference in are not likely to be clinically significant given the safety profile observed for the commercial product to date in Study TRA100773B and in the ongoing long-term studies

A population-based pharmacokinetic model suggests that the pharmacokinetic profile for eltrombopag following oral administration is best described by a 2-compartment model with dual sequential first-order absorption and lag-time which highlights the complex absorption of this drug. Based on urinary excretion and biotransformation products eliminated in feces from healthy volunteers, the oral absorption of drug-related material following administration of a single 75mg oral solution dose was estimated to be at least 52%.

Following single-dose administration in healthy subjects, plasma eltrombopag concentrations were quantifiable within approximately 1 hour and peak concentrations occurred between 2 and 6 hours after oral administration of single and repeat doses of

eltrombopag. Plasma eltrombopag exposure was significantly reduced by approximately 70% when coadministered with polyvalent cations (e.g., antacids, mineral supplements, and dairy products). A standard high-fat breakfast significantly decreased plasma eltrombopag AUC(0-∞) by approximately 59% and Cmax by 65% and delayed tmax by 1 hour. The calcium content of this meal may have also contributed to this decrease in exposure.

Plasma eltrombopag AUC(0-τ) increased in a dose proportional manner between 50 mg and 200 mg; Cmax increased in a dose proportional manner between 50 mg and 150 mg. A slightly greater than dose proportional increase was reported at lower eltrombopag doses. In healthy subjects, the plasma elimination half life of eltrombopag was approximately 21 to 32 hours. In healthy subjects receiving eltrombopag once daily (QD) for 10 days, the accumulation ratio (90% CI) was 1.44 (1.20, 1.63) for 50mg QD. Eltrombopag is highly (>99%) bound to human plasma proteins.

A mass balance study in healthy volunteers showed following a single 75mg dose (oral solution) of [14C]-eltrombopag, approximately 59% of the dose was recovered in feces (20% unchanged and 21% glutathione-related conjugates) and 31% was recovered in the urine (20% glucuronide of the phenypyrazole moiety). No unchanged eltrombopag was recovered in the urine. Samples from the circulation were comprised of the parent compound and minor metabolites (mono-oxygenation or glucuronidation). The concentration in blood cells was approximately 50-79% of plasma concentrations. In vitro studies suggest that CYP 1A2 and 2C8 are responsible for minor oxidative metabolism of eltrombopag. UGT1A1 and UGT1A3 are responsible for the glucuronidation of eltrombopag. The glutathione conjugation pathway has yet to be fully characterized. Clinical studies evaluating the effect of strong inducers or inhibitors of these CYP and UGT enzymes responsible for the metabolism of eltrombopag have not been conducted.

Pre-clinical studies suggest eltrombopag is an inhibitor CYP 2C8 & 2C9. However, a follow up clinical study using a “cocktail” approach in healthy volunteers showed eltrombopag did not inhibit or induce CYP 1A2, 2C19, 2C9, or 3A4. CYP 2C8 was not studied *in vivo*, but its *in vitro* potency for inhibition was similar to that for inhibition of CYP2C9. Both pre-clinical and clinical studies suggest eltrombopag also inhibits organic anion transporting polypeptide OATP1B1. In a clinical study of healthy volunteers, concurrent eltrombopag and rosuvastatin treatment resulted in a 2.03-fold increase in plasma rosuvastatin Cmax and 55% increase in AUC(0-∞). Pre-clinical studies using expressed human transporters suggest that eltrombopag is not a substrate for P-glycoprotein (Pgp) or OATP1B1.

In pre-clinical studies, eltrombopag was reported to be an inhibitor of UGT1A9, UGT1A3, UGT1A1, UGT2B15, UGT1A6, UGT2B7, and UGT1A4. Based on these *in vitro* data, eltrombopag inhibits UGT1A9 with the greatest potency. The effect of this inhibition was not studied clinically by the sponsor.

Plasma eltrombopag AUC(0-τ) was approximately 35% lower in healthy subjects as compared to patients with ITP. Plasma eltrombopag exposure was reported to be approximately 70% higher in some East Asian (ancestry is of the countries of East Asia or Southeast Asia, such as Japan, China, Taiwan, and Korea) subjects with ITP based on estimates from a population-based pharmacokinetic model. 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 trails conducted in Japan. Further, an analysis of the limited number of healthy East Asian subjects from studies

conducted in the West failed to substantiate the findings from the studies conducted in Japan. 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. These race effects are likely the result of a, yet undetermined, genetic variation in pathways (e.g., CYP1A2, UGT1A1, etc.) that have been identified as metabolizing eltrombopag and, to a lesser extent, the difference in body weight between subjects in the western and Japan studies.

Plasma eltrombopag AUC(0-∞) was 41% higher in subjects with mild hepatic impairment, and 80% to 93% higher in subjects with moderate to severe hepatic impairment compared with healthy subjects. It is difficult to quantify the magnitude of this effect given the high variability in the data and the failure to report unbound eltrombopag (active) concentrations for this highly protein bound drug (liver disease can affect the protein binding of drugs). Given this increased exposure, a reduced starting dose (e.g., 25 mg) should be considered in subjects with moderate hepatic impairment and eltrombopag should be used with great caution in severe hepatic impairment.

There was a trend toward reduced plasma eltrombopag exposure in the interim analysis of data from subjects with varying degrees of renal impairment, but these data were inconclusive due to substantial variability as well as significant overlap in exposure between subjects with renal impairment and healthy subjects. In addition, the sponsor failed to report unbound eltrombopag (active) concentrations for this highly protein bound drug (renal disease can affect the protein binding of drugs). Close monitoring is recommended in patients with renal impairment.

A dose-dependent but highly variable increase in platelet count was observed following administration of eltrombopag for 5 to 10 days in all repeat-dose studies. The increase in platelet count reached a maximum two weeks after the initiation of dosing, and returned to baseline within approximately two weeks after the last dose of eltrombopag. The increase in platelet count in healthy subjects showed a trend toward greater increases in platelet count associated with higher AUC values; however, this was variable.

The PD response to eltrombopag was qualitatively similar in healthy East Asian and Western subjects, with both the shape of the platelet count profile and the duration of response being comparable. However, at the same dose of eltrombopag, the absolute PD response was greater in healthy East Asian subjects than healthy Western subjects. The magnitude of this difference was lower than that report for pharmacokinetic drug exposure.

Similar to healthy subjects, the increase in platelet count for ITP patients peaked at approximately two weeks after the initiation of dosing and returned to baseline values within approximately two weeks after discontinuing eltrombopag. The increase in platelet count in the ITP population showed a trend toward greater increases in platelet count associated with higher AUC values; however, this was also highly variable. The magnitude of the platelet responses was markedly different in the two populations (healthy subjects 2-fold higher and the ITP population 5 to 50-fold higher) compared to the baseline count. The higher fold increase may, in part, reflect the lower baseline platelet counts in the ITP population.

Overall, the most common AEs in eltrombopag-treated subjects in the clinical pharmacology studies were headache, dizziness, somnolence, fatigue, nasopharyngitis, abdominal pain, and nausea. There was no apparent relationship between eltrombopag exposure and the incidence of adverse events (AEs) in the single- and repeat-dose

clinical pharmacology studies in healthy subjects exposed to eltrombopag. This also appears to be the trend in the two pivotal trials based on dose alone. No deaths were reported in any of the clinical pharmacology studies.

Pooled data from the two pivotal trials demonstrated that 16/164 (9.7%) of the subjects met FDA criteria for evaluation of hepatobiliary laboratory abnormalities (HBLA). Among eltrombopag-treated subjects (pivotal and supportive trials), a higher proportion of Asians (14/93 (15%)) experienced hepatobiliary laboratory abnormalities that met FDA criteria compared to Caucasian subjects (18/333 (5%). Given the small sample size and the sparse pharmacokinetic sampling in these trails, a correlation between eltrombopag exposure and the incidence HBLA can not be determined. However, given the higher incidence of HBLA in the Asian population it can not be ruled out. Due to this issue and the increased exposure in seen some East Asian ITP patients discussed above, a reduced starting dose (e.g., 25 mg) should be considered.

Results of a through QTc study including model simulations suggest that eltrombopag will not have a clinically significant effect on QTc.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 1, 2008
To:	Rafel (Dwaine) Rieves, M.D., Director (Acting) Division of Medical Imaging and Hematology Products (DMIHP)
Through:	Gerald Dal Pan, M.D., M.H.S., Director Office of Surveillance and Epidemiology (OSE)
From:	OSE Risk Management Team Suzanne Berkman, Pharm.D., Senior Risk Management Analyst (DRISK) Mary Dempsey, Risk Management Program Coordinator (DRISK) Claudia Karwoski, Pharm.D., Acting Director (DRISK)
Subject:	Review of risk management proposal submitted April 16, 2008
Drug Name:	Eltrombopag
Application Type/Number:	NDA 22-291
Applicant/Sponsor:	GlaxoSmithKline (GSK)
OSE RCM #:	2008-414

EXECUTIVE SUMMARY

The following review focuses on the restricted distribution and risk assessment components of the eltrombopag risk management strategy. This review does not address the proposed pharmacovigilance or proposed/ongoing pharmacoepidemiologic activities. The Sponsor proposes a restricted distribution program with a risk assessment component primarily to ensure safe and appropriate use of eltrombopag. These components do not support the proposed short-term indication nor do they adequately address the need for additional risk assessment.

There are competing issues regarding eltrombopag and risk management. First, the controlled clinical trial experience involved relatively small numbers of patients with a short, six-week duration of exposure. The extent and significance of the available safety data are inadequate to elucidate fully the significance of certain safety concerns, leading to a need for extensive further risk assessment. Second, the proposed indication (short-term treatment) does not parallel the nature of the disease state (chronic, long-term). The need to treat ITP patients for an indefinite period of time, and the inadequacy of long-term efficacy and safety data, create a dilemma for prescribers, patients, and the development of a practical risk management approach.

The appropriateness of instituting a risk management strategy to address such major risk assessment needs versus further data analysis of longer term clinical trial data to establish safety needs to be discussed. These additional data could further focus the eventual risk management strategy or support that such measures are not necessary. The risk management strategy must support and be consistent with the approved indication and labeling which define safe and appropriate use.

1 BACKGROUND

1.1 Product Information

Eltrombopag is an oral thrombopoietin receptor agonist that interacts with the transmembrane domain of the thrombopoietin receptor, inducing the proliferation and differentiation of megakaryocytes. The signaling cascade is similar, but not identical to, that of endogenous thrombopoietin. At present, the Sponsor is proposing eltrombopag for the short-term (6 week) treatment of previously-treated adults with chronic idiopathic (autoimmune) thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding. Eltrombopag is not recommended for use in patients who require an immediate increase (24 – 48 hours) in platelet count. A rise in platelet count can be noted within 1 to 2 weeks after initiating eltrombopag. The recommended starting dose is 50 mg by mouth once daily. If after 3 weeks, the platelet count remains less than 50,000/µl, the dose may be increased to 75 mg.

Because eltrombopag is orally administered once daily, it may be appealing for broader use in a variety of diseases associated with thrombocytopenia. Studies are ongoing for the use of eltrombopag for long-term treatment of ITP, treatment of thrombocytopenia

secondary to cirrhosis associated with hepatitis C, and chemotherapy-induced thrombocytopenia.

1.2 Safety Concerns

The summary of the safety concerns is based on the medical officer's draft review, the Sponsor's April 16, 2008, risk management proposal, and the Sponsor's briefing document. One-hundred fifty-five ITP patients have been exposed to eltrombopag for 6 months or more with much of the data beyond 6 weeks of treatment obtained from open-label extension studies.[1] Eltrombopag has risks that have been identified in clinical trials, as well as certain risks that are not yet completely characterized through animal or human study. Based on the adverse events noted in clinical trials and the biologic plausibility for certain adverse events, the following risks were identified for further risk management consideration:[2]

- **Hepatobiliary toxicity**
  - From the 120 day safety update provided by the Sponsor, across all eltrombopag studies, a total of 35 patients have experienced hepatobiliary toxicity (35/469, 7.5%) as defined by the Food and Drug Administration *Draft Guidance for Industry on the Premarketing Clinical Valuation of Drug-Induced Liver Injury*.[3]
  - In the ITP studies, 16 out of 164 patients (9.7%) who received any dose of eltrombopag met the FDA criteria of hepatobiliary toxicity compared to 5/67 patients (7.5%) in the placebo group. Of the 16 eltrombopag-treated patients 3 received 30 mg, 11 received 50 mg (three increased to 75 mg in TRA 100773B) and 2 received 75 mg as a starting dose. These patients ranged in age from 19-75 years. There were 9 patients who were female and the majority were Caucasian (10 patients) followed by Asian (five patients). The Sponsor states that other than for the 1 subject who died all other hepatobiliary laboratory abnormalities resolved. The medical officer concluded that there appears to be the potential for hepatobiliary toxicity in patients treated with eltrombopag. Most of the hepatobiliary adverse events were grade 0-1 during treatment. In the 50 mg treatment group a higher percentage of grade 1 values (21%) for alkaline phosphatase was observed compared to placebo (13%). The incidence of grade 2-

[1] Risk Management Plan (RMP) NDA No: 22291 submitted by GSK on April 16, 2008.
[2] Data extracted from the FDA Medical Officer's [*DRAFT*] review of NDA 22-291 unless otherwise noted. April 30, 2008.
[3] FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation [DRAFT]. October 2007. *This guidance provides support on the use of the following major indicators of potential severe DILI: (1) An excess of AT elevations to >3xULN compared to a control group. (2) Marked elevations of AT to 5x-, 10x-, or 20xULN in smaller numbers of subjects in the test drug group and not seen (or seen much less frequently) in the control group. (3) One or more cases of elevated bilirubin to 2xULN in a setting of pure hepatocellular injury …, with no other explanation …, accompanied by an overall increased rate of AT elevations >3xULN in the test drug group compared to placebo.* The draft guidance further states that assessment of rates should include:
- *3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST.*
- *Any elevations of bilirubin; elevated bilirubin to >1.5xULN, and to >2xULN.*
- *Any elevations of ALP >1.5xULN*
- *Elevation of AT (>3xULN) accompanied by elevated bilirubin (>1.5xULN, >2xULN).*
- *Possibly liver-related deaths and liver-related treatment discontinuations.*

4 ALT elevations was 8% in the 50 mg treatment group compared to 3% in the placebo treatment group. Grade 3-4 ALT elevations were 3% and 2% in the 50 mg treatment group and placebo group respectively. The incidence of grade 2-4 AST elevations was 3% in the 50 mg treatment group compared to 2% in the placebo treatment group. Grade 3-4 AST elevations were 2% in each treatment group (50 mg eltrombopag group and placebo group). In the 50 mg treatment group a higher percentage of grade 1 values (14%) for bilirubin was observed compared to placebo (8%).[2]

- The Sponsor identified 3 possible Hy's Law[4] cases which includes one patient who died. The Sponsor states that 2 of the cases were confounded and 1 involved indirect hyperbilirubinemia.

It is important to note that a typical new drug application usually will not show any cases of severe drug-induced liver disease (DILI), even for a drug that can cause liver injury. The *Draft Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation* further states, in pertinent part:

> Only the most overt hepatotoxins can be expected to show cases of severe DILI in the 1,000 to 3,000 subjects typically studied and described in a new drug application (NDA). … Most of the drugs withdrawn from the market for hepatotoxicity have had rates of death or transplantation in the range of ≤1 per 10,000, so that a single case of such an event would not be reliably found even if several thousand subjects were studied. Cases of severe DILI have rarely been seen in drug development programs of significantly hepatotoxic drugs. … Finding one Hy's Law[4] case in clinical trials is ominous; finding two is highly predictive of a potential severe DILI. It is critical, however, to determine whether mild hepatotoxicity reflects a potential severe DILI or reflects a capacity for only limited injury.

- **<u>Post-therapy decrease in platelet count</u>**
  - In the two studies supporting this application (TRA 100773A and TRA 100773B), there appears to be a trend for transient thrombocytopenia observed within 4 weeks of discontinuation of eltrombopag therapy.
  - In study TRA 100773A, 6 patients out of 117 (1 placebo, none in the 30 mg eltrombopag group, 3 in the 50 mg eltrombopag group, and 2 in the 75 mg eltrombopag group) had platelet counts < 10,000/µl and a decrease in platelet

[4] FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation [DRAFT]. October 2007. *Hy's law cases have the following components - 1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo. 2. Among subjects showing such AT elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase* (ALP) activity *>2xULN). 3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.*

count on at least one occasion < 10,000/µl compared to baseline within 4 weeks after discontinuation of study medication. All 5 patients who received eltrombopag were defined as responders. Three patients achieved platelet counts ≥ 200,000/µl. The WHO bleeding score increased from baseline in 3 patients and these 3 patients received rescue medication.

- In study TRA 100773B, 11 patients out of 114 (8 patients treated with eltrombopag and 3 patients treated with placebo) had platelet counts < 10,000/µl and at least 10,000/µl less than baseline platelet count within four weeks after discontinuation of study medication. The bleeding score increased in 3 patients.

- **Thrombotic/thromboembolic events**
  - In study TRA 100773A, 1patient had a serious adverse event of pulmonary embolism and thromboemboli. No other thromboembolic events were reported in any other study patient during the treatment or post-therapy phases of this study. Of the 12 patients who achieved a platelet count > 400,000/µl during treatment, 2 patients (both in the 50 mg treatment group) received medication for prophylaxis of thrombosis in response to their increase in platelets. These 2 patients achieved platelet counts of 555,000/µl and 625,000/µl at day 15. They were discontinued from study medication and received aspirin therapy along with antacid therapy for 3 days. No adverse events were reported in either patient.
  - In study TRA 100773B, there were no thromboembolic adverse events reported in either treatment group.
  - Thromboembolic events were reported in the open-label extension studies; however, the current review is focused on short-term use.

- **Bone marrow reticulin formation/marrow fibrosis**
  - There is concern that the risk of marrow fibrosis could be associated with eltrombopag but the data are limited to support or refute these risks.
  - Data from rats, monkeys, and mice reflect no efficacy so other hematopoietic effects may be blunted or may not occur in these species. Therefore, the absence of hematopoietic toxicity in these species may not reflect an absence of risk.
  - The ITP studies submitted to support this application (TRA 100773A and TRA 100773B) did not evaluate the bone marrow for toxicity in patients treated with eltrombopag.
  - In the 120-day safety update, the Sponsor reported that 19 patients who were treated for at least 13 months with eltrombopag in the one of the open-label extension trials had bone marrow biopsies. The Sponsor states that reticulin/collagen was reported in 9 of the 19 bone marrow biopsy reports and that 2 of 9 had grade 2 reticulin deposition.

It is not completely understood if short-term, long-term or repeated cycle treatment of ITP with eltrombopag may increase the risk of myelofibrosis. While the specific mechanism of action on a cellular level may differ slightly from romiplostim, there is still a theoretical concern regarding the risk of reticulin formation leading to marrow

fibrosis. In the absence of substantive data supporting a lack of these risks, it seems prudent to suspect a possible class effect at this time.

- **Malignancy progression**
  - There is concern that the risk of malignancy progression could be associated with eltrombopag but the data are limited to support or refute these risks. Presently, there is an ongoing trial evaluating the use of eltrombopag to treat chemotherapy-induced thrombocytopenia in patients with advanced solid tumors.
  - Data from rats, monkeys, and mice reflect no efficacy, so other hematopoietic effects may be blunted or may not occur in these species. Therefore, the absence of hematopoietic toxicity in these species may not reflect an absence of risk. While the specific mechanism of action on a cellular level may differ slightly from romiplostim, there is still a theoretical concern regarding the risk of malignancy progression. In the absence of substantive data supporting a lack of these risks, it seems prudent to suspect a possible class effect at this time.
- **Cataracts**
  - Treatment-related cataracts were observed in mice given 75 or 150 mg/kg/day and rats given 40 mg/kg/day. In these rodents, the ocular changes were observed after seven weeks of treatment.
  - In study TRA 100773B, 49 of 117 patients had ocular assessments in the safety population. In these 49 patients there were 14 reports of cataracts. Three patients had a cataract observed at baseline and none of these patients had cataract progression over the course of the study. There were 10 patients who had cataract observed at the time of the first ocular examination and 1 patient was observed to have a cataract formation after the first ocular examination.
  - In study TRA 100773B, 112 of 114 patients in the safety population had ocular assessments for cataracts. Cataracts were observed at baseline in 9 patients of which 3 patients had progression of their cataracts. There were 101 patients who had no evidence other cataract observed at baseline. Of these 101 patients, 4 patients subsequently developed cataracts.
- **Phototoxicity**
  - An *in vitro* phototoxicity study was conducted and eltrombopag was observed to be toxic in the presence of ultraviolet illumination.
  - In the ITP studies submitted to support this application (TRA 100773A and TRA 100773B), there was 1 report of photosensitivity in an eltrombopag treated patient which was characterized as a grade 2 adverse event.
- **Renal tubular toxicity**
  - A 2-year carcinogenicity study in mice showed dose-related renal tubular toxicity.
  - The Sponsor states that in the intermittent or long-term studies, renal-related adverse were generally mild to moderate (grade 1 or 2) and none led to withdrawal from study medication.

The proposed restricted distribution program and post marketing risk assessment component do not address the risk for cataract and phototoxicity or the potential risk of renal tubular toxicity.

2.0 Risk Management of Eltrombopag

2.1 Labeling

The Sponsor proposes to include the risk of hepatotoxicity in the Warnings and Precautions section of the label (package insert) along with a recommendation to monitor "hepatobiliary laboratory values" every 2 weeks for the first 3 months of treatment and monthly thereafter. This recommendation assumes treatment beyond a 6 week course. The Sponsor also proposes to develop discontinuation criteria for use when hepatobiliary adverse reactions occur. The label will include Warnings and Precautions on photosensitivity, thromboembolism, and post-discontinuation thrombocytopenia. Based on the risk management proposal submitted on April 16, 2008, the Sponsor does not plan to address the risk of malignancy, reticulin formation, renal tubular toxicity, or cataract in the proposed label (package insert). We note other submissions from the Sponsor include the risks of renal tubular toxicity and cataract in the proposed label. The Sponsor proposes a patient information leaflet.

2.2 Summary of Sponsor's Proposed Risk Management Proposal

The risk management proposal submitted April 16, 2008, was reviewed. The Sponsor states that the program goals are to:

- ensure the safe and appropriate use of eltrombopag,
- promote informed risk-benefit decisions regarding the use of eltrombopag,
- determine the incidence and risk factors for the identified and potential risk of eltrombopag use, and to
- further assess the overall safety profile of eltrombopag.

The objectives are to:

- enroll all patients and prescribers,
- assure that patients and prescribers make informed risk-benefit decisions regarding the use of eltrombopag,
- provide long-term monitoring and active pharmacovigilance of all patients receiving eltrombopag,
- provide quantitative data on the incidence and risk factors for the identified and potential risks of eltrombopag, and to
- monitor and assess off-label use.

The Sponsor proposes to meet these goals and objectives through labeling, additional educational efforts, and a restricted distribution program that requires patient and

healthcare provider enrollment through the completion of a prescriber/patient agreement in order to prescribe and receive eltrombopag. In addition, prescribers will be required to complete a safety questionnaire every 6 months for the first two years of treatment for each patient. While the Sponsor anticipates that the majority of eltrombopag will be distributed through registered specialty pharmacies, a plan to develop a mechanism for hospital pharmacies and oncology clinics to register, acquire, and dispense eltrombopag is ongoing. The Sponsor will contract with a third party to manage the entire program, which will be operational at the time of product launch.

None of the program materials have been provided.

In addition to the strategies outlined above, the Sponsor states that no direct-to-consumer media (television or radio) will be used. It is unclear if print advertisements will be utilized.

Education

- *Healthcare Providers*

  The Sponsor proposes that the approved labeling (package insert) will serve as the primary piece for healthcare provider education. We note that it will be difficult to use the label as the sole means to educate healthcare providers on all the risks identified by the Sponsor for risk management if not all of those risks are included in labeling (i.e., malignancy, reticulin formation, renal toxicity, and cataract).
  Educational materials must be consistent with the approved labeling.
  The proposal does not include mention of any materials educating healthcare providers on the elements of the program, including the need to enroll patients, the frequency of required laboratory monitoring (if any), and the requirement to complete follow-up questionnaires.
  The Sponsor proposes other routine efforts such as detailing and medical liaison support. However, in absence of the actual materials, it is difficult to determine if these efforts will truly serve an educational purpose or function primarily to promote and market eltrombopag.

- *Patients*

  The Sponsor states that the patient information leaflet will serve as the primary piece for the prescriber to review with the patient prior to treatment initiation. We note it will be difficult to use the patient information leaflet as the primary means to educate patients on all the risks identified by the Sponsor for risk management if not all of those risks are included in labeling (i.e., malignancy, reticulin formation, renal toxicity, and cataract).

  Additional materials such as a patient education booklet and a starter kit (containing the patient education booklet and a patient diary to record platelet counts) will also be created. It will be difficult to develop educational materials that include risks that are not discussed in the approved labeling. The Sponsor also states that booklet will be

distributed to patients whether or not they are enrolled in the "compliance program" and that patients can "opt in" to the "compliance program." Further, patients who enroll in the "compliance program" will receive a phone call from a trained nurse upon enrollment and be provided with specific information about compliance and safety issues. It is unclear what the "compliance program" is and how it differs from the restricted distribution and risk assessment program.

Elements to Assure Safe Use

The proposal states that all prescribers, dispensing entities, and patients will need to be authorized in order to prescriber, dispense, and be treated with eltrombopag, respectively. The following provides an overview of the various components and highlights areas requiring additional clarity/refinement.

- *Prescriber/Patient Components*

  Prescribers and patients will enroll simultaneously by completing a patient-physician agreement form. This form verifies that the prescriber will (in pertinent part):

  - enroll all patients in the program,
  - review the key benefits and risks of eltrombopag with the patient,
  - complete follow-up questionnaires for each patient every 6 months for 2 years,
  - report any adverse events during eltrombopag treatment to GSK, and
  - provide the diagnosis for treatment with eltrombopag.

  The patient attests that he/she understands the risks and benefits associated with eltrombopag.

- *Pharmacy Components*

  Eltrombopag will be available only through authorized pharmacies and dispensing clinics and will not be available through non-institutional retail pharmacies. Authorized dispensing entities will agree to (in pertinent part):

  - only dispense eltrombopag to patients enrolled in the program,
  - distribute the patient information leaflet each prescription dispensed, and
  - only dispense a 42-day supply at a time.

  Specialty pharmacies will ship eltrombopag directly to the patient. It is not clear how local dispensing entities will authorize/track each prescription dispensed to assure safe use conditions.

- *Safe Use Condition Components*

  The program will utilize the following components to assure safe use:

- Prescribers and patients must be enrolled in the program in order for the patient to receive eltrombopag.
  Comments
  - *The proposal does not include any condition for re-authorization or prompt to evaluate the appropriateness of continuing treatment beyond 6 weeks.*
  - *It is not clear how the program will document if the patient should not receive eltrombopag. For example, if the patient experiences a serious adverse event that requires drug discontinuation, how will the program assure that the patient is not inappropriately re-challenged?*

- Only authorized pharmacies will be able to dispense eltrombopag to patients enrolled in the program.
  Comment
  - *The proposal does not explain how local dispensing entities (i.e., hospitals, oncology clinics) will authorize/track each prescription dispensed to assure safe use conditions.*

- Prescribers must complete a safety questionnaire every 6 months for the first two years of treatment. The questionnaire will focus on hepatobiliary abnormalities, thromboembolic events, increased bone marrow reticulin, and malignancies.
  Comments
  - *It is not clear how the program will ensure that the safety questionnaire is completed as it does not appear to be linked to product access.*
  - *It is not clear what depth of data collection will be gleaned from this questionnaire. Further, this form does not appear to capture post-discontinuation decreases in platelet count.*
  - *The rationale for data collection limited to the first two years is not clear.*

- Prescriptions for eltrombopag will be limited to a 42-day supply.
  Comment
  - *The proposal does not include limiting refills, creating a treatment stop date, or creating a time requirement between re-initiation of treatment despite the fact that the current indication is for short-term (6 week) treatment. Therefore, the benefit and utility of a 42-day supply to assure safe use is not clear.*

- The patient information leaflet will be dispensed with each prescription.
  Comment
  - *Considering that the drug product is one for which patient labeling could help prevent serious adverse effects and that it has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients decision to use or continue to use the product, a Medication Guide could be considered for eltrombopag.*[5]

[5] 21 CFR 208.1(c).

Program Evaluation

The Sponsor proposes to report semiannually on the overall program for the first two years after launch. The Sponsor states that the report will focus on assessing the effectiveness of the elements utilized in the program. This will be accomplished by evaluating compliance with program objectives (outlined above). Two of the objectives are to "provide long-term monitoring and active pharmacovigilance of all patients" and "provide quantitative data on the incidence and risk factors for the identified and potential risks of eltrombopag." However, the proposed program evaluation focuses more on program compliance ("quantify the estimated percentage of physicians and patients receiving commercial PROMACTA" and "collection of safety questionnaires" by the third party) rather than safety data assessment.

The Sponsor also states that surveys will be developed to assess prescriber and patient "knowledge of key benefits and risks" of eltrombopag. No further information about the frequency, content, or implementation plan for these surveys is provided.

2.3 Key Comments on Sponsor Proposal

The Sponsor propose restricted distribution and risk assessment to assure safe and appropriate use of eltrombopag and further assess risk. While we agree with the program goals, certain components of the plan are not explained or absent. These issues need to be addressed to better assure appropriate use and adequate risk assessment.
The Sponsor submitted a new drug application to support the use of eltrombopag for the short-term treatment of chronic ITP. Based on the duration of use in the controlled clinical trials, "short-term" translates to 6 weeks of daily eltrombopag treatment. At present, the proposed program fails to include any measures to limit use to short-term (6 weeks) treatment or to prompt evaluation of the appropriateness of continuing therapy beyond 6 weeks. In fact, the proposal diminishes any significance to the duration of use by proposing a safety evaluation every 6 months. This misleadingly implies that use beyond 6 weeks is safe and effective (this indication has not yet been submitted to the Agency for consideration). Therefore, the proposed safety assessment every 6 months is not consistent with the proposed indication and label (package insert) which serves to define appropriate use.

The need for further risk characterization for eltrombopag is evident considering:

- the limited number of patients exposed over a short period of time in the controlled clinical development program,
- the safety concerns identified in animal data (renal toxicity, cataracts, and phototoxicity) and/or the biologic plausibility for other certain significant adverse events (reticulin formation/myelofibrosis, malignancy),
- the safety concerns <u>not</u> identified in animal data possibly because of the lack of hematopoietic effect in the species tested (rats, monkeys, mice),

- the need for options to treat thrombocytopenia associated with various diseases, and
- the potential appeal of a once daily tablet to increase platelet count.

These factors contribute to the concern regarding long-term and/or off-label use. They place burden on the program to not only attempt to mitigate risk but to support major risk assessment associated with long-term treatment in effort to enhance patient safety. The proposed program includes no baseline data collection component beyond the patient's diagnosis in order to establish and monitor who is being treated with eltrombopag. There is no mention to monitor hepatobiliary function. There is no mention of program/treatment discontinuation procedures. These procedures would attempt to mitigate and assess post-discontinuation thrombocytopenia as well as to establish data on the reasons for discontinuation (which may be related to an adverse event). The program lacks any link to assure short term-use or to direct appropriate longer term safe use conditions. The proposal includes no reauthorization component at the 6 week post-initiation time point or at any time point. It is unclear how the program will ensure that the safety questionnaire is completed. While addressing these issues will further expand the program, it is important to create a program that will elicit valuable, relevant information about eltrombopag. The need for further risk assessment with long-term use is a major driver for establishing this sort of program. If the program is not adequately designed to collect substantive data to further inform safe, appropriate use of eltrombopag, it becomes more an exercise in bureaucracy than risk management.

3 DISCUSSION

There are a number of issues to consider with eltrombopag involving its proposed indication, current safety profile, and the appropriateness of risk management under the current circumstances. The data appear to support eltrombopag for short-term use. The proposed indication is consistent with these data. Therefore at present, "appropriate use" of eltrombopag is limited to a 6 week course. However, practically thinking, the nature of the disease (chronic, long-term thrombocytopenia) and anticipated actual use of eltrombopag is not consistent with this scenario. Further, decreases in platelet count below pre-treatment levels have been identified as a known risk upon eltrombopag discontinuation. Therefore, designing the risk management program to assure appropriate use (i.e., compliance with a 6 week treatment course), may spur adverse events. However, if a program cannot be developed to support the indication, it calls into question whether a short-term treatment indication is viable. If the data cannot support long-term use and it does not make sense to limit treatment to short-term use, the proposed program will be almost entirely a means for further data collection with little effort toward risk mitigation. This raises the question whether eltrombopag needs additional clinical study or a risk management program.

While a risk management program is a path for further risk assessment, it is not meant to be a substitute for, or a means to circumvent, sufficient study through controlled clinical trials. Weighing whether eltrombopag provides a meaningful therapeutic benefit based on the current proposed indication and whether a risk management program can ensure

that the benefits outweigh the risks based on what is currently known about the product is prudent. Moreover, the label should reflect the risks identified for further risk management. Risk management plans are targeted to manage significant risks. If these risks are not characterized enough to be included in a label but significant concerns exist that warrant additional risk management activities, this further raises the question as to the need for further study prior to approval.

4 CONCLUSION

Because the clinical trial experience involved relatively small numbers of patients and limited duration of exposure, the extent and significance of the available safety data are inadequate to elucidate fully the significance of certain safety concerns. Further, the nature of the disease can require the need for long-term treatment while the data and proposed indication support short-term use. The appropriateness of instituting a risk management strategy versus further data analysis of longer term clinical trial data to establish safety and efficacy should be discussed. These additional data could further focus the eventual risk management strategy or provide support that such measures are not necessary.