DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

NDA 22-291

GlaxoSmithKline
Attention: Dennis Williams
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

Dear Mr. Williams:

Reference is made to your June 4, 2009, Proposed Pediatric Study Request for Promacta® (eltrombopag) Tablets.

To obtain needed pediatric information on eltrombopag olamine (SB-497115-GR), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies:

Introductory Comments
Adequate eltrombopag juvenile animal toxicity data exist to support initiation of pediatric trials in children ≥ 12 years old. Sequential trials in 6 to < 12 and 2 to < 6 year olds can be initiated without additional non-clinical studies and after safety has been assessed in the clinical trial in the older age cohort and found to be acceptable. Since the disease progression of refractory, immune (idiopathic) thrombocytopenia purpura (ITP) differs in children compared to adults, studies to support dosing, safety and efficacy in the pediatric population must be completed.

Specific Study Requirements
Type of studies:
Study 1: Pharmacokinetic/Pharmacodynamic (PK/PD) and Safety Study
Study 2: Efficacy, PK and Safety Study

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Indication to be studied: Treatment of thrombocytopenia in children with chronic ITP who:

1) are at risk for bleeding; and
2) are refractory to ITP therapy, have relapsed after at least one prior ITP therapy, or are not eligible for other ITP treatments.

Objective of each study:
Study 1: To characterize the PK/PD profile and collect data on the safety and tolerability of eltrombopag during a 12 week treatment period in children with chronic ITP.

Study 2: To assess the efficacy of eltrombopag as add-on therapy to standard treatment in achieving a target platelet count and to describe the PK profile, safety and tolerability of eltrombopag during a 24 week treatment period in children with chronic ITP.

Age group in which study will be performed:
Study 1 and Study 2:
Pediatric patients 2 years to < 17 years at study entry divided into three age cohorts
- Cohort 1: age 12 years to < 17 years
- Cohort 2: age 6 years to < 12 years
- Cohort 3: age 2 years to < 6 years

Cohort 1 data must be reviewed and found acceptable by the Agency prior to enrolling patients in Cohort 2. Similarly, Cohort 2 data must be reviewed and found acceptable by the Agency prior to enrolling patients in Cohort 3.

Number of patients to be studied:
Study 1: The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for eltrombopag in each age group.

Study 2: The number of patients should be distributed approximately evenly over the three age cohorts to the extent possible, given the incidence of disease. The study must include a sufficient number of patients to detect a pre-specified, clinically meaningful effect (all ages combined) on the primary endpoint. The safety database must include at least 250 pediatric patients exposed to eltrombopag to characterize the safety of the drug, with the duration of eltrombopag treatment at least 24 weeks in at least 188 patients.

Study design:
Studies 1 and 2: Patients will have a confirmed diagnosis of chronic ITP according to the American Society of Hematology/British Committee for Standards in Haematology (ASH/BCSH) guidelines [George, 1996; *BCSH, 2003*]. In addition, a peripheral blood smear and bone marrow examination must support the diagnosis of ITP with no evidence of other causes of thrombocytopenia.

Study 1: Single-arm, open-label study starting with Cohort 1. Blood samples for PK must be collected at steady state. Timing of blood samples must be such that the entire time course of plasma concentrations can be adequately captured for the entire population. Blood sampling must be age appropriate. PK estimates in the 12-17 year age group must be used to inform study design and minimize blood draw volumes in the younger age groups. Safety, PK, and platelet count data from Study 1 must be reviewed in each cohort to contribute to the confirmation or modification of the starting dose and dosing strategy for that cohort in Study 2. Safety, PK, and platelet count data from Study 1 also must be reviewed and determined to be acceptable in the older cohort(s) prior to enrolling subjects from the younger cohort(s).

Study 2: Randomized, double-blind, placebo-controlled trial in which eltrombopag is administered as add-on therapy to standard treatment for at least 24 weeks treatment duration. At least 188 patients

will complete a 24 week treatment period and 4 week follow-up period. All patients must be followed for safety for 4 weeks after discontinuation of study treatment.

Study endpoints:
Pharmacokinetic

- Plasma eltrombopag pharmacokinetic parameters must include AUC(0-t), Cmax, Ct, Vd/F and CL/F.

Efficacy/Pharmacodynamic

- The primary efficacy endpoint (Study 2) must be the proportion of patients achieving and maintaining a platelet count of ≥ 50,000/mcl for the last 6 weeks of treatment during the study.

- Secondary endpoints will include the following, with Day 1 being the first day of treatment.
  - Proportion of patients with platelet counts ≥ 50,000/mcl during treatment with eltrombopag in ≥ 60% of assessments between days 15 and 168.
  - Weighted mean platelet change (area under the platelet-time curve divided by duration) from baseline to day 168.
  - Maximum period of time with platelet count continuously ≥ 50,000/mcl during the 24 weeks of eltrombopag dosing.
  - Proportion of patients achieving platelet counts ≥ 50,000/mcl at anytime during the 24 weeks of eltrombopag dosing.
  - Proportion of patients that reduced or discontinued baseline concomitant ITP medications while receiving eltrombopag during the 24 week study period.
  - Proportion of patients that required protocol defined rescue treatment during the study.
  - Reduction of bleeding symptoms associated with ITP based on the WHO bleeding scale.

Safety

- Safety and tolerability parameters must include blood pressure, respiratory and heart rate, ocular examinations to evaluate for cataracts (slit lamp examination), clinical laboratory assessments (including but not limited to: baseline and weekly CBC, liver function tests, serum creatinine, and urinalysis; and data from bone marrow biopsy if done) and frequency of all adverse events.

The data from the relevant studies must be combined to develop exposure-response for safety and effectiveness endpoints. The goals of these analyses are: a) to provide supportive evidence of effectiveness; and b) to support the dosing recommendations.

Data Monitoring Committee:
A Data Monitoring Committee (DMC) must be utilized during the conduct of these studies to identify safety issues warranting modification or interruption of study procedures, particularly for the younger age cohorts. The DMC must have a formal charter that describes its composition and scope and the procedures by which it will abide.

Drug information:

- *Dosage form*: age-appropriate formulations. The relative bioavailability between the tablet and suspension formulations must be established in a manner consistent with the guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General

Considerations" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070239).

- *Route of administration*: oral
- *Regimen*:
  - Cohort 1 (age 12 to < 17 years): The starting dose will be 25 mg once daily.
  - Cohort 2 (age 6 to < 12 years): The starting dose will be 0.7 mg/kg once daily.
  - Cohort 3 (age 2 to < 6 years): The starting dose will be 0.7 mg/kg once daily.

  - For patients of East Asian ancestry the starting dose will be as follows.
    Cohort 1 (age 12 to < 17 years): The starting dose will be 12.5 mg once daily.
    Cohort 2 (age 6 to < 12 years): The starting dose will be 0.5 mg/kg once daily.
    Cohort 3 (age 2 to < 6 years): The starting dose will be 0.5 mg/kg once daily.

  Dosing for Cohorts 2 and 3 may be adjusted based on the result from the older age cohort. Dosing adjustments also must be based on platelet count and must follow labeled instructions. Dosing in all age groups must be adjusted to maintain platelet counts between 50,000-200,000/mcl.

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

- *Drug specific safety concerns:* Hepatotoxicity, reticulin fiber deposition within the bone marrow, thrombotic/thromboembolic complications, malignancy, cataracts, renal toxicity, hemorrhage following discontinuation of eltrombopag.

- *Statistical information, including power of study and statistical assessments:*

Study 1: The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for eltrombopag in each age cohort. The final study report must provide appropriate analyses and descriptive statistics for all PK data. Descriptive statistics must also be presented for safety and PD/effectiveness data.

Study 2: The protocol must provide a statistical analysis plan for assessing efficacy and safety. The null hypothesis of no difference between treatment groups will be tested using an alpha level of 5% (two-sided). The study must provide at least 80% power to detect a pre-specified, clinically meaningful effect on the primary endpoint. The primary analysis method should be pre-specified including any covariates to be included in the statistical model. You should stratify the primary endpoint analysis by age cohort. The primary analysis population should be the intent-to-treat population consisting of all randomized patients with any on-treatment primary endpoint data. One or more sensitivity analyses of the primary endpoint to assess the impact of missing data should be pre-specified. The statistical analysis plan must be submitted and receive division concurrence prior to the start of the study.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that eltrombopag olamine (SB-497115-GR) is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human*

Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 4, 2015. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

  Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

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

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-63293	GI-1	GLAXOSMITHKLINE	SB-497115-GR

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/s/

RICHARD PAZDUR
01/25/2010