# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207027Orig1s000

# STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

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| **BLA/Serial Number #:** | NDA 207027 / 00 |
| **Supplement #:** | Original Submission |
| **Drug Name:** | Promacta® (eltrombopag) (b) (4) for Oral Suspension |
| **Indication(s):** | Treatment of thrombocytopenia in adult and pediatric patients *1 year and older* with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy |
| **Applicant:** | Novartis |
| **Date(s):** | Submission date: 24 February 2015<br>PDUFA date: 24 August, 2015<br>Review completion date: 15 July, 2015 |
| **Review Priority:** | Priority (Pediatric Exclusivity) |
| **Biometrics Division:** | Division of Biometrics 5 (HFD-711) |
| **Statistical Reviewer:** | Chia-Wen Ko, Ph.D. |
| **Concurring Reviewers:** | Lei Nie, Ph.D., Team Leader<br>Rajeshwari Sridhara, Ph.D., Division Director |
| **Medical Division:** | Division of Hematology Products |
| **Clinical Team:** | Lori Ehrlich, M.D. Ph.D.<br>Virginia Kwitkowski, R.N., M.S. |
| **Project Manager:** | Kimberly Scott |

**Keywords:** pediatric ITP, powder formulation, pediatric written request

# EXECUTIVE SUMMARY

Based on the two clinical studies that have been submitted and reviewed by the Agency, this New Drug Application (NDA) is seeking an initial application for the use of powder formulation in young children to expand the current indication of eltrombopag to include children ages 1 and older. In addition, the Applicant is requesting the Agency's determination for pediatric exclusivity as the two clinical studies complete the Applicant's response to the Agency's Written Request for Pediatric Studies issued on November 23rd of 2011.

Eltrombopag tablet formulation was approved in 2008 for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Clinical data from PETIT and PETIT2 studies in children ages 1-17 years with chronic ITP were submitted to NDA022291/S-015 in December 2014 to expand the indication of eltrombopag tablet formula to include pediatric patients 6 years and older. That supplemental NDA was approved in June 2015.

This new NDA for eltrombopag powder formulation is seeking to expand the indication of eltrombopag to include children ages 1 and older, based on data from ages 1-5 years old children that received eltrombopag powder formulation in the PETIT and the PETIT2 studies. Because data on all age cohorts have been reviewed in the NDA22291/S-015 application for an evaluation of treatment efficacy in the overall studied pediatric population, a separate statistical review for this new application is not necessary. Interested readers may refer to the NDA022291/S-015 statistical review, for details on the PETIT and PETIT2 study design and efficacy results.

As assessed in the NDA22291/S-015 review, results from the PETIT and PETIT2 studies demonstrated treatment efficacy of eltrombopag in the studied pediatric population, including the 1-5 years age cohort. The proposed indication expansion therefore should be granted. The product label is to be revised to include results from the youngest age cohort in the two studies.

For the determination of pediatric exclusivity: The PETIT study was conducted to satisfy the *"Study 1: Pharmacokinetic/Pharmacodynamic (PK/PD) and Safety study"* and PETIT2 was conducted to satisfy the *"Study 2: Efficacy, PK, and Safety study"* requirements, of the final Written Request dated November 23, 2011. The table starting on the next page shows the requested statistical information as written in the Written Request and the submitted information in response. This Reviewer considers the statistical information as requested by the Written Request has been fulfilled. The final determination is scheduled to be made by the Pediatric Exclusivity Board on July 28, 2015.

**Pediatric Exclusivity Determination for Promacta® – Statistical Information**

| Written Request Items | Information Submitted |
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| **Statistical information (statistical analyses of the data to be performed):**<br><br>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.<br><br>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.<br><br>For such binary outcomes, we recommend using a Cochran-Mantel-Haenszel test as the primary analysis. One analysis should treat missing outcomes as failures. Every subject should be accounted for in the analysis by either being measured for the primary | **Statistical information (statistical analyses of the data performed):**<br><br>**Study 1: TRA108062/PETIT**<br>Data from both study 1 (TRA108062/PETIT) and study 2 (TRA115450/PETIT2) were combined to obtain the final PopPK/PD model parameter estimates for eltrombopag in pediatric subjects with chronic ITP. The final report provides appropriate analyses and descriptive statistics for all PK data (Population PK and PK/PD report 2013N181329).<br><br>For the Randomized Period, a total sample size of 42 evaluable subjects was required to provide 90% power at the 5% level of significance (two-sided). To ensure sufficient power for both the primary endpoint and the secondary endpoint of platelet counts ≥50 Gi/L for at least 60% of assessments between Days 15 and 43 (Week 2 to 6) of the Randomized Period, and with a further 30% increase to compensate for missing data and dropouts, 54 subjects were required. A logistic regression model that adjusted for age cohort was used to compare the proportion of subjects who achieved: a platelet count ≥50 Gi/L at least once between Days 8 and 43 (Weeks 1 to 6) of the Randomized Period.<br><br>**Study 2: TRA115450/PETIT2**<br>The primary comparison of interest was the proportion of subjects that received eltrombopag, compared with placebo, who achieved platelet counts ≥50 Gi/L for at least 6 out of 8 weeks, between Weeks 5 to 12 of Part 1. The primary efficacy analysis was evaluated using stratified Cochran-Mantel-Haenszel (CMH) chi-square test statistics that adjusted for the age cohorts (1 to 5 years, 6 to 11 years and 12 to 17 years). The Breslow- |

| Written Request Items | Information Submitted |
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| endpoint or properly accounted for if not measured for the primary endpoint. The number of subjects not measured for the primary endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results. | Day test for homogeneity of treatment effect was used to evaluate the treatment by cohort interaction. The intent-to-treat population consisting of all randomized patients was the primary analysis population for efficacy.<br>The study planned to randomize approximately 75 subjects (50 eltrombopag; 25 placebo) in order to have 90% power to detect a clinically meaningful difference of 40% between eltrombopag and placebo at the alpha level of 5% (two-sided) with respect to the primary endpoint. A total of 92 patients (63 eltrombopag, 29 placebo) were randomized in this study.<br><br>Overall, 92% (85 out of 92) randomized patients had platelet values available for Weeks 5 through 12 of Part 1 for the determination of the primary endpoint. Missing data occurred during Weeks 5 through 12 of Part 1 were treated as negative response in the primary analysis. One pre-specified sensitivity analysis of the primary endpoint was performed using multiple imputations to assess the impact of missing data. The statistical analysis plan was acceptable to the Agency. |

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