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

NDA #: **Supplement #:**	022307 0233
Drug Name:	Effient (Prasugrel)
Indication(s):	Sickle Cell Disease
Applicant:	Eli Lilly and Company
Stamp Date:	12-JAN-2016
Primary Review Date:	18-JUNE-2016
PDUFA Date:	12-JULY-2016
Review Priority:	Priority (Pediatric Exclusivity)
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Keywords: Andersen-Gill model, Negative binomial regression, MCF	

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1 EXECUTIVE SUMMARY

The Sponsor is submitting this supplemental New Drug Application (sNDA) to communicate the results of the Study H7T-MC-TADO (C)- entitled, "A Phase 3 Double-Blind, Randomized, Multicenter, Efficacy and Safety Study of Prasugrel Compared to Placebo in Pediatric Patients (aged 2 to <18 years) with Sickle Cell Disease (SCD)" as part of the evaluation of Effient (Prasugrel) in the pediatric program for Sickle Cell Disease. This submission also includes clinical study report of Study H7T-MC-TACX titled, "An open-label dose-ranging study of prasugrel in pediatric patients with SCD". This submission is submitted to fulfill the requirements of the pediatric Written Request (WR) for Effient issued by FDA on 19 December 2012, and subsequently amended on 24 July 2013 (WR Amendment 1) and 21 July 2015 (WR Amendment 2).

Sickle cell disease is an inherited blood disorder characterized by painful vaso-occlusive crisis (VOC) with limited treatment options, particularly for children. Hydroxyurea is the only pharmaceutical agent indicated for prevention of recurrent VOC and acute chest syndrome. However, hydroxyurea is not approved for children with SCD in all regions. The potential of prasugrel therapy in pediatric patients with VOC is of particular interest because of the paucity of other treatment options in children and the prospect of preventing future irreversible organ dysfunction, which may be related to multiple cycles of vascular occlusion and reperfusion injury. The pivotal Phase 3 Study TADO was designed to test the hypothesis that prasugrel compared to placebo would reduce the rate of VOC in pediatric patients. Source: 2.7.3 Summary of Clinical efficacy

1.1 Conclusion:

The Sponsor fulfilled the requirements set forth in the WR-2 dated 21 July 2015 for pediatric exclusivity. Details are provided in Table 1.1 below.

Table 1.1**:** Pediatric Exclusivity for Prasugrel- Statistical Information

Written Request Items	**Information Submitted**
Reports of the studies must be submitted to the Agency on or before January 14, 2016.	This sNDA was submitted on January 12, 2016. The Sponsor met the deadline specified in the WR.
Study 1 (TACX): The PK/PD study must be completed before, and used to inform dosing in, the efficacy trail (TADO).	*Study H7T-MC-TACX* was used to identify the dose(s) of prasugrel to be studied in H7T-MC-TADO and to assess the tolerability of pediatric patients with SCD.
Study 1 must have 33 pediatric patients with SCD, and a minimum of 29 patients must complete the study.	At least 33 pediatric patients with SCD were enrolled, and a minimum of 29 patients were treated with at least 1 dose and completed the *Study 1*.

Submit information from *Study 2* (TADO): A Phase 3, Double-blind, Randomized, Efficacy and Safety Comparison of Prasugrel and Placebo in Pediatric Patients with SCD	This sNDA does contain the full study report on Study 2. The Sponsor met the requirement specified in the WR.
Study 2: Patients with SCD ages ≥2 and <18 years of age. The following 3 age groups and numbers of patients will be studied: • ≥2to <6 years: At least 21 patients (approximately 10 in each blinded treatment group; prasugrel and placebo) must be enrolled and complete at least 9 months of the double-blind treatment period by submission. • ≥6 to <12 years: At least 70 patients (approximately 35 in each blinded treatment group [prasugrel and placebo]) must be enrolled and complete at least 9 months of the double-blind treatment period • ≥12 to <18 years: 70 patients (approximately 35 in each blinded treatment group [prasugrel and placebo]) must be enrolled and complete at least 9 months of the double-blind treatment period	*Study 2* enrolled 67 pediatric subjects ≥2 to <6 years of age. There were 132 pediatric subjects of age ≥6 to <12 years. A total of 142 pediatric subjects of age ≥12 to <18 years were enrolled. The Sponsor met the criteria specified in the WR.
The primary efficacy endpoint in *Study 2* will be the reduction in the rate of VOC, which will be a composite of the following: pain crisis or acute chest syndrome	In study 2 (TADO) vaso-occlusive crisis (VOC) was the primary efficacy endpoint. Andersen-Gill model was used to analyze the primary efficacy endpoint. See Table 1.2 below for further details.
Study 2 must have a detailed statistical plan	The Sponsor met the criteria specified in the WR.
Study 2 must be designed with at least 85% statistical power to detect a clinically meaningful treatment effect at a Type I error rate of 5% (two-sided).	Total of 341 patients were randomly assigned to prasugrel (171) and placebo (170). It was more than 220 patients required to provide 85% power to detect a 35% relative rate reduction with prasugrel.

(b) (4)

2 INTRODUCTION

2.1 Overview

Study H7T-MC-TADO was A Phase 3 Double-Blind, Randomized, Multicenter, Efficacy and Safety Study of Prasugrel Compared to Placebo in Pediatric Patients with Sickle Cell Disease (SCD). The primary objective of this study was to assess the efficacy of prasugrel compared to placebo in pediatric patients with SCD as measured by reduction in the rate of vaso-occlusive crisis (VOC), which is a composite endpoint of painful crisis or acute chest syndrome.

Table 2.1.1: List of studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
H7T-MC-TADO	Phase 3, double-blind, Placebo-controlled	9 months 0.08-mg/kg oral 9-24 months	24 months	170/171	Pediatric, with SCD and HbSβ0, Had ≥2 VOCs

Study H7T-MC-TADO was conducted at 51 study sites in 13 countries.

Date of first patient enrolled: 13 may 2013
Data cutoff date: 17 July 2015

Three-hundred and forty-one patients (171 prasugrel, 170 placebo) were randomized. Of these, 340 were treated with at least one dose.

The primary efficacy endpoint was the time to recurrence episodes of VOC. It was analyzed by the Andersen-Gill model with treatment as an independent variable and prognostic factors of hydroxyurea use and age group (2 to <6 years, 6 to <12 years, and 12 to <18 years) included in the model as covariates.

A total of 736 VOC events were included in the primary composite endpoint of vaso-occlusive pain crisis or acute chest syndrome. (b) (4)

Study H7T-MC-TACX was an open-label, dose-ranging phase 2 study of prasugrel in pediatric patients with SCD. The main purpose of this study was to explore the relationship between dose and PK and PD response in pediatric patients with SCD (b) (4) Study H7T-MC-TACX was used to identify the dose(s) of prasugrel to be studied in TADO, and to assess the tolerability of prasugrel in pediatric patients with SCD.

This study was conducted between 30 November 2011 and 01 November 2012. At least 33 pediatric patients with SCD were enrolled, and a minimum of 29 patients were treated with at least 1 dose and completed the study.

The primary PK parameter was the area under the Pras-AM concentration-time curve through the last sampling time of 4 hours post-dose ($AUC_{0\text{-}tlast}$). (b) (4)

No further discussion of study H7T-MC-TACX is provided in the remainder of this review.

2.2 Data Sources

EDR Location: \\CDSESUB1\evsprod\NDA022307\0233
Primary dataset: AGMODEL.XPT
WR Amendment 2: fda-21july2015-amend2-wr.pdf

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and analysis quality was good.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The primary objective of Study H7T-MC-TADO was to assess the efficacy of prasugrel compared to placebo in pediatric patients with SCD as measured by reduction in the rate of VOC, which is a composite endpoint of painful crisis and acute chest syndrome (defined below).

- *Acute chest syndrome was defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest x-ray.*

- *A painful crisis was defined as an onset of moderate to severe pain that lasted at least 2 hours for which there was no explanation other than vaso-occlusion and which required therapy with oral or parenteral opioids, ketorolac, or other analgesics prescribed by a health care provider in a medical setting such as a hospital, clinic, emergency room visit, or documented telephone management.*

Major secondary efficacy objectives were to assess the efficacy of prasugrel compared to placebo in pediatric patients with SCD by assessment of the following endpoints in a fixed-sequence gatekeeping procedure:

1. Reduction in the rate of sickle-cell-related pain as recorded in patient pain diaries
2. Reduction in the rate of hospitalization for VOC
3. Reduction in the rate of painful crisis
4. Reduction in the rate of red blood cell (RBC) transfusion due to SCD
5. Reduction in the intensity of sickle-cell-related pain as recorded in patient pain diaries
6. Reduction in the use of analgesics as recorded in patient pain diaries
7. Reduction in the rate of acute chest syndrome
8. Reduction in school absence secondary to sickle-cell-related pain as recorded in patient pain diaries.

Sample size:
The following assumptions were used to determine the required sample size for the study:

- The mean rate of the primary endpoint of VOC is 3 per year in the placebo group, which has taken into account about 30% of patients being on hydroxyurea since entering the study, and the standard deviation (SD) is approximately equal to the mean number of the VOC.
- Projected accrual period of approximately 18 months with last patient followed for 9 months and a maximum follow-up of 24 months for all patients. The time of entry follows a uniform distribution.
- 20% drop-out rate is assumed, and drop-out time follows a uniform distribution.
- 35% relative reduction in the rate of VOC with prasugrel treatment.
- The recurrent events of VOC follow a mixed Poisson process with a patient-specific effect to account for over-dispersion, which is an independent and identically distributed gamma random variable with mean of 1 and variance of 0.7. The over-dispersion parameter of 0.70 is assumed based on the ratio of the assumed mean and variance in the placebo group.

Based on above assumptions, the mean and median follow-up will be approximately 16 months, and 220 randomized patients will provide 85% power to detect a 35% relative rate reduction with prasugrel using the Andersen-Gill (A-G) model. To ensure the study is adequately powered, the overall event rate will be assessed during an interim analysis and sample size may be adjusted as necessary.

Table 3.2.1 below provides the distribution of patients in all six strata by treatment.

Table 3.2.1: Strata wise numbers of patients by treatment

Stratum (age group, Hydroxyurea use at baseline)	Placebo	Prasugrel	Total
>=2 to <6, No	24	25	49
>=2 to <6, Yes	9	9	18
>=6 to <12, No	41	43	84
>=6 to <12, Yes	25	23	48
>=12 to <18, No	29	26	55
>=12 to <18, Yes	42	45	87
Total	170	171	341

3.2.2 Statistical Methodologies

Primary analysis was based on the intent-to-treat (ITT) population, which was defined as all randomized patients, including patients who did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol.

Andersen-Gill model:

The Andersen–Gill (A-G) model is a generalization of the Cox proportional hazard method and has been elaborated to analyze recurrent event data. It was proposed to handle event data following Poisson processes. This method is compared with non-survival approaches, such as Poisson and negative binomial regression. In this submission, the time to recurrent episodes of VOC was analyzed by the A-G model with treatment as an independent variable and important prognostic factors of hydroxyurea use and the 3 age groups included in the model as covariates. The within-patient interdependency was accounted for by using the robust standard error estimates for the estimated regression parameters. The primary analysis for the primary efficacy endpoint was conducted on the ITT population. Results are provided in Section 3.2.4 below.

Negative binomial regression:

In addition, the primary outcome was analyzed using a negative binomial regression model with treatment and important prognostic factors of the hydroxyurea use and age group in the model and time at risk as the offset variable to adjust for variable follow-up times. This analysis was carried out using the ITT population. Results are provided in Section 3.2.4 below.

Mean Cumulative Function:

At any time *t*, the corresponding distribution of the number of events has a mean *M(t)*. This mean as a function of *t* is called the *mean cumulative function* (MCF) for the *number* of events. This function can be regarded as the "mean curve," as it is the pointwise average of all population curves passing through the vertical line at each age t. Usually, this curve is a step function with many small steps, one for each events in the population. The mean curve is regarded as continuous. *M(t)* is an increasing function of *t*. The MCF can be used to predict the total number of events in a population of units in a future period [Nelson WB. Recurrent Events Analysis for Product Repairs, Disease Recurrences, and Other Applications, *The ASA-SIAM Series on Statistics and Applied Probability.* 2003]. The MCF plot and the results are provided in Section 3.2.4 below.

Patient Disposition, Demographic and Baseline Characteristics:

- 341 total patients randomly assigned to prasugrel (171) or placebo (170)
- Mean age (range): 10.6 years (2.0 to 18.8 years [1 patient aged >18 years was inadvertently enrolled; this patient was included in efficacy analyses])
- Regions: Africa (43.4%), Mediterranean Basin (30.3%), North America (16.4%), Western Europe/Scandinavia (7.6%), West Asia (2.1%), South America (0.3%)
- Race: Black or African American (65.3%), White (34.1%)
- Gender: Male (49.3%), Female (50.7%)
- Genotype: HbSS (90.3%), HbS β^0 thalassemia (9.7%)
- Hydroxyurea use at baseline: 44.9% of all patients
- History of VOC at baseline: 100% (entry criteria required ≥2 episodes of VOC in year to baseline)

3.2.3 Sponsor's Results and Conclusions

(b) (4)

3.2.4 Reviewer's Results and Conclusions

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5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no statistical issues.

5.2 Collective Evidence

Not applicable.

5.3 Conclusions and Recommendations

Statutory requirements (stated in WR-2 dated 21 July 2015) for pediatric exclusivity are met.

- As per the Agency's recommendations, Study H7T-MC-TACX was used to identify the dose(s) of prasugrel to be studied in H7T-MC-TADO and to assess the tolerability of pediatric patients with SCD.

- The Sponsor has submitted the full Study H7T-MC-TADO reports that address the issues outlined in the WRITTEN REQUEST-AMENDMENT 2- dated July 21, 2015. Study TADO had a detailed statistical plan.

5.4 Labeling Recommendations (as applicable)

There are no labeling recommendations.

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/s/

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