CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	022307
Priority or Standard	Priority
Submit Date(s)	January 12, 2016
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PDUFA Goal Date	July 12, 2016
Division / Office	Division of Hematology Products/OHOP
Reviewer Name(s)	Rachel Ershler
Review Completion Date	June 17, 2016
Established Name	Prasugrel hydrochloride
(Proposed) Trade Name	Effient®
Therapeutic Class	$P2Y_{12}$ Platelet Inhibitor
Applicant	Eli Lilly
Formulation(s)	(b) (4)
Dosing Regimen	Not applicable
Indication(s)	(b) (4)
Intended Population(s)	(b) (4)

Template Version: March 6, 200

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Division of Hematology Products recommends that Pediatric Exclusivity be granted for prasugrel hydrochloride (Effient®) and for pediatric information to be included in the labeling as per the recommendations in the draft Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling.

This recommendation is based on the review finding that the Applicant completely responded to all elements in the Pediatric Written Request. The Pediatric Exclusivity Board has reviewed the Exclusivity Determination and has determined that Pediatric Exclusivity will be granted.

The Applicant did not request a new indication, and the Agency agrees that no new indication will be added as a result of this submission, (b) (4) .

1.2 Risk Benefit Assessment

(b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

2.1 Product Information

Prasugrel hydrochloride is an orally bioavailable, third-generation thienopyridine that inhibits platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on the surface of platelets.

Effient® (prasugrel hydrochloride) is FDA approved for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows:

- Patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI.

Supplemental NDA 22307, S-014 provided the clinical data for trials that evaluated prasugrel for the prevention of vaso-occlusive crises (VOCs) in pediatric patients with Sickle Cell Anemia (SCA). The currently marketed formulation is a tablet for oral administration. (b) (4)

The Applicant has not proposed an indication in this sNDA (b) (4) These studies were conducted in response to a Written Request issued by the FDA. Review of fulfillment of the Written Request and recommendations for pediatric exclusivity are made with this review.

2.2 Tables of Currently Available Treatments for Proposed Indications

Sickle Cell Disease (SCD) is the most common inherited red blood cell (RBC) disorder. Worldwide, it is estimated that over 200,000 children affected with SCD are born every year, primarily in sub-Saharan Africa (180,000 births per year) [1]. Approximately 2000 children in the United States are born with SCD each year, with a disease incidence of 1 in 2474 live births [2, 3]. The estimated prevalence of SCD in the US ranges from 70,000-140,000 [4].

SCD results from a single genetic point mutation (replacement of glutamic acid with valine in position 6) on the β-globin subunit of hemoglobin. This mutation leads to an abnormal form of hemoglobin, known as sickle hemoglobin (HbS). People who inherit two copies of the HbS mutation are homozygous (HbSS) and have the disease phenotype, whereas heterozygous carriers (HbAS) have sickle cell trait and do not

exhibit clinical disease. The abnormal HbS results in deformed and fragile RBCs that have a characteristic sickle shape and a reduced lifespan [5]. The sickled RBCs occlude the microvascular circulation, which leads to tissue ischemia, infarctions and chronic hemolytic anemia.

SCD is characterized by heterogeneous disease manifestations and complications that worsen with age including acute vaso-occlussive crises (VOCs), chronic pain, chronic hemolytic anemia, recurrent infections, and neurologic complications. Additionally, vascular injury from chronic ischemia leads to multi-organ dysfunction and early mortality [6]. In infants and children, SCD may cause poor nutritional status and delayed growth and puberty.

VOCs are the most common acute manifestation of SCD and cause significant morbidity [6]. Hydroxyurea is the only pharmaceutical agent that is FDA approved for the reduction in the frequency of painful VOCs in patients with SCD. However, neither hydroxyurea nor any other pharmaceutical agent is approved in the US for children with SCD. Therefore, there is a great need for novel and effective treatments in this patient population.

Table 1: Available medications for the reduction in the frequency of VOCs in SCD

Therapy	Target
Hydroxyurea*	Inhibition of DNA synthesis, immune-modulation, increase hemoglobin F in RBCs

*Currently only approved for use in adults

There is evidence that platelets play a role in sickle cell pathophysiology in general, and in VOC specifically [7]. Several studies have found elevated biomarkers of platelet activation in both children and adults with SCD [8, 9]. Additionally, several studies have suggested a benefit of antiplatelet therapy in reducing markers of platelet activation, as well as the frequency and severity of painful crisis in patients with SCD [10].

2.3 Availability of Proposed Active Ingredient in the United States

Effient is presently marketed in the United States as a tablet for oral administration. Prasugrel hydrochloride was approved on July 10, 2009 for the prevention of thrombotic cardiovascular events when (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI.

The prescribing information for Effient includes the following boxed warning for bleeding risk:

- Effient can cause significant, sometimes fatal bleeding.

- Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke.
- In patients ≥ 75 years of age, Effient is generally not recommended, except in high-risk patients.
- Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible discontinue Effient at least 7 days prior to any surgery.
- Additional risk factors for bleeding include: body weight <60 kg, propensity to bleed, concomitant use of medications that increase the risk of bleeding.
- Suspect bleeding in any patient who is hypotensive and has recently undergone invasive or surgical procedures.
- If possible, manage bleeding without discontinuing Effient. Stopping Effient increases the risk of subsequent cardiovascular events.

Additional warnings and precautions include:
- CABG-related bleeding: Risk increases in patients receiving Effient who undergo CABG
- Premature discontinuation of Effient increases the risk of stent thrombosis, MI and death.
- Thrombotic thrombocytopenic purpura (TTP): TTP has been reported with Effient
- Hypersensitivity: Hypersensitivity including angioedema has been reported with Effient including in patients with a history of hypersensitivity reaction to other thienopyridines.

2.4 Important Safety Issues With Consideration to Related Drugs

Clopidogrel (Plavix®) is an oral thienopyridine anti-platelet agent that works by irreversibly inhibiting P2Y12 on platelets. Clopidogrel is FDA approved for the following indications:

- Acute coronary syndrome
  - For patients with non-ST-segment elevation ACS to decrease the rate of the combined endpoint of cardiovascular death, myocardial infarction (MI) or stroke, as well as the rate of a combined endpoint of cardiovascular death, MI, stroke or refractory ischemia.
  - For patients with ST-elevation myocardial infarction (STEMI), to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke.
- Recent MI, recent stroke, or established peripheral arterial disease to reduce the combined endpoint of new ischemic stroke, new MI and other vascular death.

The most common adverse reaction for clopidogrel is bleeding, including life-threatening and fatal bleeding. TTP has also been reported.

The risk of bleeding is thought to be a class effect for thienopyridines. This is due to the inhibition of platelet activation and aggregation through the irreversible binding of the active metabolite of these agents to platelets.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A waiver for pediatric studies required by the Pediatric Research Equity Act was submitted on December 26, 2007 with the original NDA and was granted on July 10, 2009. The justification for a pediatric waiver was based on the fact that acute coronary syndrome and the procedure of conducting PCI has extremely limited applicability in the pediatric population. Prasugrel is not approved for any pediatric indication.

A Pediatric Written Request was issued by the Agency on December 19, 2012, and was revised on July 24, 2013 (Amendment 1) and July 21, 2015 (Amendment 2). The agreed-upon written request dictated the study design for both of the pediatric trials submitted in this sNDA. The written request included information on the age groups and number of patients to be studied, inclusion criteria, study objectives and endpoints, statistical analysis plans, and the timeline for completing and submitting the studies. A full review of the pediatric written request and determination of eligibility for pediatric exclusivity is included with this clinical review. See Sections 9.4 and 9.5.

2.6 Other Relevant Background Information

The applicant is not seeking approval of prasugrel hydrochloride for any new indications in this application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sNDA was formatted and organized according to 21 CFR 314.50, and was submitted in eCTD format. It was well organized with appropriate indexing.

3.2 Compliance with Good Clinical Practices

Per the Applicant-submitted Clinical Overview: “All clinical studies included in this submission package were conducted in compliance with the principles of Good Clinical Practice.”

3.3 Financial Disclosures

Form 3454 is attached and option 1 chosen:

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

(b) (4)

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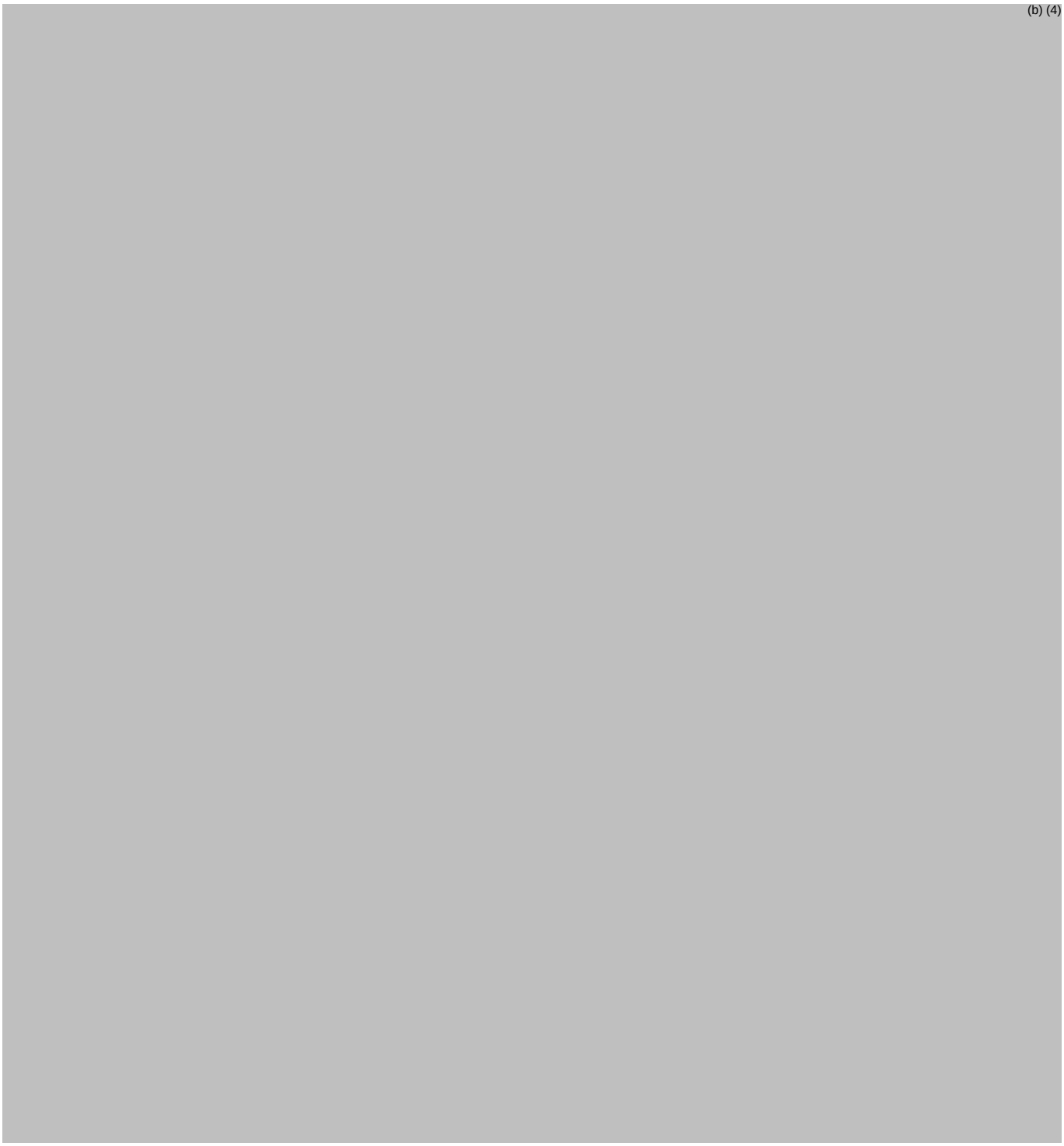


4.2 Clinical Microbiology

Not applicable to this product.

4.3 Preclinical Pharmacology/Toxicology

There were no new pharmacology/toxicology studies provided with this sNDA.

In the pre-IND meeting on December 8, 2009, it was decided that no juvenile animal studies would be needed (b) (4).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action was established with the initial NDA submission. Prasugrel hydrochloride is a member of the class of drugs known as thienopyridines (P1Y12 adenosine diphosphate [ADP] receptor antagonist) with a mechanism of action associated with irreversible inhibition of ADP-mediated platelet activation and aggregation.

Platelet inhibition has been explored as a potential strategy to reduce vaso-occlusive events associated with Sickle Cell Disease.

4.4.2 Pharmacodynamics

(b) (4)

For additional information, see clinical pharmacology review.

4.4.3 Pharmacokinetics

See clinical pharmacology review.

5 Sources of Clinical Data

Ten trials were conducted in support of this application.

5.1 Tables of Studies/Clinical Trials

Table 3: Trials Included in Application

Trial Identifier (Identifier of Study Report) Type of Study	Trial Design	Trial Objective(s)	Number of Centers	Countries where trial was conducted	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects (No. of pediatric subjects)
H7T-EW-TADP BA	Phase 1, open- label, randomized, 2-treatment crossover study	Compare relative bioavailability of pediatric (b) (4) tablet formulation	1	USA	Healthy subjects, aged 18 to 65 years	2 different oral 10-mg prasugrel formulations; single dose on 2 consecutive mornings after fasting overnight	28 (Peds: n=0)
H7T-EW-TADQ BA	Phase 1, open- label, randomized, 5-treatment, 5-sequence crossover study	Compare relative bioavailability of pediatric (oral (b) (4) to marketed tablet. Assessed effect of alterations to recommended dosing procedure (juice chaser, chew and swallow, under the tongue) on Pras-AM exposure	1	USA	Healthy subjects, aged 18 to 65 years	Random assignment to 1 of 5 treatment sequences; received 5-mg prasugrel single dose orally on 5 consecutive mornings after fasting overnight	18 (Peds: n=0)

H7T-EW-TAEQ BA	Phase 1, open-label, randomized, 5-treatment, 5-sequence crossover study	Compare relative bioavailability of pediatric (newer (b) (4) formulation (study drug in the Phase 3 registration Study TADO and expected commercial product) to the reference tablet formulation used in Study TADQ. Assessed effects of alterations to recommended dosing procedure and food on PK of Pras-AM. Compared 2-mg formulation to 5-mg formulation	1	USA	Healthy subjects, aged 22 to 60 years	Random assignment to 1 of 5 treatment sequences; 2-mg or 5-mg prasugrel; single oral doses on 5 consecutive mornings after fasting overnight	20 (Peds: n=0)
H7T-MC-TAEJ PK and PD	Phase 1b, open-label study	Characterize the PK and PD of prasugrel in adults with SCD compared to healthy adults	1	United Kingdom	13 adults with SCD (HbSS, HbSβ0 thalassemia, HbSC, and HbSβ+ thalassemia) and 13 healthy adults, aged 18 to 60 years	Initial prasugrel oral dose of 10 mg at Visit 1, followed by out-patient oral dosing of either 5 mg/day or 7.5 mg/day (depending on weight). Daily dosing to ensure platelet inhibition reached steady state	26 (Peds: n=0)
H7T-MC-TACX PK and PD	Phase 2, open-label, adaptive design, multicenter, dose-ranging PK/PD study	Characterize the relationship between prasugrel dose, exposure to the Pras-AM,	8	USA	Pediatric patients with SCD (HbSS and HbSβ0 thalassemia genotypes), aged 4 to	Part A: Prasugrel ranging from 0.03 to 0.60 mg/kg up to 3 single oral doses,	33 Part A: 24 Part B: 18 (9 of which

		and platelet inhibition in pediatric patients with SCD, as well as identify the doses of prasugrel to be used in the Phase 3 study			<18 years without VOC requiring medical attention within 15 days of screening	separated by 14 ±4 days between each dose Part B: Prasugrel at 0.06, 0.08, or 0.12 mg/kg daily oral dose at 2 (out of 3 possible) dose levels for 14±4 days	had been in Part A) (Peds: n=33)
H7T-MC-TAEK Safety	Phase 2, double-blinded, placebo-controlled, randomized, multicenter study	Assess the safety profile of prasugrel compared to placebo in adult patients with SCD before assessing prasugrel in pediatric patients with SCD. Efficacy of prasugrel for treatment of sickle- cell-related pain was also investigated as a secondary Objective.	18	Canada USA	Adult patients with SCD (HbSS, HbSβ0 thalassemia, HbSC, and HbSβ+ thalassemia genotypes), aged 18 to 55 years without a diagnosis of acute VOC within 30 days of screening	Prasugrel 5 mg/day or placebo (randomized in 2:1 manner); daily oral dose	62 (Peds: n=0)
H7T-MC-TADO Safety and Efficacy	Phase 3, double-blind, placebo-controlled, randomized, parallel-group, multinational study	Assess the safety and efficacy of prasugrel compared to placebo in reducing the rate of VOC in pediatric patients with SCD	51	Belgium Brazil Canada Egypt Ghana Italy Kenya Lebanon Oman Turkey Saudi Arabia United Kingdom USA	Pediatric patients with SCD (HbSS and HbSβ0 thalassemia genotypes), aged 2 to <18 years, who had at least 2 documented VOCs in the previous year	All patients received 0.08-mg/kg oral dose of study drug (prasugrel or placebo (b) (4) at Visit 1 for 14±4 days. Doses adjusted, if necessary, during dose-titration phase (Days 14 to 45) to achieve target level of platelet inhibition. Minimum	341 (Peds: n=341)

						possible dose was 0.04 mg/kg/day; maximum allowed dose was 0.12 mg/kg/day (no more than 10-mg absolute dose).	
H7T-MC-TADR Sensory	Phase 1, open- label study	Characterize the taste profile of proposed child-friendly product of prasugrel	1	USA	Trained experts in oral flavor analysis	Prasugrel provided as 0.1 mg/15 mL and 5 mg/15mL oral suspensions in water, Sprite®, and Ocean Spray® cranberry juice cocktail. Single presentation. After each taste analysis, product was completely expectorated via double rinse.	4 (Peds: n=0)
H7T-MC-TAEF Sensory	Phase 1, open-label study	Characterize sensory properties of prasugrel. Oral flavor, texture, and aftertaste were evaluated	1	USA	Trained experts in oral flavor analysis	Prasugrel (30 mg or 60 mg) administered orally on its own (with or without water) and then in combination with various bitterness suppression compounds. Single presentation. After each taste analysis, product was completely expectorated via double rinse.	3 (Peds: n=0)
H7T-EW-TAEP Sensory	Phase 1, open- label study	Characterize sensory properties of orally (b) (4) Flavor characteristics, mouth feel, texture	1	USA	Trained experts in oral flavor analysis	Prasugrel provided as 2-mg and 5-mg orally (b) (4) and 5-mg (b) (4) in combination with 15 mL of	3 (Peds: n=0)

		perceptions, aftertaste, and disintegration characteristics were evaluated.				water. Single presentation. After each taste analysis, product was completely expectorated via double rinse.	

Table provided by the Applicant with minor modifications.

5.2 Review Strategy

The main focus of this review is to evaluate whether the Eli Lilly has successfully fulfilled the requirement set forth in the issued pediatric written request for the eligibility determination on the pediatric exclusivity. To that end, the study reports for the 2 clinical studies submitted in this supplement were reviewed and summarized in section 5.3. The pediatric written request is included in Section 9.4 Pediatric Written Request of this review. A point by point review of the requirements included in the written request and completeness of the submission to meet these requirements is presented in Section 9.5 Pediatric Exclusivity Determination.

5.3 Discussion of Individual Studies/Clinical Trials

H7T-MC-TACX

TACX was a phase 2, open-label, multicenter, pharmacokinetic (PK) and pharmacodynamic (PD), dose-ranging study of prasugrel in pediatric patients with Sickle Cell Disease (SCD). This study was conducted in two parts (Parts A and B). The design of the trial is presented in Figure 1.

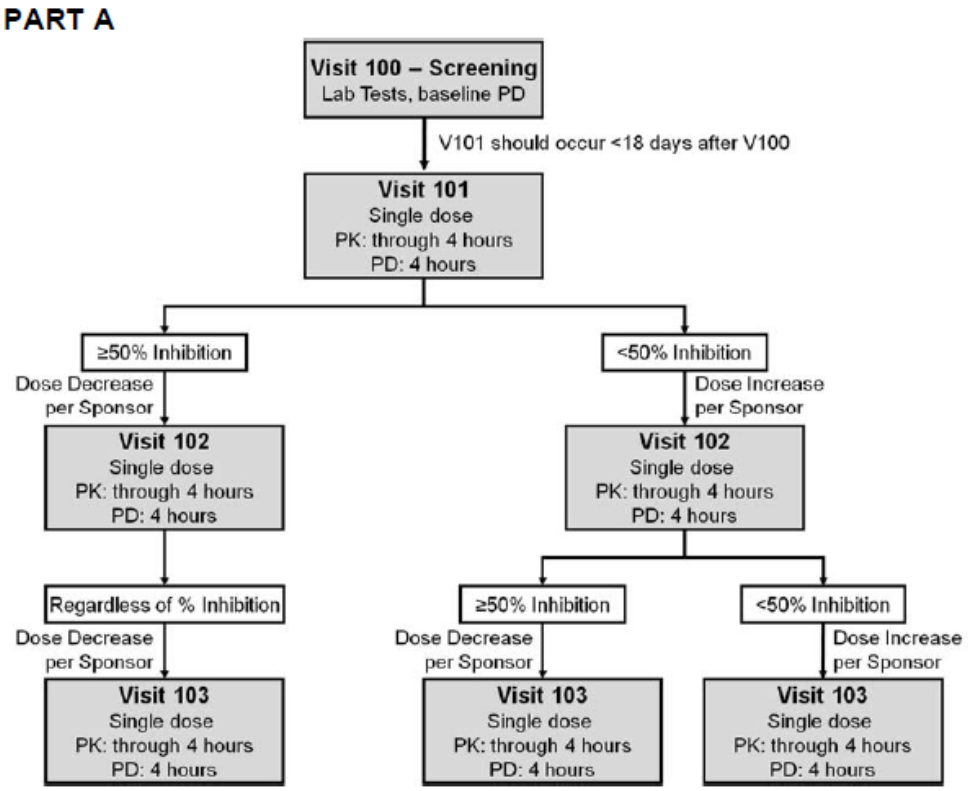
Part A:
Part A was conducted as an open-label adaptive-design trial in which patients received up to 3 single doses of prasugrel separated by 14 ± 4 days between each dose. The goal of Part A was to characterize the PK-PD relationship of the prasugrel active metabolite (Pras-AM) during single-dose ranging in pediatric patients with SCD. Part A was intended to determine the range of prasugrel single doses that produces a percent of inhibition of platelet activation (% inhibition) of 20-50%. Once known, the appropriate starting dose could be selected for the once-daily dosing regimen used in Part B.

Escalating single doses were administered once daily between 0.03 to 0.6 mg/kg, which corresponded to absolute doses of 0.9 to 48 mg.

Part B:
The goal of Part B was to assess the active metabolite PK-PD response, efficacy, safety, and tolerability of prasugrel treatment. Patients received once-daily maintenance

doses of prasugrel over 2 dosing periods, each lasting 14 ± 4 days. The starting dose of 0.08 mg/kg was chosen based on both non-compartmental analyses (NCA) and descriptive PK-PD analyses of single-dose data from Part A in conjunction with population PK (Pop PK) and PK-PD modeling and simulations. All patients received a dose that was expected to produce approximately 30% platelet inhibition for the first 14 ± 4 days.

Patients received the initial dose of 0.08 mg/kg at the study site and PD response was measured 4 hours later. Based on platelet inhibition for each patient, patients were then assigned to receive either 0.08 or 0.06 mg/kg for the first dosing period. Study drug was taken at home daily thereafter. The second dose level was chosen based on an individual patient's PD response at steady state following the first dosing period. Patients who received 0.08 mg/kg during the first dosing period were either up titrated to 0.12 mg/kg dose level or down titrated to 0.06 mg/kg dose level to target a range of 30-50% platelet inhibition for the second dosing period. Patients who received 0.06 mg/kg during the first dosing period were assigned to 0.08 mg/kg during the second dosing period.



Abbreviations: PD = pharmacodynamic(s), PK = pharmacokinetic(s).
Part A: Each additional dose will occur 14±4 days after the previous dose. Approximately 6 weeks will be required for the interim analysis of PK and PD data from Part A, prior to starting Part B.
Part B: Doses A and B are based on expected mean steady-state percent inhibition. In both parts, a minimum of 14 days is needed between visits at which blood samples will be collected for PK analysis for patients <20 kg.

Figure 1: Design of Clinical Trial TACX--Parts A and B

Key Eligibility Criteria

Patients were eligible for this study if all of the following criteria were met:

- Male or female with SCD (HbSS and HbSβ^0 thalassemia)
- Body weight of ≥12 kg
- Age 2 to <18 years at the time of screening
- Patients on hydroxyurea had to be on a stable dose for the 60 days prior to enrollment without signs of hematologic toxicity at screening

Exclusion criteria included patients who had a diagnosis of vaso-occlusive crisis within 15 days prior to screening, had a concomitant medical illness, renal or liver dysfunction, or an abnormal or conditional transcranial Doppler within the last year. Bleeding exclusion criteria included any clinical findings associated with an increased risk of bleeding, recent surgery, or plan for surgery within the next 60 days.

Trial Objectives

Primary Objective
To characterize the relationship between prasugrel dose, exposure to prasugrel active metabolite (Pras-AM), and platelet inhibition in pediatric patients with SCD.

Secondary Objectives
- To evaluate, in the pediatric SCD population, the adequacy of a correlation model to estimate the Pras-AM concentration from the measured concentration(s) of its active metabolite(s).
- Assess the short-term efficacy, safety, and tolerability of prasugrel in pediatric patients with SCD.

Pharmacokinetic (PK) and Pharmacodynamic (PD) Variables

Primary PK Parameter
Area under the Pras-AM concentration-time curve through the last sampling time of 4 hours post-dose (AUC[0-t_{last}])

PD Variables
- Vasodilator-associated phosphoprotein (VASP) platelet reactivity index
- Derived PRI percent platelet inhibition
- VN P2Y12 reaction units (PRU)
- Derived percent platelet inhibition
- Device-reported percent platelet inhibition

Dates of Study:
November 30, 2011 to November 1, 2012

Enrollment:
- Total entered: n=33
- Total completed: n=29
- Part A: n=24 (Age 2 to <6 years: n=3; 6 to <12 years: n=12; 12 to <18 years: n=9)
- Part B: n=18 (9 continued from Part A)

Demographics

Table 4: TACX Demographics

	Part A N=24	Part B N=18
Gender		
Male	10	8
Female	14	10
Age in Years		
Mean	10.99	10.38
Median	10.6	11.04
Range	4.3 to 17.6	4.3 to 17.9
Race		
Black	23	17
Native Hawaiian or Other Pacific Islander	1	1
BMI (kg/m^2)		
Mean	18.93	18.13
Median	18.15	17.35
Range	12.1 to 28.2	14.9 to 29.8

Table 5: TACX Trial, Baseline Medical History of Enrolled Patients

Medical Condition	Part A (N=24) n(%)	Part B (N=18) n(%)	Overall (N=33) n(%)
Hb SS	21 (87.5)	15 (83.3)	30 (90.9)
Hb $S\beta^0$ Thalassemia	3 (12.5)	3 (16.7)	3 (9.1)
Acute Chest Syndrome	19 (79.2)	13 (72.2)	24 (72.7)
Vaso-Occlusive Crisis	17 (70.8)	14 (77.8)	24 (72.7)
Splenectomy	5 (20.8)	7 (38.9)	9 (27.3)
≥ 1 Pre-existing medical condition	10 (41.7)	8 (44.4)	13 (39.4)

(b) (4)

(b) (4)

Part B – Summary of Results

Eighteen patients received multiple doses of prasugrel and contributed to PK assessments in study Part B, and all contributed full PK profiles at Visit 201 and Visit 202 with the exception of 1 patient, whose Pras-AM concentrations were all below the quantifiable lower limit of the assay (BQL) at Visit 201. This resulted in a total of 35 patient visits (PK profiles) across 5 patients aged 2 to <6 years, 5 patients aged 6 to <12 years, and 8 patients aged 12 to <18 years. (b) (4)

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Safety Results:
See section 7.

TACX Conclusions

(b) (4)

H7T-MC-TADO

TADO was a Phase 3, double-blind, randomized, parallel group, multinational study in pediatric patients ages 2 to <18 years with sickle cell disease (homozygous hemoglobin S [HbSS] or heterozygous hemoglobin S beta 0 [HbSβ^0] thalassemia genotypes) who had ≥2 episodes of VOC in the past year. During the double-blind treatment period, patients were titrated to once-daily doses of either placebo or prasugrel for a minimum of 9 months to a maximum of 24 months.

Patients were enrolled into the following age cohorts:
- Age 2 to <6 years
- Age 6 to <12 years
- Age 12 to <18 years

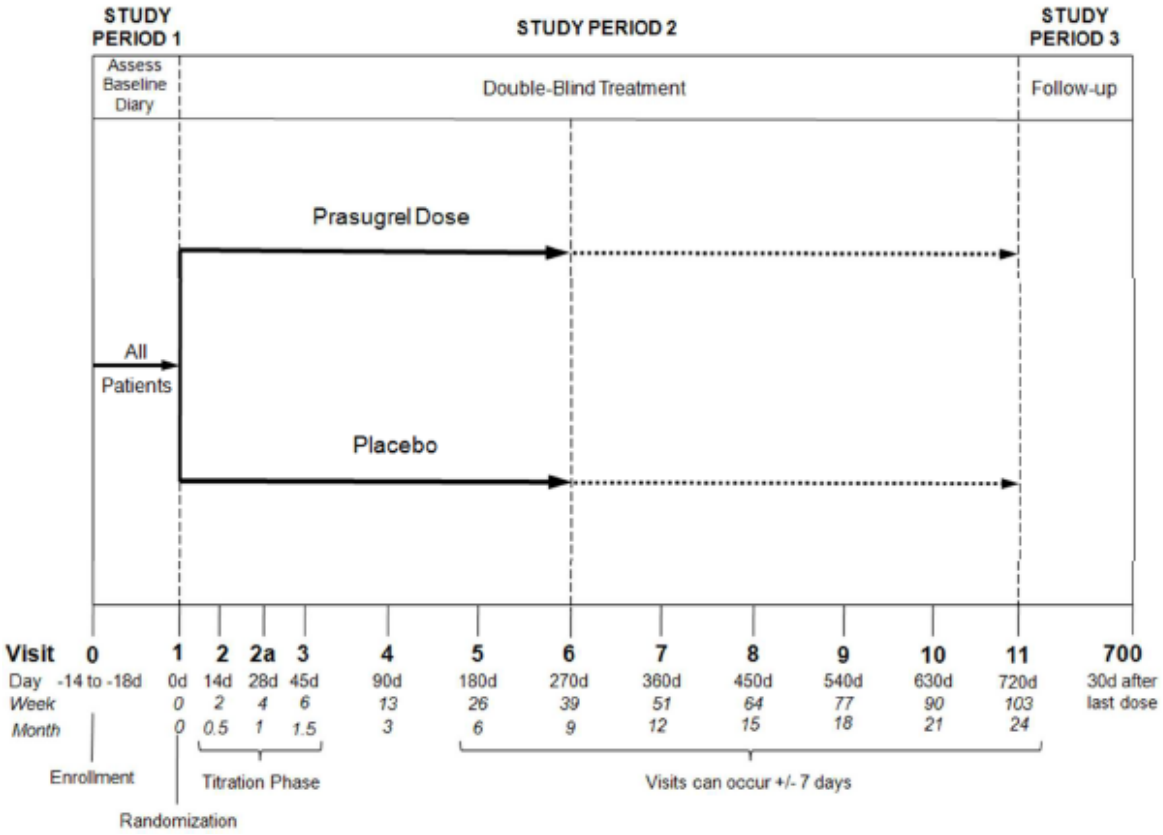
Patients were enrolled at Visit 0 and randomization occurred at Visit 1. The first study visits after randomization occurred at specific time points in order to titrate the patients to the appropriate levels of platelet P2Y12 receptor inhibition and assess patient safety.

All patients received a dose of 0.08 mg/kg at Visit 1 and continued this dose daily for 14 ± 4 days. At Visit 2, the patients were assessed for platelet reactivity using the VN-P2Y12 device. Depending on the results, the dose either remained the same, was increased or decreased to reach the target range of 231-136 P2Y12 reaction units (PRU) (b) (4) Patients who had a dose adjustment at Visit 2 returned after 14 ± 4 days for Visit 2a, at which time their platelet reactivity was reassessed and another dose adjustment was made, if necessary. All patients returned for Visit 3 and platelet reactivity was measured only for those patients who had a dose adjustment at Visit 2a. The maximum permitted dose was 0.12 mg/kg. Table 7 presents a summary of the study drug used. Table 8 illustrates the dose titration used in this study.

After approximately 3 months of treatment, future visits occurred approximately 3 months apart and patients completed their sixth visit within the first 9 months of the

study. Pain diaries were filled out daily by patients age 4 to <18 years through 9 months.

There was an optional open-label extension (OLE) period planned. However, the OLE period was not fully implemented due to the Sponsor decision to discontinue the study (b) (4). The design of the trial is presented in Figure 2.



(Source: TADO CSR, Section 9.1)

Figure 6: Design of Clinical Trial TADO

Table 7: TADO Study Drug

Study Drug	Strength	Formulation
Prasugrel hydrochloride	0.5, 1.0, 2.0, 3.0, and 5.0 mg	Tablet
Placebo to match prasugrel	Not applicable	Tablet

Table 8: Study TADO, Prasugrel Dose Titration

Visit 1	Visit 2		Visit 2a		Visit 3	
Dose (mg/kg)	PRU	Dose (mg/kg)	PRU	Dose (mg/kg)	PRU	Dose (mg/kg)
	136–231	0.08	No visit		NR	0.08
			136–231	0.12	NR	0.12
			>231	0.12	NR	0.12
					136–231	0.10
					>231	0.10
0.08	>231	0.12	<136	0.10	<136	0.08
			136–231	0.06	NR	0.06
			>231	0.06	NR	0.06
					136–231	0.04
					>231	0.04
	<136	0.06	<136	0.04	<136	DC

Abbreviations: DC = discontinued; NR = not required; PRU = P2Y12 reaction units.
(Source: TADO CSR, Section 9.3)

Trial Objectives

Primary Objective
To assess the efficacy of prasugrel compared to placebo in pediatric patients with sickle cell disease as measured by reduction in the rate of vaso-occlusive crises (VOC), which is a composite endpoint of painful crisis or acute chest syndrome.

Definition of VOC: Onset of moderate to severe pain that lasts at least 2 hours, for which there is no explanation other than vaso-occlusion and which requires 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, or documented telephone management.

Definition of acute chest syndrome: An acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest x-ray.

Major Secondary Efficacy Objectives
To assess the efficacy of prasugrel compared to placebo in pediatric patients with SCD by assessment of the following endpoints:
- Reduction in the rate of sickle-cell-related pain as recorded in patient pain diaries
- Reduction in the rate of hospitalization for VOC

- Reduction in the rate of painful crisis
- Reduction in the rate of red blood cell (RBC) transfusion due to SCD
- Reduction in the intensity of sickle-cell-related pain as recorded in patient pain diaries
- Reduction in the use of analgesics as recorded in patient pain diaries
- Reduction in the rate of acute chest syndrome
- Reduction in school absence secondary to sickle-cell-related pain as recorded in patient pain diaries

Additional Secondary Efficacy Objectives
To assess the efficacy of prasugrel compared to placebo in pediatric patients with SCD as measured by:
- Incidence of transient ischemic attack (TIA)/ischemic stroke
- Time from randomization to first and second VOC
- Length of hospitalization for VOC

Safety Objectives
To assess the safety of prasugrel compared to placebo in pediatric patients with SCD as measured by:
- The incidence of hemorrhagic events that required medical intervention, including hemorrhagic stroke
- The incidence of hemorrhagic and non-hemorrhagic treatment-emergent adverse events (TEAEs)
- The tolerability of prasugrel compared with placebo as measured by the rate of permanent study drug discontinuation due to hemorrhagic and non-hemorrhagic TEAEs.

PK Objectives
To assess the PK of prasugrel in pediatric patients with SCD by characterizing the area under the concentration-time curve (AUC) for prasugrel active metabolite (Pras-AM).

PD Objectives
- Characterize PD related to the antiplatelet effects of prasugrel compared to placebo in pediatric patients with SCD
- Evaluate in a substudy the attenuation of platelet activation by prasugrel compared with placebo in pediatric patients with SCD by measuring whole-blood and urine biomarkers of platelet activation

PK/PD Objective
- To assess the PK-PED relationship between Pras-AM and antiplatelet effects of prasugrel in pediatric patients with SCD

Statistical Evaluation Methods:

- Primary efficacy endpoint: The time to recurrent episodes of VOC was analyzed by the Andersen-Gill model with treatment as an independent variable and important 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. The within-patient interdependency was accounted for by using the robust standard error estimates for the estimated regression parameters.

- Major secondary efficacy endpoints: A fixed-sequence gatekeeping testing strategy for the major secondary efficacy objectives was to be implemented to control the overall type I error rate at a 2-sided alpha level of 0.05. The major secondary efficacy endpoints were to be tested in the following order: (1) the reduction in the rate of sickle-cell-related pain as recorded in patient pain diaries versus placebo using a mixed-effects model repeated measures (MMRM) analysis; (2) the reduction in the hospitalization rate for VOC using the Andersen-Gill model; (3) the reduction in the rate of painful crisis using the Andersen-Gill model; (4) the reduction in the rate of RBC transfusion due to SCD using the Andersen-Gill model; (5) the reduction in the intensity of sickle-cell-related pain as recorded in patient pain diaries using an MMRM analysis; (6) the reduction in the use of analgesics using an MMRM analysis; (7) the reduction in the rate of acute chest syndrome using the Andersen-Gill model; and (8) the reduction in school absence using an MMRM analysis.

- Safety: Safety endpoints were summarized using descriptive statistics, and treatment group comparisons were performed using a Fisher's Exact test.

- PK and PD: The PK of the measured Pras-AM concentrations was evaluated using a population PK model and/or non-compartmental methods. Summary statistics were provided for each PD parameter. The comparison between treatment groups was carried out with the analysis of covariance (ANCOVA) model and MMRM analysis. Relationship between exposure to Pras-AM and PRU and/or PRI was evaluated by descriptive or population-based methods.

Key Eligibility Criteria

Patients were eligible for this study if all of the following criteria were met:

- Male or female with SCD (HbSS or HbSβ^0 thalassemia)
- Age 2 to <18 years
- ≥ 2 episodes of VOC in the past year
- Body weight ≥ 19 kg (Addendum 3 allowed the enrollment of patients weighing ≥ 12 kg at sites that were able to accommodate cold storage and handling of the 0.5 mg prasugrel tablet).
- Transcranial Doppler within the last year that was not conditional or abnormal for all patients ≤ 16 years of age.

- If on hydroxyurea, patients had to be on a stable dose for at least 60 days prior to randomization without signs of hematologic toxicity.

Key exclusion criteria included a diagnosis of acute VOC within 15 days prior to screening, concomitant medical illness that, in the opinion of the investigator, was associated with reduced survival, hepatic dysfunction, renal dysfunction, hematocrit <18%, abnormal or conditional transcranial Doppler within the last year, history of any TIA/stroke, chronic RBC transfusion for the prevention of stroke, and contraindication for antiplatelet therapy.

Dates of Study
May 13, 2013 to August 8, 2015

Enrollment
- Randomized: 341 patients (171 prasugrel, 170 placebo)
- Treated (at least 1 dose): 340 patients (170 prasugrel, 170 placebo)
- Completed 9 months of double-blind period (Visit 6): 275 patients (135 prasugrel, 140 placebo)
- Completed 24 months of double-blind period: 2 patients (0 prasugrel, 2 placebo)

Demographics

Table 9: Study TADO, Demographics and Baseline Characteristics (ITT Population)

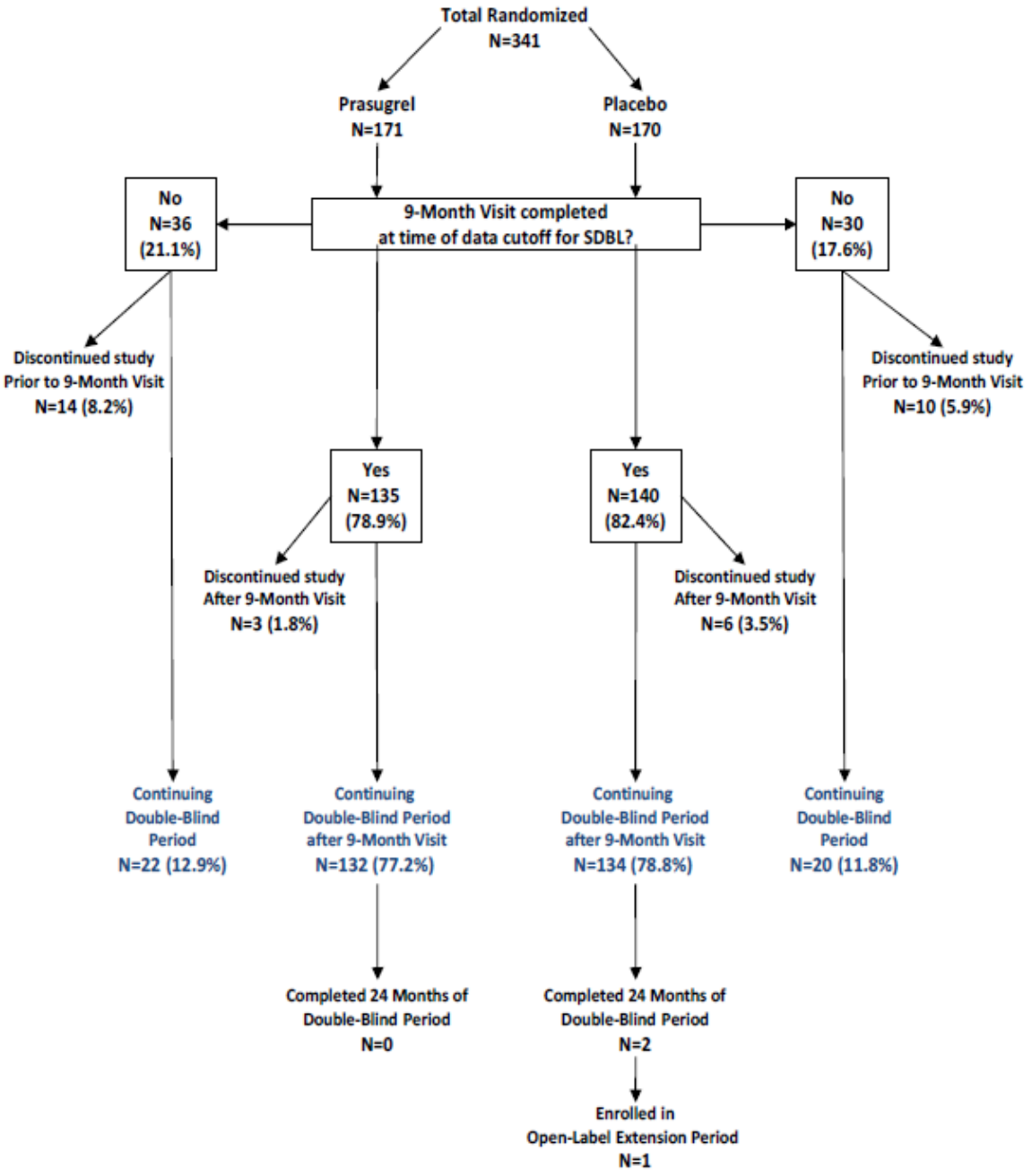
	Prasugrel (N=171) n (%)	Placebo (N=170) n (%)	Total (N=341) n (%)
Age			
Median (years)	11.05	11.18	11.07
Mean years (SD)	10.6 (4.3)	10.58 (4.35)	10.59 (4.33)
Range (years)	2.04 – 17.84	2.45 – 18.78	2.04 – 18.78
Age Group			
2 to <6 years	34 (19.9)	33 (19.4)	67 (19.6)
6 to <12 years	66 (38.6)	66 (38.8)	132 (38.7)
12 to <18 years	71 (41.5)	70 (41.2)	141 (41.3)
18 years	0	1 (0.6)	1 (0.3)
Sex			
Male	84 (49.1)	84 (49.4)	168 (49.3)
Female	87 (50.9)	86 (50.6)	173 (50.7)
Ethnicity			
Hispanic or Latino	2 (1.2)	1 (0.6)	3 (0.9)
Not Hispanic or Latino	94 (55.0)	98 (57.6)	192 (56.3)
Not Applicable	75 (43.9)	71 (41.8)	146 (42.8)
Race			
White	58 (33.9)	58 (34.3)	116 (34.1)
Black	113 (66.1)	109 (64.5)	222 (65.3)
Asian	0	0	0
BMI (kg/m^2)			
Median	15.90	15.60	15.80
Mean (SD)	17.12 (3.62)	16.50 (2.79)	16.81 (3.24)
Range	11.9 – 33.2	12.4 – 27.2	11.9 – 33.2

Table 10: Study TADO, Hydroxyurea use at baseline

	Prasugrel (N=171) n (%)	Placebo (N=170) n (%)	Total (N=341) n (%)
Hydroxyurea Use at Baseline			
Yes	77 (45)	76 (44.7)	153 (44.9)
No	94 (55)	94 (55.3)	188 (55.1)

Patient Disposition

The majority of patients (60.8%) remained on the initial starting dose of 0.08 mg/kg. Patient disposition is summarized in Figure 7.



(Source: TADO CSR, Section 10.1)

Figure 7: Study TADO, patient disposition at the time of data cutoff

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6.1 Indication

The indication evaluated was the reduction in the rate of vaso-occlusive crisis in pediatric patients with SCD.

6.1.1 Methods

For details see sections 5.3

6.1.2 Demographics

For details see sections 5.3

6.1.3 Subject Disposition

For details see sections 5.3

6.1.4 Analysis of Primary Endpoint(s)

For details see section 5.3

6.1.5 Analysis of Secondary Endpoints(s)

For details see section 5.3

6.1.6 Other Endpoints

Results of PK and PD evaluations are provided in the sNDA submission.

6.1.7 Subpopulations

(b) (4)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

(b) (4)

(b) (4)

(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable .

6.1.10 Additional Efficacy Issues/Analyses

Not applicable

7 Review of Safety

Safety Summary

Two studies were conducted in the pediatric patients in support of the prasugrel SCD clinical development program, Study TACX and Study TADO. The prasugrel safety profile in children and adolescents with SCD is based largely on the pivotal Phase 3 study, TADO. The main safety objectives of Study TADO include comparisons of the incidence of hemorrhagic events, as well as non-hemorrhagic treatment-emergent adverse events (TEAEs) and permanent study drug discontinuations due to either hemorrhagic or non-hemorrhagic TEAEs. No differences were observed between treatment groups with respect to deaths, SAEs, study drug discontinuations due to AEs, TEAEs overall, hemorrhagic TEAEs, non-hemorrhagic TEAEs, AEs possibly related to study drug or AEs possibly related to study procedure.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There is a large clinical trial and post-marketing database supporting the safety and tolerability of prasugrel in adult patients with acute coronary syndromes. From March 2009 through January 2015, it is estimated that cumulative post-marketing exposure worldwide is approximately 2.7 million adult patients. Cumulatively, including the pediatric SCD trials TACX and TADO, approximately 2189 Phase 1 study participants and 42,231 patients have been enrolled on prasugrel clinical studies.

In clinical studies of SCD, a total of 54 adults with SCD and received at least 1 dose of prasugrel in clinical trials. In Studies TACX and TADO, a total of 203 children and adolescents with SCD (33 in TACX and 170 in TADO) have received at least 1 dose of

prasugrel. Safety conclusions for the purpose of this review are based on the two pediatric studies in SCD, TACX and TADO.

7.1.2 Categorization of Adverse Events

In studies TACX and TADO, adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Per the Applicant, safety data from the two pediatric SCD studies have not been integrated due to important differences in study design.

7.2 Adequacy of Safety Assessments

Safety assessments were conducted on all patients who received at least 1 dose of the study drug, and included assessment of the incidence of hemorrhagic events requiring medical intervention, treatment-emergent adverse events (TEAEs) including both and hemorrhagic TEAEs and non-hemorrhagic TEAEs, study drug discontinuation due to adverse events (AEs) or hemorrhagic AEs and clinical laboratory results.

Reviewer Comment: *Data collection of toxicities in studies TACX and TADO was adequate to determine if there were significant toxicities associated with prasugrel use in pediatric patients with sickle cell disease.*

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study TACX
In Part A of study TACX, 24 pediatric patients received up to 3 single doses of prasugrel ranging from 0.03 to 0.6 mg/kg, which corresponded to an absolute dose range of 0.9 to 48 mg (TADO CSR, Section 11.3). In Part B of Study TAXC, a total of 18 pediatric patients (9 of whom previously participated in Part A) received an initial dose of 0.08 mg/kg. Based on PD response to the initial dose at 4 hours, 16 patients were assigned to 0.08 mg/kg for the first dosing period of 14 ± 4 days, and 2 patients were assigned to the 0.06 mg/kg dose for the first dosing period. Seven patients who received 0.08 mg/kg during the first dosing period had a dose decrease to 0.06 mg/kg dose for the second dosing period of 14 ± 4 days, while 8 patients had a dose increase to 0.12 mg/kg. The actual absolute daily doses of prasugrel administered during Part B ranged from 1 to 7 mg.

Study TADO

In the double-blind treatment period of Study TADO, a total of 170 patients in the prasugrel treatment group and 170 patients in the placebo group received at least 1 dose of study drug and were evaluated as part of the safety analysis population (TADO CSR, Section 12.1). The mean duration of exposure by treatment group through the cutoff date of the submission database lock (SDBL) was 293.2 days for the prasugrel treatment group and 307.1 days for the placebo group. No difference was observed between treatment groups with respect to mean duration of exposure (TADO CSR, Table TADO.12.1).

In evaluating the mean duration of treatment exposure by age group, no differences were observed between the prasugrel treatment group and the placebo group (TADO CSR, Table TADO.14.111). In the prasugrel treatment group, the mean duration of exposure was 176.6 days for patients 2 to <6 years of age, 324.5 days for patients 6 to <12 years of age, and 320.7 for patients 12 to <18 years of age. In addition, the proportion of patients who had a duration of treatment exposure ≥9 months (270 days) was similar between treatment groups (prasugrel: 73.5%; placebo: 78.8%; TADO CSR, Table TADO.12.1). The distribution of patients by age group who had a duration of treatment exposure ≥9 months (270 days) was as follows (TADO CSR, Table TADO.14.111):

- Age 2 to <6 (years): 10 prasugrel patients; 11 placebo patients; 21 total patients
- Age 6 to <12 (years): 58 prasugrel patients; 60 placebo patients; 118 total patients
- Age 12 to <18 (years): 57 prasugrel patients; 63 placebo patients; 120 total patients.

7.2.2 Explorations for Dose Response

(b) (4)

(b) (4)

7.2.3 Special Animal and/or In Vitro Testing

No juvenile animal studies were conducted.

7.2.4 Routine Clinical Testing

During both studies, standard laboratory tests, including chemistry, hematology, and urinalysis panels, were collected at regular intervals. A pregnancy test (if applicable) was completed at baseline.

Reviewer Comment: *Clinical testing was adequate to monitor for known adverse events of prasugrel.*

7.2.5 Metabolic, Clearance, and Interaction Workup

No relevant studies were conducted in pediatric patients.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The risk of bleeding is thought to be a class effect for thienopyridines. This is due to the inhibition of platelet activation and aggregation through the irreversible binding of the active metabolite of these agents to platelets.

See section 2.4 for additional information.

Reviewer Comment: *Study TACX and Study TADO included adequate assessments and monitoring for potential adverse effects of the thienopyridine class of drugs, most notably bleeding.*

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during Study TACX.

Two deaths were reported in Study TADO, one in the prasugrel group and one in the placebo group.

Summary of Deaths

Patient TADO 300-3661
A 12-year-old black female, was randomized to the prasugrel treatment group. The final dose for the patient was 0.12 mg/kg (4-mg absolute daily dose). Approximately 10 months after starting on study drug, the patient was hospitalized following an episode of convulsion. The patient's condition deteriorated and she died the same day. This death occurred 284 days after randomization, and 1 day after the last dose of study drug. Based on the results of an autopsy, the cause of death was determined as intracranial hemorrhage due to ruptured intracerebral aneurysm. Findings suggestive of marked increase in intracranial pressure and massive intracranial hemorrhage at the base of the brain were noted. All other systems were normal. The patient had recently been diagnosed and treated for malaria 9 days before her death. The patient had a PRU value of 195 approximately 9 days prior to the event, which was within the target level of platelet reactivity for the study. The patient had normal transcranial Doppler (TCD) velocity at baseline. The event was not considered by the investigator to be related to study drug or protocol procedures.

Patient TADO 302-8766
An 11-year-old black male, was randomized to the placebo group. Approximately 8 months after receiving the first dose of blinded study drug, the patient was hospitalized with a diagnosis of painful crisis. On the third day of hospitalization, the patient became febrile. The next day, the patient experienced life-threatening hypoglycemia and was treated with intravenous (IV) glucose. On the same day, he was diagnosed with severe anemia, received a blood transfusion, and study drug was discontinued. The patient's condition deteriorated despite oxygen and blood transfusion, and the patient died the following day. The cause of death was determined as septicemia. The patient had a background of severe anemia and infection in an unidentified site. The patient had also recently been diagnosed and treated for malaria 10 days before his death. The clinical events resulting in the fatal outcome were not considered by the investigator to be related to study drug or protocol procedures.

Reviewer Comment: *The two deaths that were reported on Study TADO were likely due to underlying SCD and unlikely to be related to the study drug or protocol procedures.*

7.3.2 Nonfatal Serious Adverse Events

Study TACX
Both non-hemorrhagic and hemorrhagic AEs requiring medical intervention were collected and summarized. A summary of adverse events in Study TACX is shown in Table 13. A summary of the serious adverse events (SAEs) is shown in Table 14.

Hemorrhagic SAEs
No serious hemorrhagic events were reported in either Part A or Part B of Study TACX.

Non-hemorrhagic SAEs
A total of 3 non-hemorrhagic SAEs occurred in 2 patients in Part A. One patient experienced 2 SAEs (SCA with crisis and acute chest syndrome). Both events were considered moderate in severity. A second patient experienced SCA with crisis, which was classified as severe. In Part B, 3 non-hemorrhagic SAEs occurred in 2 patients. One patient experienced 2 SAEs of hypersplenism; both events were considered severe. A second patient experienced SCA with crisis, which was moderate in severity. None of these SAEs were deemed to be related to study drug by the site investigator. All patients recovered during the study with the exception of the single patient in Part A who experienced severe SCA with crisis; this patient did recover outside the reporting period for this study.

Table 13: Study TACX, Summary of Adverse Events

	Part A (N=24) n (%)	Part B (N=18) n (%)
Death	0 (0.0)	0 (0.0)
SAEs	2 (8.3)	2 (11.1)
AE which led to study drug discontinuation	0 (0.0)	0 (0.0)
TEAEs	12 (50.0)	11 (61.1)
Hemorrhagic TEAE	0 (0.0)	3 (16.7)
Non-hemorrhagic TEAE	12 (50.0)	11 (61.1)
AE possibly related to study drug	0 (0.0)	3 (16.7)
AE possibly related to study procedure	1 (4.2)	0 (0.0)

Abbreviations: AE=adverse event; N=total number of treated patients; n=number of patients with at least 1 condition; SAE=serious adverse event, TEAE=treatment-emergent adverse event

Table 14: Study TACX, Serious Adverse Events

	Part A (N=24)			Part B (N=18)		
	n1	(%)	n2	n1	(%)	n2
Any Serious AE	2	(8.3)	3	2	(11.1)	3
Hypersplenism	0	(0.0)	0	1	(5.6)	1
Sickle cell anemia with crisis	2	(8.3)	2	1	(5.6)	1
Acute chest syndrome	1	(4.2)	1	0	(0.0)	0

Abbreviations: N = total number of enrolled patients receiving at least one dose of study drug; n1 (%) = Number and percentage of patients experiencing at least one event; n2 = Number of events.

Study TADO

In Study TADO, the frequency and percentage of TEAEs, deaths, SAEs, and study drug discontinuations were summarized for each treatment arm. Hemorrhagic AEs were also summarized by bleeding location and provocation of the event. A summary of AEs in Study TADO is provided in Table 15. No clinically significant differences were observed between treatment groups with respect to SAEs, TEAEs overall, hemorrhagic TEAEs, non-hemorrhagic TEAEs, AEs possibly related to study drug or AEs possibly related to study procedure. A summary of SAEs occurring in ≥2% of subjects is provided in Table 16.

Hemorrhagic SAEs

A total of 2.9% (n=5) of patients in the prasugrel treatment group had ≥1 event compared to 1.8% (n=3) patients in the placebo group. The only serious hemorrhagic event observed in >1 patient in the prasugrel treatment group was epistaxis (2 patients). In both cases, the event was considered by the investigator as possibly related to study drug, and the patient recovered from the event.

Non-hemorrhagic SAEs

A total of 51.2% (n=87) of patients in the prasugrel treatment group had ≥1 serious Non-hemorrhagic event compared to 56.5% (n=96) of patients in the placebo group. Serious non-hemorrhagic events observed in ≥2% of patients in the prasugrel treatment group were SCA with crisis (37.6%), acute chest syndrome (8.8%), anemia (7.6%), malaria (5.9%), hemolysis (2.4%), and pneumonia (2.4%). In evaluating these events, no relevant clinical differences were observed between treatment groups.

Table 15: Study TADO, Summary of Adverse Events

	Prasugrel (N=170) n (%)	Placebo (N=170) n (%)	Total (N=340) n (%)
Death	1 (0.6)	1 (0.6)	2 (0.6)
SAEs	88 (51.8)	96 (56.5)	184 (54.1)
AE which led to study drug discontinuation	6 (3.5)	5 (2.9)	11 (3.2)
TEAEs	159 (93.5)	162 (95.3)	321 (94.4)
Hemorrhagic TEAE	32 (18.8)	33 (19.4)	65 (19.1)
Non-hemorrhagic TEAE	157 (92.4)	162 (95.3)	319 (93.8)
AE possibly related to study drug	12 (7.1)	12 (7.1)	24 (7.1)
AE possibly related to study procedure	5 (2.9)	1 (0.6)	6 (1.8)

Abbreviations: AE=adverse event; N=total number of treated patients; n=number of patients with at least 1 condition; SAE=serious adverse event, TEAE=treatment-emergent adverse event

Table 16: Study TADO, Summary of Serious Adverse Events by Decreasing Frequency in Prasugrel Arm

	Prasugrel (N=170) n (%)	Placebo (N=170) n (%)	Total (N=340) n (%)
Patients with ≥1 SAE	88 (51.8)	96 (56.5)	184 (54.1)
Sickle cell anemia with crisis	64 (37.6)	75 (44.1)	139 (40.9)
Acute chest syndrome	15 (8.8)	10 (5.9)	25 (7.4)
Anemia	13 (7.6)	10 (5.9)	23 (6.8)
Malaria	10 (5.9)	11 (6.5)	21 (6.2)
Hemolysis	4 (2.4)	0	4 (1.2)
Pneumonia	4 (2.4)	3 (1.8)	7 (2.1)
Plasmodium falciparum infection	3 (1.8)	2 (1.2)	5 (1.5)
Back pain	2 (1.2)	0	2 (0.6)
Epistaxis	2 (1.2)	1 (0.6)	3 (0.9)
Headache	2 (1.2)	1 (0.6)	3 (0.9)
Lobar pneumonia	2 (1.2)	1 (0.6)	3 (0.9)
Osteomyelitis (acute)	2 (1.2)	0	2 (0.6)
Pyrexia	2 (1.2)	5 (2.9)	7 (2.1)
Acute tonsillitis	1 (0.6)	3 (1.8)	4 (1.2)

Abbreviations: N=total number of treated patients; n=number of patients with at least 1 condition; SAE=serious adverse event

7.3.3 Dropouts and/or Discontinuations

Study TACX
There were no AEs leading to study drug discontinuation

Study TADO
Six (3.5%) subjects in the prasugrel treatment group discontinued study drug secondary to AEs (epistaxis: n=2, pregnancy: n=2, deep vein thrombosis: n=1, Parvovirus B19 infection: n=1). Five (2.9%) subjects in the placebo group discontinued treatment due to AEs. In Study TADO, there were no clinically relevant differences in study drug discontinuations observed between treatment groups.

7.3.4 Significant Adverse Events

In Study TADO, there were 4 SAEs that were considered by the investigator to be life-threatening; 2 events in patients treated with prasugrel (anaphylactic reaction and parvovirus B19 infection) and 2 events in patients receiving placebo (hypoglycemia and hematoma). The SAEs in the 2 patients treated with prasugrel were not considered related to study drug. The event of anaphylactic reaction coincided with an SAE of anemia, which was treated with a blood transfusion on the same day. Among the SAEs

in the 2 patients receiving placebo, only the hematoma was considered related to study drug.

7.3.5 Submission Specific Primary Safety Concerns

There were no new safety concerns that arose in Study TACX or Study TADO.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study TACX
In Part A, there were no AEs considered to be related to the study drug. One event (vessel puncture site pain) was considered possibly related to a study procedure and was considered mild in severity. In Part B, there were 3 AEs (epistaxis, eyelid bleeding, and middle ear effusion) in 3 patients that were possibly related to study drug.

Hemorrhagic TEAEs
No hemorrhagic AEs were observed in Part A.

In Part B, there were 3 hemorrhagic TEAEs in 3 patients. None of these events required medical intervention. One patient had drops of blood from a stye and another patient had an episode of epistaxis. Both of these events were considered related to study drug by the study investigator. Another patient had a knee abrasion that was not considered related to study drug. All 3 events were classified as mild and the patients recovered

Non-hemorrhagic TEAEs
In Part A of Study TACX, a total of 50% (n=12) of patients reported ≥1 TEAE. The most commonly reported TEAE (sickle cell anemia [SCA] with crisis; n=6; 25%) was related to the underlying medical condition of SCD. In Part B, a total of 11 patients (61.1%) reported ≥1 TEAE. For 6 of 11 patients, the TEAEs reported were related to SCD (including SCA, SCA with crisis, and hypersplenism).

Study TADO

A summary of treatment-emergent adverse events occurring in ≥5% of patients is shown in Table 17.

Table 17: Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients in Either Treatment Group by System Organ Class

	Number (%) of Patients	
System Organ Class Preferred Term	Prasugrel (N=170)	Placebo (N=170)
At least 1 TEAE	159 (93.5)	162 (95.3)
Blood and lymphatic system disorders		
Sickle cell anemia with crisis	104 (61.2)	119 (70.0)
Anemia	15 (8.8)	16 (9.4)
Hemolysis	9 (5.3)	5 (2.9)
Infections and infestations		
Upper respiratory tract infection	37 (21.8)	34 (20.0)
Malaria	36 (21.2)	31 (18.2)
Tonsillitis	16 (9.4)	13 (7.6)
Nasopharyngitis	14 (8.2)	16 (9.4)
Rhinitis	11 (6.5)	4 (2.4)
Urinary tract infection	11 (6.5)	11 (6.5)
Pneumonia	9 (5.3)	4 (2.4)
Acute tonsillitis	5 (2.9)	12 (7.1)
Pharyngitis	4 (2.4)	10 (5.9)
General disorders and administration site conditions		
Pyrexia	34 (20.0)	38 (22.4)
Pain	18 (10.6)	17 (10.0)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	22 (12.9)	20 (11.8)
Acute chest syndrome	15 (8.8)	14 (8.2)
Cough	14 (8.2)	17 (10.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	17 (10.0)*	41 (24.1)
Back pain	15 (8.8)	20 (11.8)
Gastrointestinal disorders		
Abdominal pain	13 (7.6)	16 (9.4)
Gastritis	8 (4.7)	10 (5.9)
Diarrhea	7 (4.1)	10 (5.9)
Vomiting	7 (4.1)	10 (5.9)
Constipation	6 (3.5)	12 (7.1)
Nervous system disorders		
Headache	23 (13.5)	25 (14.7)

Abbreviation: TEAE = treatment-emergent adverse event.

Hemorrhagic TEAEs
During the double-blind treatment period of Study TADO, a total of 18.8% (n=32) of patients in the prasugrel treatment group had ≥1 treatment-emergent hemorrhagic event compared to 19.4% (n=33) of patients in the placebo group. A total of 67 events were reported in the prasugrel treatment group and 44 events were reported in the placebo group. Treatment-emergent hemorrhagic events reported in ≥1% of patients in the prasugrel treatment group were epistaxis (12.9%), laceration (1.8%), hematoma (1.2%), and hematuria (1.2%; TADO CSR). A total of 6.5% (n=11) of patients in the prasugrel treatment group experienced ≥1 hemorrhagic event requiring intervention compared to 4.7% (n=8) of patients in the placebo group, and no difference was observed between treatment groups. The most frequently reported bleeding event location for patients in the prasugrel treatment group was the nose (prasugrel: 23 patients; placebo: 20 patients). For the majority of patients in the prasugrel treatment group who had ≥1 hemorrhagic event, the event was categorized as spontaneous.

In evaluating hemorrhagic events, no clinically relevant differences were observed between the prasugrel treatment group and the placebo group with respect to TEAEs, AEs possibly related to study drug, or AEs possibly related to study procedure.

Non-hemorrhagic TEAEs
A total of 93.5% (n=159) of patients in the prasugrel treatment group had ≥1 non-hemorrhagic treatment-emergent event compared to 95.3% (n=162) of patients in the placebo group, and no difference was observed between treatment groups. Non-hemorrhagic TEAEs observed in ≥10% of patients in the prasugrel treatment group were SCA with crisis (61.2%), upper respiratory tract infection (21.8%), malaria (21.2%), pyrexia (20.0%), headache (13.5%), pain (10.6%), and pain in extremity (10.0%).

7.4.2 Laboratory Findings

Study TACX
Most patients had low baseline values for hemoglobin, hematocrit, and erythrocyte count, and high baseline values for reticulocyte count. Any treatment-emergent abnormalities were generally consistent with what would be expected in patients with SCD, for example, elevated lactate dehydrogenase (LDH) and elevated bilirubin.
No other clinically significant changes in hematology, clinical chemistry, or urinalysis parameters were observed during the study.

Study TADO
In evaluating mean change from baseline to endpoint in blood chemistry, hematology, and urinalysis parameters in Study TADO, no significant differences were observed between the prasugrel treatment group and the placebo group. For treatment-emergent abnormal laboratory results for hematology, a higher proportion of patients in the prasugrel treatment group (42.2%; n=54) had a treatment-emergent abnormal low mean platelet volume value at least 1 time post-baseline compared to patients in the placebo

group (27.5%; n=36). No other differences were observed between treatment groups for hematology parameters.

7.4.3 Vital Signs

Vital signs parameters were not summarized for Study TACX.

Blood Pressure
In the repeated measures analysis of mean change in systolic blood pressure (BP), the overall mean change observed in the prasugrel treatment group greater compared to the placebo group (2.0 vs. -0.4). A small mean decrease in systolic BP was observed in the placebo group, while a small mean increase from baseline was observed in the prasugrel treatment group. No difference in diastolic BP was observed between treatment groups.

Heart Rate
In evaluating treatment-emergent abnormal vital signs, a higher proportion of patients in the prasugrel treatment group had ≥1 treatment-emergent high value for pulse post-baseline compared to the placebo group (6.0% vs. 1.2%). However, there was no difference between treatment groups in the mean change from baseline to endpoint heart rate.

Reviewer Comment: *The slight increase in systolic blood pressure in patients receiving prasugrel is unlikely to be clinically significant. Of note, no significant effect of prasugrel on BP has been observed in studies of adult patients with acute coronary syndrome.*

7.4.4 Electrocardiograms (ECGs)

ECGs were not routinely collected as part of these studies.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Not applicable because prasugrel is a small molecule.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No evaluations were conducted evaluating the dose dependency of adverse events.

7.5.2 Time Dependency for Adverse Events

Safety data presented for Study TADO focused on events that occurred during the on-treatment period. The on-treatment period was defined as the period from the first dose of study drug through the earliest date among the following: 10 days after the last dose of double blind treatment; first dose date of open-label treatment if applicable.

There were no clinically significant differences observed between treatment groups with respect to AEs. Therefore, there were no conclusions made regarding the time to onset of adverse events or the duration of events.

7.5.3 Drug-Demographic Interactions

There were no evident interactions between drug safety and age, gender, and weight.

7.5.4 Drug-Disease Interactions

No relevant evaluation was completed.

7.5.5 Drug-Drug Interactions

In pediatric patients with SCD in Study TADO, no evidence of an adverse interaction has been observed between prasugrel and concomitant treatment with NSAIDs or hydroxyurea. No apparent PD interaction was observed between hydroxyurea and prasugrel in Study TADO (Study TADO PD Report). No additional formal drug interaction studies have been performed for this submission.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No malignancies were reported.

Reviewer Comment: *The subjects enrolled in this study were not followed long enough to evaluate for the development of malignancy. However, there is no clinical data to suggest an increased risk of malignancy with prasugrel use.*

7.6.2 Human Reproduction and Pregnancy Data

Pregnant and breastfeeding women were excluded from clinical studies for this submission. However, 2 patients in the prasugrel group became pregnant during Study TADO. Both patients were discontinued from study drug due to pregnancy. In both cases, the outcome was elective termination of the pregnancy.

Studies of prasugrel in pregnant or lactating women have not been conducted, and the safety of prasugrel in pregnant or lactating women has not been established.

7.6.3 Pediatrics and Assessment of Effects on Growth

No relevant evaluations were completed

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In Study TACX, no patients appear to have taken >120% of the prescribed study drug dose based on study drug dispensed and returned over the time between visits. During the double-blind treatment period of Study TADO, a total of 14 patients (prasugrel: n=7; placebo: n=7) appear to have taken >120% of the prescribed study drug dose based on information regarding study drug dispensed and returned. Among these patients, a total of 2 patients in the prasugrel treatment group each had an epistaxis event, one of which was an SAE.

No TEAEs attributed to prasugrel abuse have been reported in Study TACX or Study TADO. Specific data regarding rebound and withdrawal in pediatric patients are not available.

Prasugrel does not appear to have drug abuse potential because it does not appear to have CNS effects.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Not applicable because no indication is sought.

9 Appendices

9.1 Literature Review/References

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4. Brousseau DC, et al. The number of people with sickle-cell disease in the United States: national and state estimates. *Am J Hematol.* 2010;85:77-78.
5. Kanter J, et al. Management of sickle cell disease from childhood through adulthood. *Blood Reviews.* 2013;27(6): 279-287.
6. Platt OS, et al. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med.*1991;325(1):11-16.
7. Kaul DK, Tsai HM, Liu XD, Nakada MT, Nagel RL, Coller BS. Monoclonal antibodies to alphaVbeta3 (7E3 and LM609) inhibit sickle red blood cell-endothelium interactions induced by platelet-activating factor. *Blood.* 2000;95(2):368-374.
8. Lee SP, Ataga KI, Orringer EP, Phillips DR, Parise LV. Biologically active CD40 ligand is elevated in sickle cell anemia: potential role for platelet-mediated inflammation. *Arterioscler Thromb Vasc Biol*. 2006;26(7):1626-1631.
9. Amin MA, Amin AP, Kulkarni HR. Platelet distribution width (PDW) is increased in vasoocclusive crisis in sickle cell disease. *Ann Hematol*. 2004;83(6):331-335.
10. Osamo NO, Photiades DP, Famodu AA. Therapeutic effect of aspirin in sickle cell anaemia. *Acta Haemat.* 1981;66(2):102-107.

9.2 Labeling Recommendations

Proposed labeling changes were included within the sNDA. Modifications were made to section 8.4 to include the following:

Safety and effectiveness in pediatric patients have not been established. In a randomized, placebo-controlled trial, the primary objective of reducing the rate of vaso-occlusive crisis (painful crisis or acute chest syndrome) in pediatric patients, aged 2 to less than 18 years, with sickle cell anemia was not met.

9.3 Advisory Committee Meeting

An advisory committee was not convened for this application because no indication was sought.

9.4 Pediatric Written Request

NDA 022307

WRITTEN REQUEST – AMENDMENT 2

Eli Lilly and Company
Attention: Anindita Sen, MS, PhD
Director, Global Regulatory Affairs – Bio Medicines
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Sen:

Please refer to your correspondence dated April 20, 2015, requesting changes to FDA's December 19, 2012, Written Request for pediatric studies for EFFIENT® (prasugrel).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request with the specific changes shown. All other terms stated in our Written Request issued on December 19, 2012, and as amended on July 24, 2013, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Patients to be Studied:

Study 2 (TADO):

Age group in which study will be performed: patients with SCD ages ≥2 and <18 years of age. The following 3 age groups and numbers of patients will be studied:

- ≥2 to <6 years: At least ~~50~~21 patients (approximately ~~25~~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 endpoints:*

Major secondary efficacy endpoints will include the following:

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 acute chest syndrome~~
~~5~~4. Reduction in the rate of blood transfusion for complications of SCD
~~6~~5. Reduction in the intensity of sickle cell-related pain as recorded in patient pain diaries
~~7~~6. Use of analgesics as measured in patient pain diaries
7. Reduction in the rate of acute chest syndrome
8. School attendance as measured in patient pain diaries

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

  Study 2 must have a detailed statistical plan. A preliminary statistical analysis plan (SAP) must be submitted for comment prior to initiating the efficacy and safety study~~, and you must obtain agreement on the final statistical plan prior to 25% enrollment~~. Agreement on the final SAP must be achieved prior to the submission database lock.

Regarding the TADO Study, we also find your proposal to exclude the modified FACES Pain Scale-Revised (FPS-R) data of patients aged 4 to 6 year from the primary analyses of the patient diary data is acceptable. You should amend the protocol accordingly for the study; however, no amendment to the WR is required. Also, your proposal to change the order for analysis of the secondary endpoints such that "reduction in the rate of acute chest syndrome" will be #7 instead of #4 in the hierarchy for analysis in the study is acceptable and you should amend the protocol accordingly for the study. Note that although no amendment to the WR is required for this change, the list of secondary endpoints in the WR is revised for consistency.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated December 19, 2012, as amended by this letter and by previous amendment dated July 24, 2013, must be submitted to the Agency on or before January 14, 2016, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) or supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission EFFIENT® (prasugrel), via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, 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:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- 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/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Linhua Tzeng-Goh, Regulatory Project Manager, at 240-402-4619.

Sincerely,

{See appended electronic signature page}

Gregory H. Reaman, MD
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

9.5 Pediatric Exclusivity Determination

The clinical trials reviewed in this sNDA, TACX and TADO, were conducted in response to a Written Request provided by the FDA. The Division of Hematology Products was of the opinion that the Applicant met or exceeded all aspects of the Written Request, and the comparison of the Written Request and information provided in the trials is presented in Table 18. This comparison was based on the final Pediatric Written Request dated July 21, 2015.. The Division was notified via email on May 23, 2016 that the Pediatric Exclusivity Board had reviewed the Exclusivity Determination and agrees that Pediatric Exclusivity will be granted. Formal notification of this decision is pending at the time of this review.

Table 18: Pediatric Exclusivity Determination

Written Request Items	Information Submitted/Sponsor's Response
Types of studies/Study Design: Non-clinical Studies: Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described below. <u>Study 1 (TACX):</u> A phase 2 PK and PD dose escalation and dose-ranging (Part A) and dose tolerability (Part B) study of prasugrel in pediatric patients with SCD. A cohort of older children (8 to<18 years of age) must be evaluated before enrollment of younger children. <u>Study 2 (TADO):</u> A phase 3, randomized, double-blind, placebo-controlled trial in which patients are randomized 1:1 to receive either prasugrel or placebo for at least 9 months and up to a maximum of 24 months. Study 1 (TACX) must be completed before, and used to inform dosing in the efficacy trial (TADO).	**Types of studies:** <u>Study 1 (TACX):</u> A phase 2, open-label, adaptive design, multicenter, dose escalation and dose-ranging PK/PD study in pediatric patients with SCD. A cohort of older children (age 8 to <18 years) was conducted before enrollment of children < 8 years. <u>Study 2 (TADO):</u> A phase 3, randomized, double-blind, placebo-controlled, efficacy and safety comparison of prasugrel in pediatric patients with sickle cell disease. Patients were randomized 1:1 to receive either prasugrel or placebo for a minimum of 9 months to a maximum of 24 months. Study 1 (TACX) was completed before, and used to inform the dosing in, the efficacy trial (TADO); however, inter-patient variability in platelet inhibition was high, which led to the dose-titration strategy used in TADO. **Review Division Comments:** The types of studies conducted were the same as the

	WR and are acceptable to the Division. The Applicant met the requirements of the WR.
Indication(s) to be studied: Prasugrel for the prevention of vaso-occlusive crises (VOC) in pediatric patients with sickle cell disease (SCD) 2 to <18 years of age.	**Indication(s) studied:** Prasugrel for the prevention of vaso-occlusive crises (VOC) in pediatric patients with sickle cell disease (SCD) 2 <18 years of age. **Review Division Comments:** The Applicant met the criteria specified in the WR.
Objective of each study: <u>Study 1 (TACX):</u> To identify the dose(s) of prasugrel to be studied in study 2 (TADO) and to assess the tolerability of prasugrel in pediatric patients with SCD <u>Study 2 (TADO):</u> To assess the efficacy and safety of prasugrel for the reduction of VOC in pediatric patients with SCD	Objectives of each study: <u>Study 1 (TACX):</u> Primary Objective: • To characterize the relationship between prasugrel dose, exposure to prasugrel active metabolite (Pras-AM), and platelet inhibition in pediatric patients with SCD. Secondary Objectives: • Evaluate, in the pediatric SCD population, the adequacy of a correlation model to estimate the Pras-AM concentration from the measured concentration(s) of its inactive metabolite(s). • Assess the short-term efficacy, safety, and tolerability of prasugrel in pediatric patients with SCD. **Review Division Comments:** The objectives for Study 1 (TACX) while slightly different in language did match the objectives requested by the Agency in the WR. The Agency and the Applicant agreed to use a dose exposure analysis (platelet inhibition) as the target for dose selection. Assessment of the tolerability of prasugrel in pediatric patients with SCD was included as a secondary objective. The Division concludes that these objectives meet the goals of the WR, as Study 1 (TACX) was used to inform the dosing to be studied in study 2 (TADO), and tolerability was assessed using the following safety outcome variables: • Hemorrhagic events requiring medical intervention • Treatment-emergent adverse events (TEAEs) and hemorrhagic TEAEs

	• Study drug discontinuation due to adverse events (AEs) or hemorrhagic AEs • Clinical laboratory results Study 2 (TADO): Primary Objective: 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 or acute chest syndrome. **Review Division Comments:** The wording of the primary objective as written in the protocol did not include assessment of safety as stated in the WR. However, the study collected adequate safety information. This is acceptable to the Division. The Applicant met the requirements of the WR.
Age group and population in which study will be performed: Study 1 (TACX): This study should enroll pediatric patients with SCD ages ≥ 2 to <18 years old. Age groups to be studied: • ≥ 2 to < 6 years: At least 7 patients must be enrolled, and at least 5 must complete the study • ≥ 6 to < 12 years: At least 12 patients must be enrolled, and at least 10 must complete the study. • ≥ 12 to < 18 years: At least 12 patients must be enrolled, and at least 10 must complete the study. Study 2 (TADO): This study should enroll pediatric patients with SCD ages ≥ 2 to < 18 years old. Age groups to be studied: • ≥ 2 to < 6 years: At least 21 patients (approx. 10 in each treatment group) 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 (approx. 35 in each blinded treatment group) must be enrolled, and complete at least 9 months of	**Age group and population in which study was performed:** Study 1 (TACX): This study enrolled pediatric patients with SCD ages ≥ 2 to <18 years old. Age groups studied and number of patients enrolled: • ≥ 2 to < 6 years: 7 enrolled, 5 completed • ≥ 6 to < 12 years: 14 enrolled, 12 completed • ≥ 12 to < 18 years: 12 enrolled, 12 completed Study 2 (TADO): This study enrolled pediatric patients with SCD ages ≥ 2 to <18 years old. Age groups studied and number of patients enrolled: • ≥ 2 to < 6 years: 23 patients (12 prasugrel, 11 placebo) completed the 9 month visit. • ≥ 6 to < 12 years: 126 patients (62 prasugrel, 64 placebo) completed the 9 month visit. • ≥ 12 to < 18 years: 126 patients (61 prasugrel, 65 placebo) completed the 9 month visit. **Review Division Comments:** The language used in the WR was only intended to

the double-blind treatment period. • ≥ 12 to < 18 years: At least 70 patients (approx. 35 in each blinded treatment group) must be enrolled, and complete at least 9 months of the double-blind treatment period.	ensure enrollment of a sufficient number of subjects to adequately estimate PK/PD parameters (Study 1) and efficacy (Study 2). The Division believes that the Applicant not only fulfilled, but exceeded the requirement (in the WR) of enrolling a sufficient number of subjects.

Number of patients to be studied or power of study to be achieved:	**Number of patients studied or power achieved:**
Study 1 (TACX): This study should enroll at least 33 pediatric patients with SCD. A minimum of 29 patients must complete the study. Study 2 (TADO): At least 204 pediatric patients with SCD should be enrolled and complete at least 9 months of the double-blind treatment period. Study 1 and Study 2: Must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If unable to enroll an adequate number of these patients, the applicant should provide a description of the effort to do so and an explanation for why they were unsuccessful. Study 1 and Study 2: The collection of PK data 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 with 80% power for prasugrel in each age group. This means, a minimum of 10 patients in each age group of ≥ 2 to <12 years and ≥ 12 to <18 years must be sampled for PK in both studies combined. This requirement may be met by collecting PK in either study alone or throughout	Study 1 (TACX): • 33 pediatric patients (ages 4 to <18 years) were enrolled (24 in Part A, 18 in Part B), and 29 completed the study. Nine of the patients in Part B had previously participated in Part A. • Ethnic and racial minorities: 32 patients listed as "Black or African American, not Hispanic or Latino". One patient listed as "Native Hawaiian or Other Hispanic or Latino Pacific Islander". Study 2 (TADO): • At the time of data cutoff, 275 pediatric patients with SCD had enrolled and completed the 9-month visit in the double-blind treatment period. 259 patients had at least 270 days of exposure to the study drug. • Ethnic and racial minorities: Of the 341 patients in the ITT population, 34% identified as "white", 65% as "Black or African American", and 1% as "multiple". Study 1 and Study 2: PK data was collected from 145 patients enrolled in Study 1 (n=33) or Study 2 (n=112). The PK parameters were estimated using a non-linear mixed-effects model. This analysis included 21 patients age 2 to <6 years, 66 patients age 6 to <12 years, and 58 patients 12 to <18 years. **Review Division Comments:** The Applicant collected PK samples from more than the minimum number of patients required in the WR

both studies.	for both age groups. This Applicant met the minimum requirements of the WR.
Entry criteria: Patients with SCD 2 to < 18 years of age. The remainder of the entry criteria was not specified in the WR.	**Entry criteria used:** Study 1 (TACX): • Male and female patients with SCD (homozygous S [HbSS] and heterozygous hemoglobin S beta zero [HbS β^0] genotypes) • Body weight ≥ 12 kg • Age 2 to <18 years of age • Patients ≤ 16 years of age must have had a transcranial Doppler within the last year • Patients on hydroxyurea had to be on a stable dose for 60 days prior to enrollment without signs of hematologic toxicity at screening • Parent/legal representative in competent mental condition to provide written informed consent. Study 2 (TADO): • Male and female patients with SCD (homozygous S [HbSS] and heterozygous hemoglobin S beta zero [HbS β^0]) • Age 2 to < 18 years of age • ≥ 2 episodes of VOC in the past year • Body weight ≥ 19 kg (Addendum: TADO(3) allowed enrollment of patients weighing ≥12 kg at sites that were able to accommodate cold storage and handling of the 0.5 mg prasugrel tablet. **Review Division Comments:** The Applicant met the criteria specified in the WR.
Study design: Study 1 (TACX): A Phase 2 PK and PD dose escalation and dose-ranging (Part A) and dose tolerability (Part B) study.	**Study design used:** Study 1 (TACX): This was a Phase 2, open-label, multicenter, PK and PD study of prasugrel in 33 pediatric patients with SCD. The study was conducted in 2 parts (Parts A and B). Part A (dose escalation): An open-label, adaptive-design trial in which patients received up to 3 single doses of prasugrel separated by 14 ± 4 days between each dose. Escalating single doses were administered between

Study 2 (TADO): A Phase 3 randomized, double-blind, placebo-controlled trial in which patients are randomized 1:1 to receive either prasugrel or placebo for at least 9 months and up to a maximum of 24 months. Evaluation of all patients must continue through a follow-up period of 4 weeks after last dose of study drug.	0.03 to 0.60 mg/kg, which corresponded to absolute doses of 0.9 to 48 mg. Part B (dose tolerability): Patients received once-daily doses of prasugrel over 2 dosing periods, each lasting 14 ± 4 days. The initial dose level was 0.08 mg/kg, which was predicted to produce a mean of approximately 30% platelet inhibition at steady-state based on dose- and exposure-response relationships observed using the data from Part A in conjunction with data from previous studies in the adult acute chest syndrome population. Platelet inhibition was measured 4 hours after the initial dose. Based on platelet inhibition for each individual patient, patients were then assigned to receive either 0.08 or 0.06 mg/kg for the first dosing period. Prasugrel was taken at home daily thereafter. The second dose level was chosen based on an individual patient's platelet inhibition at steady-state following the first dosing period. Patients who received 0.08 mg/kg during the first dosing period were either up titrated to a 0.12 mg/kg dose level or down titrated to a 0.06 mg/kg dose level to target a range of 30%-50% platelet inhibition for the second dosing period. Patients who received 0.06 mg/kg during the first dosing period were assigned to 0.08 mg/kg during the second dosing period. One patient who was noncompliant during the first dosing period was reassigned to 0.08 mg/kg during the second dosing period. Dose tolerability was assessed using the following safety variables: • Hemorrhagic events requiring medical intervention • Treatment-emergent adverse events (TEAEs) and hemorrhagic TEAEs • Study drug discontinuation due to adverse events (AEs) or hemorrhagic AEs • Clinical laboratory results Study 2 (TADO): A Phase 3, double-blind, placebo-controlled, randomized, parallel group, multinational study in outpatient pediatric patients with SCD. During the double-blind treatment period, patients were titrated to once-daily doses of either placebo or prasugrel for a minimum of 9 months to a maximum of 24

Study 1 and Study 2: The collection of PK data 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 with 80% power for prasugrel in each age group. This means, a minimum of 10 patients in each age group of ≥ 2 to <12 years and ≥ 12 to <18 years must be sampled for pharmacokinetics in studies TACX and TADO combined. This requirement may be met by collecting PK in either study alone or throughout both studies. PK samples must be collected through approaches such as rich sampling or optimal sparse sampling. Such data must then be appropriately analyzed using methods such as mixed effects modeling or non-compartmental analysis.	months. There was an optional open-label extension (OLE) period planned. However, the OLE period of this study was not fully implemented due to the Applicant decision to discontinue the study for failure to meet the primary or secondary efficacy endpoints. The double-blind phase of the study was ongoing at the time of the submission database lock (SDBL). Patients were discontinued from the study following the Applicant decision to stop the trial. Data collected following SDBL will be provided in the 120-day safety update, which includes the follow-up of patients at least 4 weeks off study drug. **Review Division Comments** The study designs for Study 1 (TACX) and Study 2 (TADO) were acceptable to the Division and met the requirements of the WR. Study 1 and Study 2: PK data was collected from 145 patients enrolled in Study 1 (n=33) or Study 2 (n=112). The PK parameters were estimated using a non-linear mixed-effects model. This analysis included 21 patients age 2 to <6 years, 66 patients age 6 to <12 years, and 58 patients 12 to <18 years. PK samples were collected using a rich sampling approach in Study 1 and rich and sparse sampling approaches in Study 2. In addition, a non-compartmental model was used to analyze the PK data collected from both studies. **Review Division Comments** The PK sampling and analysis plan for Study 1 (TACX) and Study 2 (TADO) met the requirements of the WR.
Clinical endpoints: PK/PD Endpoints (Study 1 and Study 2): Prasugrel apparent clearance and volume of distribution must be determined from either or both Study 1 and Study 2 Data from study 1 (TACX) and Study 2 (TADO) must be used to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure response relationships for measures of	**Clinical endpoints used:** PK/PD Endpoints (Study 1 and Study 2): The apparent volume of distribution is 52 L and the apparent clearance is 177 L/hr (Report No. H7T-NC-TADO, Table 8.3) for prasugrel's active metabolite based on the population PK model. This analysis included data from both Study 1 (TACX) and Study 2 (TADO). The Applicant explored exposure-response

safety and effectiveness. The Review Division must agree on the PD endpoint(s) to be used in Study 1 and Study 2).	relationships for effectiveness (evaluated as the rate of VOC/year in Study TADO) and safety (evaluated as the number of bleeding events requiring medical intervention in Study TADO). No discernable relationship between either of these endpoints and exposure to prasugrel's active metabolite was observed. Data collected from Study TADO was used to explore these relationships. Additionally, dose- and exposure-response relationships were explored in Study 1 (TACX) to support the proposed dose for Study 2 (TADO). **Review Division Comments** The PK/PD endpoints for Study 1 (TACX) and Study 2 (TADO) met the requirements of the WR.
Safety Endpoints (Study 1 and Study 2): • Assessment of the incidence of hemorrhagic events requiring medical intervention (defined as medical attention from a trained medical professional that results in therapy or further investigation). • Assessment of the incidence of hemorrhagic treatment-emergent adverse events (TEAEs) • Assessment of the tolerability of prasugrel compared to placebo as measured by the rate of study drug discontinuation due to hemorrhagic and non-hemorrhagic TEAEs	Safety Variables (Study 1): • Hemorrhagic events requiring medical intervention • Treatment-emergent adverse events (TEAEs) and hemorrhagic TEAEs • Study drug discontinuation due to adverse events (AEs) or hemorrhagic AEs • Clinical laboratory results Safety Objectives (Study 2): To assess the safety of prasugrel compared to placebo in pediatric patients with SCD as measured by: • The incidence of hemorrhagic events requiring medical intervention, including hemorrhagic stroke • The incidence of hemorrhagic and non-hemorrhagic treatment-emergent adverse events (TEAEs) • The tolerability of prasugrel compared to placebo as measured by rate of permanent study drug discontinuation due to hemorrhagic and non-hemorrhagic TEAEs **Review Division Comments** The Applicant included assessment of both hemorrhagic and non-hemorrhagic TEAEs, which exceeds what was provided in the WR.

Efficacy Endpoints (Study 2): The primary efficacy endpoint will be the reduction in the rate of VOC, which will be a composite of the following: pain crisis or acute chest syndrome. Pain crisis will be defined as a new onset of pain that lasts at least 2 hours for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids or ketorolac, or other analgesics prescribed by a health care provider in a medical setting such as a hospital, clinic, emergency room visit, or telephone management. Acute chest syndrome will be defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest x-ray. Major Secondary Efficacy Endpoints: • Reduction in the rate of sickle cell-related pain as recorded in patient pain diaries* • Reduction in the rate of hospitalization for VOC • Reduction in the rate of painful crisis • Reduction in the rate of blood transfusion for complications of SCD • Reduction in the intensity of sickle cell-related pain as recorded in patient pain diaries • Use of analgesics as measured in patient pain diaries • Reduction in the rate of acute chest syndrome • School attendance as measured in patient pain diaries. * The pain diary to be used in this study must include a validated pain scale, to be submitted along with the study protocol for review by the Agency prior to the deadline.	Efficacy Endpoints (Study 2): Primary Objective: The reduction in the rate of VOC, which is a composite endpoint of painful crisis or acute chest syndrome. A painful crisis was defined as an onset of moderate to severe pain that lasted for 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. Acute chest syndrome was defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest x-ray. Major Secondary Efficacy Objectives: 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: • Reduction in the rate of sickle cell-related pain as recorded in patient pain diaries* • Reduction in the rate of hospitalization for VOC • Reduction in the rate of painful crisis • Reduction in the rate of blood transfusion for complications of SCD • Reduction in the intensity of sickle cell-related pain as recorded in patient pain diaries • Use of analgesics as recorded in patient pain diaries • Reduction in the rate of acute chest syndrome • Reduction in school absence secondary to sickle-cell-related pain as recorded in patient pain diaries. *The pain scale used in TADO was the modified FACES Pain Scale-Revised (FPS-R), which is a validated pain scale. **Review Division Comments:** School attendance and reduction in school absence are capturing the same concept. The Division finds this acceptable. The Applicant met the requirements of the WR.

	Teleconference with the FDA on March 19, 2014 to discuss assessment of pain in 4-5 year olds. Agreement was reached to exclude 4-5 year olds from the primary analysis of the monthly pain rating and pain intensity measured using FPS-R. On March 31, 2015, a Type C meeting was held between the Sponsor and the FDA. Agreement was reached to exclude patients 4-6 years from primary analysis of monthly pain rating and pain intensity based on modified FPS-R.

Timing of assessments: • The PK/PD study (TACX) must be completed before, and used to inform dosing in the efficacy trial (TADO). • Results of trial TACX and relevant adult data used to propose pediatric dose(s) must be submitted along with the final protocol for TADO before initiation of trial TADO. • Justification of the proposed dose and trial design for TADO must be agreed upon by the Agency before initiation of the trial. This may require additional dose exploration if the available information is not adequate.	**Timing of assessments:** • Study 1 (TACX) was completed on 11/1/2012 and Study 2 (TADO) began enrollment on 5/13/2013. The dose- and exposure-response relationships observed in Study 1 were used to inform dosing for Study 2. • The TACX data summary and the TADO protocol were submitted with EOP2 Briefing Document (BD) on 12/18/2012. The TAEK data summary was also submitted with the EOP2 BD. The EOP2 meeting was held on 1/18/2013 and the EOP2 meeting minutes state: "The Agency acknowledged that the EOP2 BD is adequate to fulfill the requirement that TACX results be submitted prior to the initiation of study TADO". TACX CSR was submitted separately on 5/7/2013. TADO first patient visit was 4/25/2013. • EOP2 preliminary comments were received by the Sponsor on 1/11/2013. EOP2 meeting minutes state, "The planned starting dose and titration strategy appear to be reasonable". **Review Division Comments:** The Division concludes that the Applicant met the time line provided in the WR and fulfilled this requirement.

Data Monitoring Committee: Study 1 (TACX): At a minimum, an external, independent safety reviewer must be utilized in Study TACX for periodic review of study data. Study 2 (TADO): A data safety monitoring board or committee (DSMB/DSMC) must be utilized in Study TADO for periodic review of study data and for the recommendation of changes as needed.	**Data Monitoring Committee:** Study 1 (TACX): The WR was sent by the Agency on 12/19/2012, which was after the completion of Study TACX (completion date: 11/1/2012). No DSMB/DSMC was used in Study TACX, which was designed as a phase 2 PK-PD study. There was ongoing oversight of the events of the study. The study was open-label. Thus, the PI was monitoring the safety of the treated subjects and fell under the normal monitoring activities. There were no deaths reported during the study and no AEs leading to study drug discontinuation. In Part A, there were no hemorrhagic AEs or AEs considered to be related to the study drug. In part B, there were 3 AEs (epistaxis, eyelid bleeding and middle ear effusion) that were possibly related to study drug. All 3 events were mild in severity. **Review Division Comments:** The Division intended for the safety reviewer to be external to the Sponsor/Applicant. The PI who monitored the safety of this trial is acceptable as an external reviewer. The Applicant met the requirements of the WR. Study 2 (TADO): There was an external DMC with a Charter in place describing the boundaries for safety to be monitored for the study. Additionally, there were standard periodic blinded safety reviews by physicians of Lilly and (b) (4) safety groups responsible for this study.
Drug information: • **Route of administration:** Study drug will be administered orally (PO), per the labeled route of administration (PO) for prasugrel • **Regimen:** Dosing and regimen for Study 2 (TADO) must be supported by the results in Study 1 (TACX) • **Formulation:** An age-appropriate formulation must be used	**Drug information:** • **Route of administration:** The study drug was administered orally (PO) per the labeled route of administration (PO) for prasugrel • **Regimen:** The results of Study 1 informed the dose selection and dose-titration strategy used in Study 2. • **Formulation:** (b) (4) Dosage: Study 1 (TACX): Part A: Prasugrel ranging from 0.03-0.60 mg/kg

	(absolute doses of 0.9 to 48 mg) up to 3 single oral doses each separated by 14 ± 4 days. Part B: Prasugrel at 0.06, 0.08 or 0.12 mg/kg (absolute doses of 1-7 mg) once daily for 14 ± 4 days at 2 (out of 3 possible) dose levels. The dose was based on PD responses of individual patients (initial dose targeted a range of 30% platelet inhibition; second dose targeted a range of 30-50% platelet inhibition). <u>Study 2 (TADO):</u> All patients received prasugrel 0.08 mg/kg or placebo at Visit 1 for 14 ± 4 days. Doses adjusted, if necessary, during the dose-titration phase (Days 14-45) to achieve target level of platelet inhibition. Minimum possible dose was 0.04 mg/kg/day. Maximum allowed dose was 0.12 mg/kg/day (no more than 10 mg absolute dose).
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. In accordance with section 505A(e)(2), 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 approval); 2. the Agency grants pediatric exclusivity, including publishing 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 indicating you have not marketed the new pediatric formulation. 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 prepared 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	Two different age-appropriate flavored [redacted] were developed and used in Study1 (TACX, ODT) and in Study 2 (TADO, ODT3). [redacted]. **Review Division Comment:** The Applicant did not develop a commercially marketable formulation [redacted] The Division finds this acceptable. The Applicant met the requirements of the WR.

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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information. Bioavailability: Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.	Bioavailability: • (b) (4) • • **Review Division Comments:** The study performed meets the requirements of the WR.
Drug specific safety concerns: Study 1 and 2: Given the known risk of bleeding associated with prasugrel administration, (a) the proposed pediatric trials must exclude any SCD patient considered to be at high risk for stroke, using currently accepted clinical criteria, and (b) patients must be adequately monitored for bleeding complications during prasugrel treatment and for the duration of the study period. Safety endpoints will include	**Drug specific safety concerns evaluated:** Study 1 and 2: Transcranial Doppler (TCD) studies were used to identify patients who were most at risk of stroke. Patients who had an abnormal or conditional TCD within the last year were excluded. Additional exclusion criteria included any clinical findings that, in the judgment of the investigator, are associated with an increased risk of bleeding, recent surgery (within 30 days prior to screening). Patients who

assessment of the following: • Incidence of hemorrhagic events requiring medical intervention (defined as medical attention, from a trained medical professional, that results in therapy or further investigation • Incidence of hemorrhagic TEAEs • Rate of study drug discontinuation due to hemorrhagic and non-hemorrhagic TEAEs	were scheduled to undergo surgery within 60 days of enrollment were also excluded. Prior and concomitant therapy exclusion criteria included packed red blood cell or whole blood transfusion therapy within 30 days prior to dosing, any nonsteroidal anti-inflammatory drug use within 5 days prior to screening, any aspirin, warfarin, thienopyridine, or other antiplatelet medication use within 10 days prior to dosing, and anticipated use of aspirin, warfarin, thienopyridine, or other antiplatelet medication during the study period. Safety endpoints included: • The incidence of hemorrhagic events requiring medical intervention, including hemorrhagic stroke • The incidence of hemorrhagic and non-hemorrhagic treatment-emergent adverse events (TEAEs) • Rate of study drug discontinuation due to hemorrhagic and non-hemorrhagic TEAEs **Review Division Comments:** The Applicant met the criteria specified in the WR.
Extraordinary results: In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this WR. If you believe this is the case, you must contact the Agency to seen an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.	**Extraordinary results:** There were no new safety findings. (b) (4) **Review Division Comments:** The Applicant met the criteria specified in the WR.
Statistical information (statistical analyses of the data to be performed): <u>Study 1 (TACX):</u> Statistical information was not specified in the	**Statistical information (statistical analyses of the data to be performed):** <u>Study 1 (TACX):</u>

WR. Study 2 (TADO): Study 2 must have a detailed statistical plan. A preliminary statistical analysis plan (SAP) must be submitted for comment prior to initiating the efficacy and safety study. The agreement on the final SAP must be achieved prior to submission database lock. The study 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). You must obtain agreement with the Division with regard to the treatment effect prior to initiating the study. For the purpose of satisfying the WR, this treatment effect might, for example, be defined as a 35% reduction in the VOC rate. To ensure that the study is adequately powered, you should obtain an estimate of the overall event rate from an interim analysis, and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. You may estimate the overall event rate based on a blinded and pooled analysis of all groups, in which case no alpha-spending adjustment is required for this interim analysis. If, however, you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment would be required.	PK/PD: The PK parameters for Pras-AM were estimated using both non-compartmental analysis (NCA) and population analysis. Dose- and exposure-response relationship were explored to assess the relationship between dose or Pras-AM exposures and clinically relevant measure(s) of platelet inhibition (VN and VASP) Safety: Safety endpoints were summarized using descriptive statistics. Efficacy: In Part B, the responses for each question related to incidence and severity of patients' pain were reported as the percentage of patients answering "yes" and were summarized by dose. A summary of each question across doses was done for Part B and presented as the possible combinations of responses for a patient at baseline and each dose. The number and percentage of each combination was presented. Study 2 (TADO): Alignment on SAP was achieved on 8/25/2015 (via email from FDA RPM) prior to submission database lock (8/31/2015). The study was designed with 85% statistical power to detect a 35% relative rate reduction with prasugrel. All tests of treatment effects were conducted at a 2-sided alpha level of 0.05, unless otherwise stated. To ensure that the study was adequately powered, a blinded interim analysis was conducted by Lilly to obtain an assessment of the overall event rate of the primary endpoint after 75% of projected enrollment (approximately 165 patients). The study had sufficient events and did not require an adjustment to the sample size. Efficacy: Primary efficacy endpoint: The time to recurrent episodes of VOC was analyzed by the Andersen-Gill model with treatment as an independent variable and important 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. The

	within-patient interdependency was accounted for by using the robust standard error estimates for the estimated regression parameters. Major secondary efficacy endpoints: A fixed-sequence gatekeeping testing strategy for the major secondary efficacy objectives was to be implemented to control the overall type I error rate at a 2-sided alpha level of 0.05. The major secondary efficacy endpoints were to be tested in the following order: (1) the reduction in the rate of sickle-cell-related pain as recorded in patient pain diaries versus placebo using a mixed-effects model repeated measures (MMRM) analysis; (2) the reduction in the hospitalization rate for VOC using the Andersen-Gill model; (3) the reduction in the rate of painful crisis using the Andersen-Gill model; (4) the reduction in the rate of RBC transfusion due to SCD using the Andersen-Gill model; (5) the reduction in the intensity of sickle-cell-related pain as recorded in patient pain diaries using an MMRM analysis; (6) the reduction in the use of analgesics using an MMRM analysis; (7) the reduction in the rate of acute chest syndrome using the Andersen-Gill model; and (8) the reduction in school absence using an MMRM analysis. <u>Safety:</u> Safety endpoints were summarized using descriptive statistics, and treatment group comparisons were performed using a Fisher's Exact test. <u>PK:</u> The PK parameters for Pras-AM were estimated using NCA and population PK modeling. <u>PD:</u> Summary statistics were provided for each PD parameter. The comparison between treatment groups was carried out with the analysis of covariance (ANCOVA) model and MMRM analysis. <u>PD/PD:</u> The exposure-response relationship for effectiveness (rate of VOC/year) and safety (number of bleeding events requiring medical intervention) were explored using the population PK data.

	Review Division Comments The statistical analysis plan met the criteria specified in the WR.
Labeling that may result from the studies: 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 prasugrel 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).	**Labeling that may result from the studies:** Changes made to section 8.4 of the USPI per FDA guidance: Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling. **8.4 Pediatric Use CO 2.5.6.** Safety and effectiveness in pediatric patients have not been established. In a randomized, placebo-controlled trial (b) (4), the primary objective of reducing the rate of vaso-occlusive crisis (painful crisis or acute chest syndrome) in pediatric patients, aged 2 to less than 18 years, with sickle cell anemia was not met. **Review Division Comments:** The Applicant met the criteria specified in the WR .
Format 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 post-marketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or pediatric patient. In	**Format of reports submitted:** Full study report not previously submitted to the Agency (TADO CSR) including full analysis, assessment, and interpretation of the data were submitted. The report included information on the representation of pediatric patients of ethnic and racial minorities according to the categories and designations in the WR. Periodic Safety Update Report (PSUR) in the Format of ICH E2C (R2) was submitted, which covers the reporting period of 26 February 2014 through 25 February 2015. During this time period, an estimated 638,000 patients received prasugrel from post-marketing sources. The data reported in the post-marketing setting are consistent with the known safety profile of prasugrel. Overall, there was no change in the nature, seriousness or frequency of reported events, based on the post-marketing data. PSUR 2016 and a summary document reviewing the changes between PSUR 2015 and PSUR 2016 will be provided at the time of the 120 day update (May 2016).

general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance. 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/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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.	Clinical Pharmacology studies were created (programmed) in SDTM format (as opposed to being converted like the phase 2 and 3 studies). At the time the ClinPharm studies were created Lilly (b) (4) was using an older version of the SDTM implementation Guide (version 3.1.1). Lilly is now using version 3.1.2. Lilly requested and received a waiver from the FDA to not have to upversion the ClinPharm studies to the newer version (to not have to convert them to the newer version using the 3.1.2 implementation guide). **Review Division Comments:** The Applicant met the criteria specified in the WR.
Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before January 14, 2016. 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.	**Timeframe for submitting reports of the studies:** The clinical studies were submitted to the Agency with NDA 022307, S-014 on January 12, 2016. **Review Division Comments:** The Applicant met the criteria specified in the WR.

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/s/

RACHEL E ERSHLER
06/17/2016

NICOLE J GORMLEY
06/18/2016