15 September 2016
EMA/640689/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Efient

prasugrel

Procedure no: EMEA/H/C/000984/P46/034

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

On 18 May 2016, the MAH submitted a completed paediatric study for Efient, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Prasugrel hydrochloride (prasugrel) is an ADP receptor antagonist and inhibitor of platelet activation and aggregation mediated by the P2Y12 ADP receptor (Niitsu et al. 2005; Jakubowski et al. 2007) and may reduce the frequency and severity of VOC in patients with SCD. The use of prasugrel in pediatric patients with VOC was investigated because of the paucity of other treatment options in children and the prospect of preventing future irreversible organ dysfunction, which may be related to multiple cycles of vascular occlusion and reperfusion injury.

The overall clinical development programme for prasugrel is co-sponsored by an alliance of Eli Lilly and Company (Lilly) and Daiichi Sankyo Co., Ltd (Daiichi Sankyo). The Marketing Authorisation for prasugrel was transferred in the EU from Eli Lilly Nederland B.V. to Daiichi Sankyo Europe GmbH on 10th of December 2015.

This submission concerns the completed Study H7T-MC-TADO (Study TADO) of prasugrel in paediatric patients with Sickle Cell Disease (SCD) with Eli Lilly and Company as sponsor. It is submitted to comply with the requirements of Article 46 of Regulation (EC) No 1901/2006, as amended. Last patient visit occurred on 17 December 2015.

Following SDBL and review of the topline information by Eli Lilly and Company along with the external TADO Steering Committee, the study was stopped as the primary and key secondary endpoints were not met. Sites were instructed on 16 September 2015 to stop study drug and conduct discontinuation visits for all active study participants within the next 60 days. A summary of safety and selected efficacy results from the beginning of the study, including data collected after SDBL, will be provided with the 120-day safety update.

The MAH states that results of the TADO trial indicate that prasugrel did not have a positive benefit-risk profile for the treatment of paediatric patients (aged 2 to <18 years) with SCD, due to a lack of efficacy (benefit) rather than in increase in safety concerns (risk).

Because the study did not meet the primary or secondary efficacy endpoints, DSE and MAH in the EU is not requesting the addition of a new indication to the label, nor any changes to the SmPC or PIL as no new safety issues were identified.

2.2. Information on the pharmaceutical formulation used in the study

At Visits 1 to 3 in the double-blind treatment period, Verify*Now*® (VN)-P2Y12 reaction units (PRU) were measured, as required by the protocol, to titrate to the appropriate maintenance dose for each patient. Prasugrel was administered as a chewable tablet at a maintenance dose that targeted a PRU range of 231 to 136 (corresponding to an inhibition of platelet aggregation of approximately 30% to 60%). Dosing was weight based (mg/kg) and administered daily.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study H7T-MC-TADO: Determining Effects of Platelet Inhibition on Vaso-Occlusive Events (DOVE) Trial: A Phase 3, Double-Blind, Randomized, Efficacy and Safety Comparison of Prasugrel and Placebo in Pediatric Patients with Sickle Cell Disease.

2.3.2. Clinical study

Clinical study number and title

Study H7T-MC-TADO. Determining Effects of Platelet Inhibition on Vaso-Occlusive Events (DOVE) Trial.

Description

This was a Phase 3, double-blind, randomized, efficacy and safety comparison of prasugrel and placebo in pediatric patients with Sickle Cell Disease. It was a multicentre study conducted at 51 study sites in 13 countries and included 55 principal investigators.

Methods

Objective(s)

Primary objective

The primary objective of this study was to assess the efficacy of prasugrel monotherapy compared to placebo in pediatric patients with sickle cell disease (SCD) as measured by reduction in the rate of vaso-occlusive crisis (VOC), which is a composite endpoint of painful crisis or acute chest syndrome. A painful crisis was defined as an onset of moderate to severe pain that lasted at least 2 hours for which there was no explanation other than vaso-occlusion and which required therapy with oral or parenteral opioids, ketorolac, or other analgesics prescribed by a health care provider in a medical setting such as a hospital, clinic, emergency room visit, or documented telephone management. Acute chest syndrome was defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

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:

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

7. Reduction in the rate of acute chest syndrome
8. Reduction in school absence secondary to sickle-cell-related pain as recorded in patient pain diaries.

Other secondary efficacy objectives

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

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.

Pharmacokinetic objective

Assess the pharmacokinetics (PK) of prasugrel in pediatric patients with SCD by characterizing the exposure to prasugrel active metabolite (Pras-AM).

Pharmacodynamic objective

- Characterize pharmacodynamics (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 to placebo in pediatric patients with SCD by measuring whole-blood and urine biomarkers of platelet activation.

PK/PD Objective

Assess the PK-PD relationship between Pras-AM and antiplatelet effects of prasugrel in pediatric patients with SCD.

Open-label extension period objective

- To evaluate long-term safety of prasugrel in pediatric patients with SCD
- To evaluate long-term efficacy of prasugrel in pediatric patients with SCD.

Study design

Phase 3, double-blind, 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 months. There was an optional open-label extension (OLE) period planned; however, the OLE period of Study TADO was not

fully implemented due to the Sponsor decision to discontinue the study for failure to meet the primary or secondary efficacy endpoints.

Diagnosis and Main Criteria for Inclusion

The main **inclusion criteria** were for males and female patients with SCD (homozygous hemoglobin S [HbSS] and heterozygous hemoglobin S beta zero [HbS β 0] genotypes), 2 to <18 years of age, who had ⩾2 episodes of VOC in the past year, and had a body weight ⩾19 kg. Addendum TADO(3) allowed the enrollment of patients weighing 12 to <19 kg at sites that were able to accommodate cold storage and handling of the 0.5-mg prasugrel tablet. For sites where the 0.5-mg tablet was not available, Addendum TADO(6) allowed every-other-day dosing with 1-mg tablets for patients weighing 12 to <19 kg who needed a reduction from the initial 0.08-mg/kg dose to a lower mg/kg dose that would have required a 0.5-mg tablet.

The main **exclusion criteria** were a diagnosis of acute VOC within 15 days prior to screening, a concomitant medical illness that in the opinion of the investigator was associated with reduced survival, hepatic dysfunction characterized by alanine aminotransferase (ALT) ⩾3 × upper limit of normal (ULN); renal dysfunction that required chronic dialysis or creatinine ⩾1.2 mg/dL; contraindication for antiplatelet therapy; history of intolerance or allergy to approved thienopyridines; hematocrit <18%; met predefined bleeding risk criteria; or met prior/concomitant therapy exclusion criteria. Particular effort was made to exclude patients at risk for stroke. This included the requirement of a transcranial Doppler within the last year for all patients ⩽16 years of age; exclusion of patients with a history of abnormal or conditional transcranial Doppler (velocity in middle or anterior cerebral, or internal carotid artery ⩾170 cm/sec) within the last year, regardless of age; exclusion of patients with a history of chronic RBC transfusion for the prevention of stroke; and exclusion of patients with any history of TIA/stroke.

Study population /Sample size

Number of Patients:

- **Planned:** 220 patients: 110 prasugrel, 110 placebo (204 to complete at least 9 months of double-blind period)

Treatments

Placebo to match prasugrel was administered orally daily. Double-Blind Treatment Period: 9 to 24 months.

At Visits 1 to 3 in the double-blind treatment period, Verify*Now*® (VN)-P2Y12 reaction units (PRU) were measured, as required by the protocol, to titrate to the appropriate maintenance dose for each patient. Prasugrel was administered as a chewable tablet at a maintenance dose that targeted a PRU range of 231 to 136 (corresponding to an inhibition of platelet aggregation of approximately 30% to 60%). Dosing was weight based (mg/kg) and administered daily.

Outcomes/endpoints

Efficacy

- Rate of VOC, which is a composite endpoint of painful crisis or acute chest syndrome
- Rate of sickle-cell-related pain as recorded in patient pain diaries
- Rate of hospitalization for VOC

- Rate of painful crisis
- Rate of RBC transfusion due to SCD
- Intensity of sickle-cell-related pain as recorded in patient pain diaries
- Use of analgesics as recorded in patient pain diaries
- Rate of acute chest syndrome
- School attendance as recorded in patient pain diaries
- Incidence of TIA/ischemic stroke
- Time from randomization to first and second VOC
- Length of hospitalization for VOC.

Safety

- Incidence of hemorrhagic events requiring medical intervention, including hemorrhagic stroke
- Incidence of hemorrhagic and non-hemorrhagic TEAEs
- Rate of study drug discontinuation due to hemorrhagic and non-hemorrhagic TEAEs.

Pharmacokinetics

- Area under the concentration-time curve for Pras-AM.

Pharmacodynamics

- VN-P2Y12 and vasodilator-stimulated phosphoprotein (VASP) was used to measure platelet inhibition.

PK/PD

- PRU and/or VASP platelet reactivity index (PRI) and their relationship to area under the concentration-time curve for Pras-AM.

Statistical Methods

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.

Safety

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

Pharmacokinetics

The PK of the measured Pras-AM concentrations was evaluated using a population PK model and/or non-compartmental methods.

Pharmacodynamics

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.

PK/PD

Relationship between exposure to Pras-AM and PRU and/or PRI was evaluated by descriptive or population-based methods.

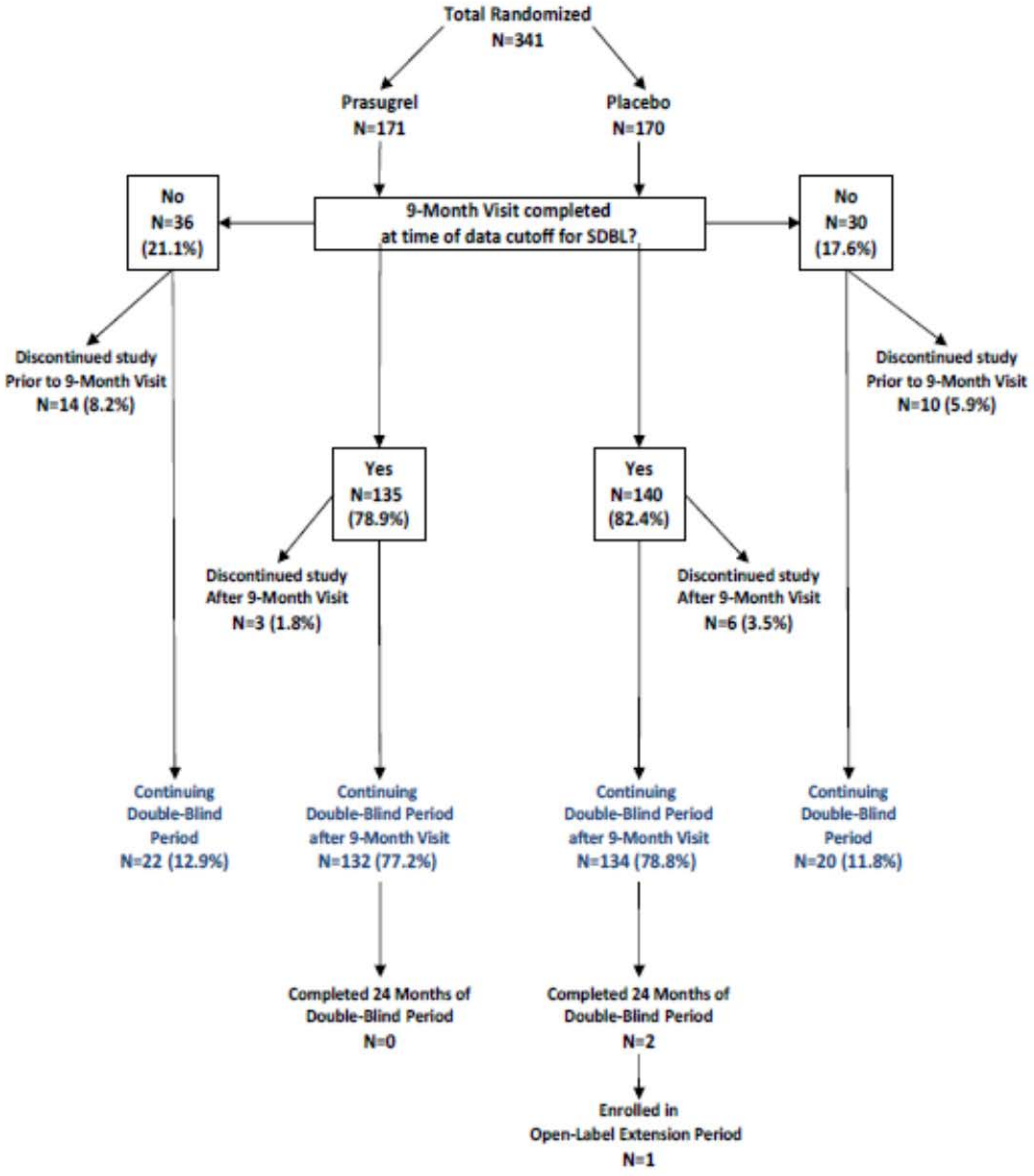
Results

Recruitment / Number analysed

- **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

One patient was enrolled in the OLE and was treated for approximately 1 month following transition from the double-blind treatment period. Data from the OLE period will be presented with the 120-day safety update.

Overall retention during the double-blind treatment period exceeded 90% and there were no subjects lost to follow-up.



Abbreviation: SDBL = submission database lock.
Note: 9-month visit is Visit 6.
Source: T01_00_01.rtf

Figure TADO.10.1. **Patient disposition at time of data cutoff for submission database lock.**

Baseline data

The mean age was 10.6 years, with 67 patients 2 to <6 years old, 132 patients 6 to <12 years old, 141 patients 12 to <18 years old, and 1 patient 18 years old. The majority of patients were Black or African American (65.3%) and half of patients were female (50.7%). Sub-Saharan Africa (Ghana and Kenya) constituted 43.4% of patients, and the Mediterranean Basin (Egypt, Lebanon, and Turkey) 30.2%. The only statistically significant difference was that the prasugrel group had a higher mean BMI compared with the placebo group; however, the difference was relatively small (<1 kg/m2) and was not considered clinically meaningful.

There were no other significant differences in demographic or baseline characteristics between treatment groups.

Almost half of the study patients (44.9%) were using hydroxyurea at baseline. Hydroxyurea use varied by region. The majority of patients in America and the Middle East were on hydroxyurea at baseline, but only 6.8% of patients in Africa were on hydroxyurea at baseline.

The percentage of patients using hydroxyurea increased with age, with 27% of patients aged 2 to <6 years, 36% of patients aged 6 to <12 years, and 61% of patients aged 12 to <18 years on hydroxyurea at baseline.

The most common preexisting conditions were asthma (19 patients; 5.6%), and constipation (12 patients; 3.5%).

Overall, the most common medications stopped prior to study randomization were analgesics (paracetamol [10.6%], ibuprofen [9.1%], and diclofenac [7.6%]). A total of 6 patients (1.8%) discontinued hydroxyurea. These frequently used medications are commonly associated with the care of patients with SCD.

Almost all patients (99.4%) were on a concomitant medication at some time during the study. The most commonly used concomitant medications were folic acid, in 78.6% of patients, and paracetamol, in 76.0% of patients.

Efficacy results

Summary of VOC

The total number of VOC events was 818, with 365 in the prasugrel arm and 453 in the placebo arm. At least 1 VOC occurred for 115 of the 171 prasugrel-treated patients (67.3%) and 123 of the 170 placebo-treated patients (72.4%). A total of 54.4% of VOCs required intravenous fluids, 42.3% required hospitalization, and 12.1% required transfusion. When terms are combined for emergency room, outpatient and inpatient hospitalizations, approximately 80% of VOCs were managed in the hospital setting while only 13.2% of VOC events were managed by documented telephone consultation.

Primary Efficacy Measure

Based on the phases of the sickle cell painful crisis (Ballas 1995), any VOC event that occurred within 7 days of a preceding event was excluded from the primary efficacy analysis. A total of 736 VOC events were included in the analysis of the primary endpoint, 328 events in the prasugrel group and 408 events in the placebo group (Table TADO.11.4). During the double-blind period, the rate of VOCs (number per patient-year) was lower for the prasugrel group (2.295) compared with the placebo group (2.767), but this difference was not statistically significant (p=0.117).

Results of sensitivity analyses were consistent with results of the primary analysis. When documented telephone-managed events were excluded from the analysis, the rate ratios of VOC events were similar to the overall rate ratio. A sensitivity analysis that included all VOC events was performed; this analysis included events that occurred within 7 days of a preceding event, but not those that occurred on the same day. This analysis included a total of 794 VOC events; 352 events in the prasugrel group and 442 events in the placebo group. Results were consistent with the primary analysis results.

The mean cumulative distribution curve (Figure TADO.14.6) suggests similar mean numbers of VOCs experienced between treatment groups through 12 weeks. After this time point, the VOC event rate is higher in the placebo group relative to the prasugrel group. A landmark analysis showed no statistically

significant differences in the VOC rate ratios before or after 6 months, 9 months, or 1 year. Although there was a significant treatment difference after 9 months, this difference must be cautiously interpreted due to the decreasing number of patients in the double-blind treatment period of the study over time and differences in demographic characteristics, such as age and region, of patients in the study after 9 months compared to the overall study population.

Table TADO.11.4. Summary and Analysis of the Rate of Vaso-Occlusive Crisis ITT Population

Summary and Analysis of the Rate of Vaso-Occlusive Crisis
Intent-to-Treat Population
H7T-MC-TADO

Page 1 of 1
08:57 01OCT2015
Unblinded PDPM

Treatment	No. of Patients with Events (%)	Total No. of Events	Total Length of Follow Up (Patient-Year)	Rate (No. of Events per Patient-Year)	Crude Rate Ratio	Rate Ratio 95% CI (Lower, Upper)*a	p-value*a
Prasugrel (N=171)	115 (67.3)	328	142.890	2.295	0.830	0.83 (0.66, 1.05)	.117
Placebo (N=170)	123 (72.4)	408	147.444	2.767			

Abbreviations: CI = confidence interval; N = total number of randomized patients; No. = number.
*a: Rate ratio (prasugrel vs. placebo), 95% CI for the rate ratio, and p-value are from the Andersen-Gill model with treatment, hydroxyurea use, and age group as independent variables.
Note: Age group: 2 to < 6 years old, 6 to < 12 years old, and 12 to < 18 years old. An 18-year old patient is counted in the 12 to <18 years group.
Note: Vaso-Occlusive crisis is a composite endpoint of painful crisis or acute chest syndrome. To ensure only unique episodes are included in the analyses, any event that happened within 7 days from the prior event onset date will not be counted as a new episode.
Note: Percentages (%) are based on the number of randomized patients in a treatment group.

Program Location: ...\ELI_LILLY\LY640315\VTA88166\Biostatistics\Production\Tables\CSR\T07_00_00.sas
Output Location: ...\ELI_LILLY\LY640315\VTA88166\Biostatistics\Output\Production_Out\CSR\T07_00_00.rtf
Data Set Location: ...\ELI_LILLY\LY640315\VTA88166\Biostatistics\Data\Derived\CSR

Subgroup Analyses of the primary efficacy measure

There were no statistically significant differences between treatment groups or significant subgroup-by-treatment interactions. The numerical decrease in VOC rate with prasugrel was consistent across genders, genotypes, and by baseline BMI.

The subgroup-by-treatment interaction for age group was not statistically significant. Patients aged 12 to <18 years treated with placebo had the highest VOC rate; a trend was observed for this age group with a lower rate of VOC for the prasugrel group than for the placebo group (2.339 versus 3.213; rate ratio: 0.72; 95% CI: 0.51, 1.02). The VOC rate was similar between treatment groups for the 2 younger age groups. For patients not on hydroxyurea, the rate of VOC was lower for the prasugrel group (1.978) than the placebo group (2.677), but this difference was not statistically significant, with a rate ratio of 0.74 (95% CI: 0.54, 1.01). The VOC rates among placebo-treated patients on hydroxyurea (2.857) or off hydroxyurea (2.677) and prasugrel-treated patients on hydroxyurea (2.612) were more consistent.

The rate of VOC was higher among black than white patients in both treatment groups, and there was a larger treatment difference for black patients. Results by region were consistent with the results by race, with a higher event rate and larger treatment difference among patients from Africa and America, who self-identified primarily as black, than among patients from the Middle East, who self-identified primarily as white.

Results of subgroup analyses may be confounded with each other (i.e., race, region, age and hydroxyurea use) such that it is difficult to distinguish the unique effects of each subgroup.

The rate of VOC during the study was similar between treatment groups in patients who had 2 VOCs in the prior year and in patients who had 6 or more VOCs in the prior year. Among patients who had 3 to 5 VOCs in the prior year, the rate of VOC during the study was lower in the prasugrel group than in the placebo group, but the difference was not statistically significant. Among patients who did not have a splenic sequestration or hepatic sequestration event in the prior year, the rate of VOC during the study was similar between treatment groups. The rate of VOC during the study was much lower in the prasugrel group than in the placebo group for patients who had splenic or hepatic sequestration events during the prior year. The difference was statistically significant among patients who had hepatic sequestration during the prior year, but this was a very small subgroup so conclusions cannot be made based on this result.

Efficacy conclusions by the MAH

- A total of 736 VOC events were included in the analysis of the primary composite endpoint of vaso-occlusive pain crisis or acute chest syndrome. Prasugrel did not significantly reduce the rate of the primary endpoint compared to placebo.
- The majority of the 818 VOC events during the study were managed in a health care setting, with 54.4% requiring intravenous fluids, 42.3% requiring hospitalization, and 12.1% requiring transfusion. Only 13.2% of VOC events were managed by documented telephone consultation.
- There was a trend toward an effect of prasugrel on VOC in the 12 to <18 year age group and in patients who were not receiving hydroxyurea; however, there were no significant treatment-by-subgroup interactions.
- Prasugrel had no effect on the rates of hospitalization for VOC, RBC transfusion, rate of pain, pain intensity, analgesic use, or school absence secondary to sickle-cell-related pain as assessed by daily pain diaries. There was no effect of prasugrel on rates of other secondary outcomes, including duration of hospitalization for VOC, time from randomization to first or second VOC, or incidence of TIA/ischemic stroke.
- The majority of patients on prasugrel were within the target range of PRU and mean PRU values at the FTD were maintained through the 9 months of treatment. However, no clear relationship was seen between PD measures and VOC rate ratio.

PK/PD results

Pharmacokinetic samples were analyzed for Pras-AM concentration in plasma. After removing concentration records with results reported as pending or "no test," a total of 129 prasugrel treated patients contributed a total of 624 PK concentrations following dosing to steady state with fully-titrated prasugrel doses ranging from 0.04 mg/kg to 0.12 mg/kg. Seventeen of the 129 patients were excluded from subsequent analysis because all samples from the patient were below the assay's quantitation limit (N=16) and/or all of the patient's samples were assayed outside the stability window (N=2) (one patient met both criteria). In addition, one patient was excluded from the PK analysis because the patient had only one time point with a quantifiable concentration. Lastly, 6 samples across 6 different patients were BQL and were treated as missing. After removing all excluded samples, the PK analysis was conducted using 530 samples from 111 patients. See Section 14.3.4.1 for a complete listing of samples excluded from the analysis, with the reason(s) for exclusion.

Mean concentrations at doses of 0.04 mg/kg (N=2) and 0.10 mg/kg (N=2) are not plotted due to insufficient data. In general, postdose concentrations increase and reach a C_{max} between 0.5- and 1.0-hour postdose, then decrease through the last sampling time of 4 hours.

Overall, the PK results indicate that Pras-AM exposure increases with increasing dose. Pras-AM concentrations appear rapidly in plasma, peaking at 0.5 to 1 hour and declining to near the 0.50-ng/mL quantitation limit by 4-hours postdose. The inter-subject variability in Pras-AM AUC is high, with geometric coefficients of variation of about 50%.

Pharmacodynamic results

Pharmacodynamic analyses were conducted on data from randomized patients who received at least 1 dose of study drug, and had at least 1 post-baseline PD measure. The PD population included 166 (97%) of 171 patients randomized to the prasugrel group, and 169 (99.4%) of 170 patients in the placebo group.

Study TADO PD objectives are provided in Section 8.2.5 and results of PD analyses are provided in a separate Study TADO PD Report. The following results were observed in the Study TADO PD Report:

- At the FTD, prasugrel treatment resulted in a statistically significant reduction in platelet reactivity from baseline, as determined by both VN-P2Y12 and VASP assays, with the majority of patients at their FTD being in the target PRU range.
- The mean PRU values at the FTD were largely maintained through the 9 months of treatment.
- While the majority of patients on prasugrel were within the target range of 136-231 PRU, device-reported and derived percent inhibition was lower than expected at ~20%-26%.
- No clear relationship was seen between PD measures and VOC rate ratio.

Steady-state exposure/PD results

Descriptive exposure – PD analyses were limited to patients contributing both PK and PD data at identical absolute doses at steady-state. The population comprised 110 of the 111 patients who contributed to the PK assessments previously presented. One patient was excluded from these analyses due to a change in absolute dose between the last PD assessment at Visit 6 and the PK assessment conducted at Visit 10. This patient received 0.08 mg/kg throughout the study, but due to an increase in body weight during the study, the dose changed from 1.5 mg at Visit 6 to 2 mg at Visit 10.

The PD analyses included only PD measurements from the last visit for which PD results were available for a given subject, and where comparison of steady-state PK and steady-state PD at the same dose level was possible. PD data from earlier visits for a given subject were not included in descriptive PK-PD analyses.

For exposure – VN-P2Y12 analyses, 3 patients were excluded because they did not have VNP2Y12 data available at Visit 6. Therefore, the exposure – VN-P2Y12 analyses comprised 107 patients.

For exposure – VASP analyses, 25 of the 110 patients did not have VASP data available at the last visit for which PD samples were collected and analyzed. Therefore, exposure – VASP analyses comprised 85 patients.

Safety results

Patients were randomized to either prasugrel or placebo for a minimum of 9 months (270 $\pm$ 7 days) to a maximum of 24 months during the double-blind period. Mean exposures to study drug were similar

between treatment groups, and 259 patients (76.2%) had at least 270 days of exposure to study drug. Durations of exposure were similar for patients aged 6 to <12 years and 12 to <18 years but shorter for patients aged 2 to <6 years because many of them were enrolled at a later date than the older 2 age groups. In the youngest age group, 21 patients had at least 270 days of exposure to study drug. The majority of patients were still on treatment at Month 9.

Brief Summary of Adverse Events

Table TADO.12.2 contains an overview of AEs reported during the on-treatment period. The percentage of patients with hemorrhagic events was similar between treatment groups, with no statistically significant difference for hemorrhagic-related deaths, SAEs, AEs leading to study drug discontinuation, TEAEs, or AEs possibly related to study drug or study procedure. Results were similar for non-hemorrhagic events and for AEs overall, with no statistically significant difference observed between treatment groups for any category of events (Table TADO.12.2).

There was 1 death in each treatment group, with 1 additional death reported after data cutoff for SDBL in the placebo group that is not reflected in the safety tables.

Brief Summary of Adverse Events by Age Group

Analyses of AEs by age group showed no statistically significant differences between treatments for the 2 to <6 year olds, 6 to <12 year olds, or for the 12 to <18 year age group in any event category. Categories of hemorrhagic events included deaths, SAEs, AEs leading to study drug discontinuation, TEAEs, and AEs possibly related to study drug or to study procedure. Results of analyses by age group were similar for non-hemorrhagic events and for AEs overall, with no statistically significant difference observed between treatment groups for any category in any age group.

Table TADO.12.2. Overview of Adverse Events during the On-Treatment Period
Safety Population

Overview of Adverse Events during the On-Treatment Period
Safety Population
H7T-MC-TADO

Page 1 of 1
09:00 01OCT2015
Unblinded PDPM

	Prasugrel (N=170) n (%)	Placebo (N=170) n (%)	Total (N=340) n (%)	p-value
Any Event				
Death	1 (0.6)	1 (0.6)	2 (0.6)	.999
Serious AE	88 (51.8)	96 (56.5)	184 (54.1)	.446
AE which led to study drug discontinuation	6 (3.5)	5 (2.9)	11 (3.2)	.999
Treatment-emergent AE	159 (93.5)	162 (95.3)	321 (94.4)	.638
AE possibly related to study drug	12 (7.1)	12 (7.1)	24 (7.1)	.999
AE possibly related to study procedure	5 (2.9)	1 (0.6)	6 (1.8)	.215
Any Hemorrhagic Event				
Death	1 (0.6)	0	1 (0.3)	.999
Serious AE	5 (2.9)	3 (1.8)	8 (2.4)	.723
AE which led to study drug discontinuation	2 (1.2)	1 (0.6)	3 (0.9)	.999
Treatment-emergent AE	32 (18.8)	33 (19.4)	65 (19.1)	.999
AE possibly related to study drug	8 (4.7)	6 (3.5)	14 (4.1)	.786
AE possibly related to study procedure	1 (0.6)	0	1 (0.3)	.999
Any Non-hemorrhagic Event				
Death	0	1 (0.6)	1 (0.3)	.999
Serious AE	87 (51.2)	96 (56.5)	183 (53.8)	.384
AE which led to study drug discontinuation	4 (2.4)	4 (2.4)	8 (2.4)	.999
Treatment-emergent AE	157 (92.4)	162 (95.3)	319 (93.8)	.368
AE possibly related to study drug	6 (3.5)	6 (3.5)	12 (3.5)	.999
AE possibly related to study procedure	4 (2.4)	1 (0.6)	5 (1.5)	.371

Abbreviations: AE = adverse event; N = total number of treated patients; n = number of patients with at least one condition; TEAE = treatment-emergent adverse event.
Note: Percentages(%) are based on the number of treated patients in a treatment group.
Note: P-value is from Fisher's Exact test.
Note: TEAE defined as an event that first occurs or worsens (increases in severity) after the first dose of study drug.
Note: AE possibly related to study drug or procedure is based on investigator's judgment.
Note: Hemorrhagic events are identified if an event is entered on the bleeding endpoint form.

Deaths

There were 3 deaths during the study—2 patients on placebo and 1 on prasugrel. 1 death in the placebo group occurred after the data cutoff date for the SDBL and is therefore not included in the AE listings and summaries of this report.

- Approximately 10 months after starting on study drug, a prasugrel-treated patient was hospitalized following an episode of convulsion; the patient' s condition deteriorated and they died the same day. An autopsy determined the cause of death to be intracranial hemorrhage due to ruptured aneurysm. The event was not considered by the investigator to be related to study drug or protocol procedures.
- Approximately 8 months after the first dose of study drug, a placebo-treated 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 glucose. On the same day, the patient was diagnosed with severe anemia, received a blood transfusion, and study drug was discontinued. Despite oxygen and blood transfusion, the patient's condition deteriorated and they died the following day; the cause of death was determined as septicemia. Per investigator opinion, the events of septicemia, painful crisis, severe anemia, and hypoglycemia were not related to blinded study drug or protocol procedures.

One additional death in Study TADO was reported after data cutoff for the submission. A brief summary of this case is provided below:

- Approximately 9 months after the first dose of blinded study drug, a placebo-treated patient was hospitalized due to severe anemia and hemolytic crisis. Treatment for the patient included blood transfusions, ceftriaxone, amikacin, intravenous fluids, and diclofenac. The patient's condition stabilized and they were able to walk unaided and eat. On the sixth day of hospitalization, the patient's condition deteriorated despite oxygen therapy and a third blood transfusion, and the patient died. Results of the autopsy reported that the cause of death was multiple organ failure in a sequestrative sickling crisis. The event of severe anemia was considered by the investigator to be unrelated to study drug or protocol procedures.

Other SAEs

Similar proportions of patients in the prasugrel and placebo groups experienced at least 1 SAE (p=0.446). The most common SAEs were related to the underlying SCD; there were no statistically significant differences between treatment groups for any SAE.

There were 4 SAEs that were considered by the investigator to be life-threatening; 2 cases in patients treated with prasugrel (anaphylactic reaction and parvovirus B19 infection) and 2 cases in patients treated with placebo (hypoglycemia and hematoma). The 2 cases in 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 2 remaining cases in patients treated with placebo, only the hematoma was considered related to study drug.

Adverse Events that led to treatment discontinuation

Adverse events that led to treatment discontinuation were infrequent and occurred in similar proportions in the prasugrel and placebo groups. No statistically significant difference in the proportion of patients discontinuing treatment for any particular event was observed. The events of epistaxis, deep vein thrombosis, parvovirus B19 infection (prasugrel group) and anemia, thrombotic thrombocytopenic purpura, and disorder of orbit (placebo group) were considered serious. The treatment assignment for one patient was unblinded during the study due to experiencing serious

symptoms that warranted knowledge of treatment assignment. This patient was diagnosed with a life-threatening case of parvovirus and had study drug withdrawn at the start of the event. The patient subsequently discontinued from the study.

A total of 3 hemorrhagic AEs led to treatment discontinuation; 2 in the prasugrel group and 1 in the placebo group. The 2 prasugrel-treated patients discontinued due to epistaxis events. Both of these events were considered SAEs that were possibly related to study treatment; one had a maximum severity of severe and one was moderate. One patient in the placebo group discontinued study drug due to menorrhagia of moderate severity, which was not considered to be an SAE.

Two patients in the prasugrel group became pregnant during the study. One patient had completed 435 days of study drug treatment at the time of discontinuation from both study treatment and from the study due to pregnancy. The other patient had completed 183 days of study drug treatment at the time of study drug discontinuation due to pregnancy; the patient continued participation in the study. In both cases, the outcome was elective termination of the pregnancy.

Haemorrhagic events requiring medical intervention

No statistically significant difference was observed between treatment groups in the rate of patients with hemorrhagic events requiring medical intervention. Overall, the percentage of patients with events was similar between treatment groups.

TEAEs

Similar proportions of patients in the prasugrel and placebo groups experienced at least 1 TEAE during the double-blind on-treatment period. The only statistically significant difference between treatment groups was for the preferred term of pain in extremity.

Safety conclusions by the MAH

- Three patient deaths occurred during the study; 2 in the placebo group (1 after data cutoff for the SDBL) and 1 in the prasugrel group. No deaths were considered to be related to study drug by the investigator.
- There were no statistically significant between-treatment differences observed for bleeding-related deaths, SAEs, AEs leading to study drug discontinuation, or in the rate of permanent study drug discontinuation due to hemorrhagic or non-hemorrhagic TEAEs.
- There were no significant between-treatment differences observed in the incidence of hemorrhagic events requiring medical intervention, or in the incidence of hemorrhagic or non-hemorrhagic TEAEs.
- Overall, no new safety findings were identified for prasugrel treatment in this population.

2.3.3. Discussion on clinical aspects

The H7T-MC-TADO study was a relatively large study designed to determine the efficacy of prasugrel monotherapy compared to placebo in a paediatric population with SCD. More study subjects than originally intended were included and the retention rate was high.

The primary objectives are considered appropriate as are the statistical analyses conducted. As the primary and key secondary endpoints were not met, the MAH and the external TADO Steering Committee decided to stop the study.

Efficacy: Prasugrel did not significantly reduce the rate of the primary endpoint compared to placebo.

Safety: There were no significant between-treatment differences observed in the incidence of hemorrhagic events requiring medical intervention, or in the incidence of hemorrhagic or non-hemorrhagic TEAEs. Overall, no new safety findings were identified for prasugrel treatment.

3. Rapporteur's overall conclusion and recommendation

The decision to close the study is considered acceptable and it is recognized that prasugrel did not reduce the rate of VOD in a paediatric population with SCD.

However, the study has contributed safety data in a paediatric population. As a consequence, the SmPC should be updated via a variation application to reflect these data and to avoid creating a potential for off label use. Currently, the paragraph regarding Paediatric Population in Section 4.2 of the SmPC states that the safety and efficacy of Efient in children below the age 18 has not been established as no data are available. However, with the conclusion of the present study, safety data in the paediatric population has been generated. Based on the data submitted, the MAH should submit a Type IB variation for an updated text regarding Paediatric Population in Section 4.2 of the SmPC and include a cross reference to Section 5.1 where a brief summary of the H7T-MC-TADO study should be provided, as agreed below.

UPDATE 9 September:

The MAH Daiichi Sankyo has committed to submit a variation for an updated text regarding Paediatric Population in Section 4.2 of the SmPC and include a cross reference to Section 5.1 with a brief summary of the H7T-MC-TADO study to be added within 60 days after the receipt of the PAM conclusion. A wording has been agreed with the MAH.

The updated wording in Section 4.2 and 5.1 of the SmPC should read:

● SmPC, 4.2:
Paediatric population
The safety and efficacy of Efient in children below age 18 has not been established. **Limited data are available in children with sickle cell anaemia (see section 5.1)**.~~No data are available.~~

● SmPC 5.1:
Paediatric population
Study TADO tested the use of prasugrel (n=171) vs placebo (n=170) in patients, ages 2 to less than 18 years of age, with sickle cell anaemia for reduction of vaso occlusive crisis in a phase III study. The study failed to meet any of the primary or secondary endpoints. Overall, no new safety findings were identified for prasugrel as monotherapy in this patient population.

☒ Fulfilled:

In view of the available data regarding the paediatric population the MAH should submit a type IB variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.