EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2013
EMA/CHMP/616148/2013
Committee for Medicinal Products for Human Use (CHMP)

Efient

(prasugrel)

Procedure No. EMA/H/C/000984/A46/0031

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

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

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An agency of the European Union

Administrative information

Invented name of the medicinal product:	Efient
INN (or common name) of the active substance:	Prasugrel
MAH:	Eli Lilly Nederland BV
Currently approved Indication	Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).
Pharmaco-therapeutic group (ATC Code):	B01AC22
Pharmaceutical form and strengths:	5 and 10 mg film coated tablets
Rapporteur:	Jens Heisterberg

Introduction

On 29 April 2013, 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.

Scientific discussion

Information on the development program

Study H7T-MC-TACX is one of a series of precursor studies, the results of which will inform dosing decisions in future studies of prasugrel in children with sickle cell disease.

Currently, there is an ongoing Phase 3 study with clinical efficacy endpoints investigating prasugrel in children with sickle cell disease:

EudraCT Number: 2012-003837-41

Sponsor Protocol Number: H7T-MC-TADO

Sponsor Name: Eli Lilly and Company

Full Title: a Phase 3, double-blind, randomized, efficacy and safety comparison of prasugrel and placebo in pediatric patients with sickle cell disease.

Medical condition: Efficacy and safety comparison of prasugrel and placebo in pediatric patients with sickle cell disease

Population: Children, adolescents, under 18

Start Date: 2013-04-15

Country: GB

Information on the pharmaceutical formulation used in the study

In the study, orally disintegrating tablets (ODT) in mg/kg dosing were administered up to a dose producing a device-reported percent inhibition of 50% as measured by the VerifyNow® P2Y12 (VN) analysis. The following strengths were administered: 0.2, 0.3, 0.5, 1.0, 2.0, 3.0, and 5.0 mg. The tablets were packaged in child-resistant blister packs.

Clinical aspects

1. Introduction

The MAH submitted a final report for:

Study H7T-MC-TACX entitled “An Open-Label, Dose-Ranging Study of Prasugrel in Pediatric Patients with Sickle Cell Disease”

Background

In the United States (US) it is estimated that over 100,000 people have sickle cell disease (SCD) (Sickle Cell Disease Associates of America, Inc, www.sicklecelldisease.org/). SCD is an inherited blood disorder in which a less-hydrophilic variant of hemoglobin that polymerizes in low oxygen causing red blood cells (RBCs) to assume a sickled shape (HbS) is expressed rather than normal hemoglobin (HbA). In patients with SCD, the HbS polymerizes when deoxygenated. This polymerization triggers a cascade of events that lead to cellular activation that includes endothelial cells, monocytes, and platelets with occlusion of the microvasculature as a consequence.

A principal complication of SCD is the vaso-occlusive crisis (VOC), also termed “painful crisis” or “severe pain episode,” which manifests clinically as pain in various locations and can result in ischemia or infarction/necrosis of the affected organ (Serjeant 1997).

- Current treatment for sickle cell disease

Current pharmacological treatment for SCD consists largely of supportive care during crisis (for example, analgesia, or hydration). For adults with SCD, hydroxyurea is approved to reduce the frequency of VOC and to reduce the need for blood transfusions (DROXIA package insert, Rev 04/2010).

Hydroxyurea increases fetal hemoglobin (HbF), and along with sickle cell genotype, the level of HbF is an important determinant of clinical complications with SCD, including VOC, because HbF inhibits polymerization of sickle hemoglobin. However, neither hydroxyurea nor any other pharmaceutical agent is approved in the US for the treatment of pediatric patients with SCD. In addition, there are concerns regarding genotoxicity and carcinogenesis with the long-term use of hydroxyurea (Hankins and Aygun 2009). The HUG-KIDS study monitored the safety of hydroxyurea at a maximum tolerated dose for 1 year in 52 children aged 5 to 15 years (Kinney et al. 1999). Neutropenia was the most common side effect from treatment (5.2%), with the majority of neutropenia toxicities being mild. The recent BABY-HUG trial assessed the efficacy and safety of hydroxyurea (20 mg/kg per day) compared to placebo for 2 years in 193 patients with SCD aged 9 to 18 months at randomization (Wang et al. 2011). The only drug-related toxicity finding was mild-to-moderate neutropenia. Although hydroxyurea significantly decreased pain compared to placebo in BABY-HUG, more than 60% of the patients treated with hydroxyurea had 1 or more pain events. However, after 2 years of treatment, more than 60% of the patients treated with hydroxyurea still had 1 or more pain events (Wang et al. 2011).

The limited pharmacotherapeutic options to reduce the frequency and severity of VOC in patients with SCD attests to the medical need that remains to be addressed, especially in the pediatric population. There is thus a need for developing safe and effective agents for SCD that would address the unmet medical need and provide a significant public health benefit.

- Role of platelets in sickle cell disease

There is evidence that platelets play a role in sickle cell pathophysiology in general and in VOC specifically. Several studies have found elevated markers of platelet activation in both children and adults with SCD (Amin et al. 2004; Harbury and Schade 1989; Inwald et al. 2000; Lee et al. 2006; Tomer 2004; Wun et al. 1998). These markers were further elevated during VOC. In addition, some studies have suggested a benefit of antiplatelet therapy in reducing markers of platelet activation as well as the frequency and severity of painful crisis with SCD (Cabannes et al. 1984; Osamo et al. 1981; Semple et al. 1984).

- Prasugrel in sickle cell disease

Prasugrel hydrochloride (hereafter referred to as prasugrel), an adenosine diphosphate (ADP) receptor antagonist, is an inhibitor of platelet activation and aggregation mediated by the P2Y12 ADP receptor (Jakubowski et al. 2007; Niitsu et al. 2005). As ADP plays a central role in platelet activation and aggregation (Jakubowski et al. 2007), additional release of ADP during the hyperactive hemolysis of sickled red cells in turn induces platelet activation, thus further contributing to vaso-occlusion. Based on its mechanism of action, prasugrel may serve as an effective agent to reduce the frequency and severity of VOC in patients with SCD. The potential of prasugrel therapy in pediatric patients with VOC is of particular interest because of the paucity of other treatment options in children and the prospect of preventing future irreversible organ dysfunction, which may be related to multiple cycles of vascular occlusion and reperfusion injury.

Study TAEJ was a Phase 1b open-label, single-center pharmacokinetics (PK) and pharmacodynamics (PD) study of prasugrel in 13 healthy adults and 12 adults with SCD. Exposure to prasugrel's active metabolite (Pras-AM) was comparable between healthy adult patients and adult patients with SCD across a prasugrel dose range of 5 to 10 mg. Prasugrel was safe and well tolerated when administered to adults with SCD for approximately 11 days; specifically, there were no serious adverse events (SAEs), study drug discontinuations or hemorrhagic adverse events (AEs).

Study TAEK was a Phase 2 double-blind, randomized (2:1) comparison of 5-mg prasugrel and placebo administered for 30 days in 62 adult patients (41 randomized to prasugrel, 21 randomized to placebo) with SCD. With 30 days of treatment, prasugrel was safe and well tolerated in adults with SCD. Prasugrel treatment resulted in approximately 33% to 40% platelet inhibition as measured by VerifyNow™P2Y12 (VN), suggesting that SCD patients achieved a substantial PD response with prasugrel treatment and that VN can measure the platelet inhibitory effects of prasugrel in patients with SCD. Pain rate and intensity and biomarkers of platelet activation were numerically decreased in adult patients with SCD who were dosed with prasugrel compared to placebo. These studies supported initiation of a Phase 2, open-label, PK-PD dose escalation study in pediatric patients aged 2 to <18 years with SCD (Study H7T-MC-TACX), and results from Study TACX are reported here.

2. Clinical study

Study number: H7T-MC-TACX

Title: "An open-label, dose-ranging study of prasugrel in pediatric patients with sickle cell disease"

Description

The study is a Phase 2, exploratory, open-label, multi-centre, non-randomized, dose-ranging, PK and PD study of prasugrel in pediatric patients with sickle cell disease. It is one of several studies which

were to be conducted as precursors for an ongoing Phase 3 placebo-controlled study with clinical efficacy endpoints. The present study was conducted at 8 study centres in 1 country (US). It was initiated on 30 November 2011 and had last patient last visit on 01 November 2012.

Methods

- Objective(s)

Primary objective:

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

Secondary objectives:

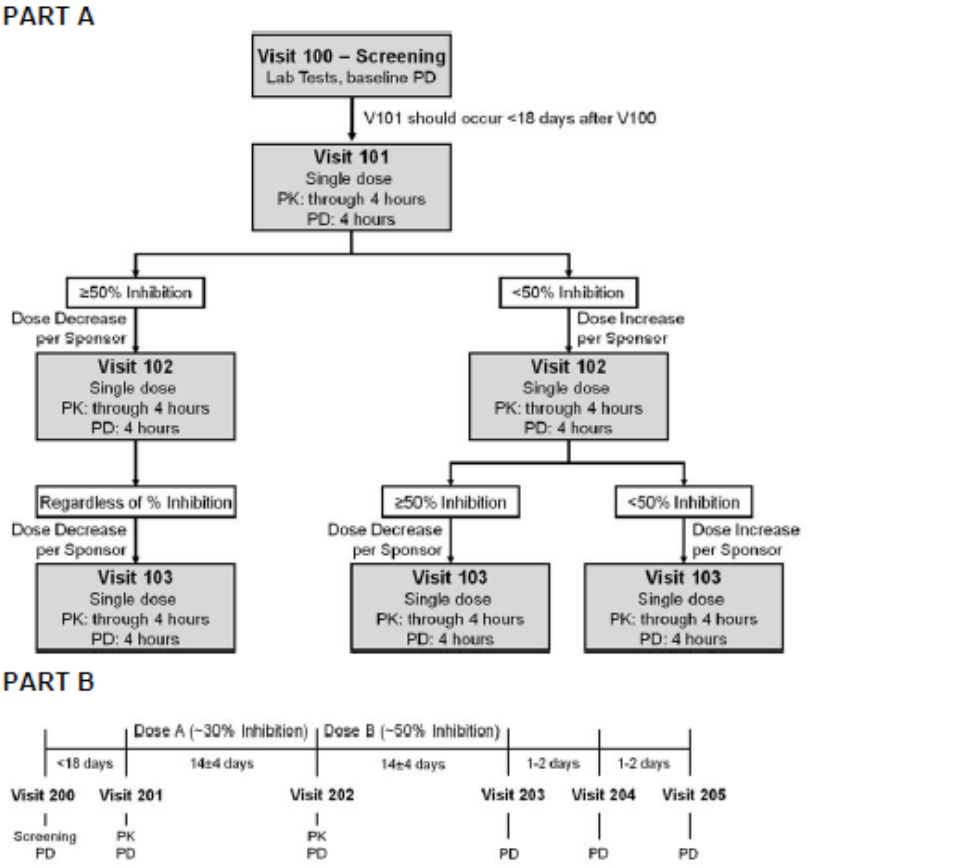
- Evaluate, in the pediatric SCD population, the adequacy of a correlation model to estimate the Pras-AM concentration from the measured concentration(s) of its inactive metabolite(s)
- Assess the short-term efficacy, safety, and tolerability of prasugrel in pediatric patients with SCD

- Study design

This was a phase 2 open-label, multicenter, PK and PD study of prasugrel in 33 pediatric patients with SCD conducted in 2 parts (Parts A and B).

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. During Part A, the first 2 patients received a dose of 0.03 mg/kg, which was expected to be sub-therapeutic. Doses were increased or decreased as appropriate, depending on the PD response to previous doses. Approximately 6 weeks was required for the interim PK/PD analysis prior to starting Part B.

In Part B, patients received once-daily maintenance doses of prasugrel over two 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 population PK-PD (Pop PK-PD) modeling of data from Part A in conjunction with data from previous studies in the adult ACS population. 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 mg/kg 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 a 0.12 mg/kg dose level or down titrated to a 0.06 mg/kg dose level to target a range of 30 to 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.



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 TACX.9.1. Study design for Parts A and B.

- Study population /Sample size

The study was not powered to evaluate efficacy although this was explored in Part B of the study. Approximately 35 patients were to complete the study; approximately 20 patients in Part A and approximately 15 patients in Part B. This was expected to provide approximately 60 single-dose exposures across approximately 20 patients in Part A (provided each patient received 3 different doses), and approximately 30 steady-state exposures across approximately 15 patients in Part B.

Planned: Approximately 35 patients

Entered: 33 patients (24 patients in Part A, 18 patients in Part B)

Treated (at least 1 dose): 33 patients

Completed: 29 patients

Inclusion criteria: Patients included males and females with SCD (homozygous sickle cell [HbSS] and hemoglobin [HbS] β0 thalassemia genotypes) with a body weight ≥12 kg, and 2 to < 18 years of age at screening. 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 the 60 days prior to enrollment without signs of hematologic toxicity at screening. Patients must have had a parent/legal representative who was in

competent mental condition to provide written informed consent on behalf of the study participant before entering the study.

Exclusion criteria: Exclusion criteria included patients who had a diagnosis of vaso-occlusive crisis (VOC) within 15 days prior to screening, had a concomitant medical illness (for example, terminal malignancy), renal or liver dysfunction, or an abnormal or conditional transcranial Doppler within the last year. Bleeding exclusion criteria included any clinical findings, in the judgment of the investigator, associated with an increased risk of bleeding, recent surgery (within 30 days prior to screening), or were scheduled to undergo surgery within the next 60 days. Prior and concomitant therapy exclusion criteria included packed RBC or whole blood transfusion therapy within 30 days prior to dosing, any nonsteroidal antiinflammatory drug (NSAID) 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.

- Treatments

During Part A, prasugrel was administered as single doses at each visit by the clinical staff. The first 2 patients received a dose of 0.03 mg/kg, which was expected to be sub-therapeutic. Doses were increased or decreased as appropriate, depending on the PD response to previous doses in other patients and/or in the same patient. Single dose escalation in Part A was evaluated in a cohort of older children (8 to <18 years) before similar or lower single doses were assessed in younger children. Treatment duration during Part A: Up to 3 single doses of prasugrel with 14±4 days between doses.

In Part B, the initial dose level was 0.08 mg/kg. This dose was predicted to produce a mean of approximately 30% platelet inhibition at steady state based on Pop PK-PD modeling of data from Part A in conjunction with previous experience in the adult acute chest syndrome population. Patients received the first 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 mg/kg or 0.06 mg/kg for the first dosing period. Study drug was taken at home daily thereafter. The second dose level (initiated on Visit 202 at the study site, and self-administered thereafter until the day before Visit 203) was chosen based on an individual patient's PD response at steady state following the initial dosing period. All patients were either up titrated to a 0.12-mg/kg dose level or down titrated to a 0.06-mg/kg dose level to achieve appropriate level of platelet inhibition. Treatment duration during Part B: 20-36 days of treatment and an additional 3 to 5 days for 3 visits after treatment ends.

The investigator or his/her designee was responsible for explaining the correct use of the investigational agent to the patient and parents/legal representatives, verifying that instructions were followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

The patient and/or parents/legal representatives were instructed to contact the investigator as soon as possible if he or she had a complaint or problem with the investigational product so that the situation could be assessed.

Patients completing Part A were not required to participate in Part B of the study.

- Outcomes/endpoints

<u>Pharmacokinetic/Pharmacodynamic:</u>

Primary:

- PK: The primary pharmacokinetic parameter was the area under the Pras-AM concentration-time curve through the last sampling time of 4 hours postdose (AUC[0-tlast])

- PD: Pharmacodynamic variables included vasodilator-associated phosphoprotein (VASP) platelet reactivity index (PRI) and derived percent platelet inhibition and VN P2Y12 reaction units (PRU), derived percent platelet inhibition, and device-reported percent platelet inhibition

Secondary:

- Biomarkers: Biomarker parameters included platelet-neutrophil aggregates (PNA) and/or platelet monocyte aggregates (PMA), soluble CD40 ligand and soluble P-selectin

Safety:

Secondary:

- Hemorrhagic events requiring medical intervention, treatrment-emergent adverse events (TEAEs) and hemorrhagic TEAEs, study drug discontinuation due to AEs or hemorrhagic AEs, clinical laboratory results

Efficacy:

Secondary:

- At Visits 201, 202 and 203, the patient was asked to respond to specific questions related to the incidence and severity of their SCD pain

Bioanalytical:

Secondary:

- Plasma concentrations of the active metabolite (R138727) were determined using validated liquid chromatography with tandem mass spectrometry methods

- Statistical Methods

Pharmacokinetics/Pharmacodynamics: The PK of Pras-AM was analyzed by both noncompartmental (NCA) and population methods. Likewise, PK-PD relationships were assessed descriptively and through population modeling approaches. Noncompartmental PK analyses (NCA) were conducted using Model 200 (extravascular dosing), linear-log trapezoidal method, and uniform weighting scheme in WinNonlin version 5.3. Descriptive PK-PD, or exposure-response analyses were then performed to assess the relationship between Pras AM exposures and clinically relevant measure(s) of platelet inhibition (VN and VASP) at 4 hours postdose following single doses in Part A and at steady-state platelet inhibition following multiple doses at Visit 202 and Visit 203 in Part B. Relationships were further characterized by simple first- and second-order regression curves, where appropriate.

A mixed model was used to compare the dose effect of each PD and biomarker parameter after 14±4 days of daily dosing. The subject effect was fit as a random effect and the dose effect as a fixed effect, with baseline measurement as a covariate. All PD and biomarker parameters, including changes from baseline, were summarized by dose using descriptive statistics. A one-sample t-test was used to test if the change from baseline for each dose is significantly different than zero. For Part B, a mixed model was used to compare the dose effect of each PD and biomarker parameter after 10 to 18 days of daily dosing. PD results were described using ping-pong and box-whisker plots. A listing of each PD parameter was created for each part of the study. A sensitivity analysis was performed for Part B to assess the effect that treatment compliance has on the PD parameters.

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.

Bioanalytical: Metabolites R138727_MP, R106583, and R119251 were analyzed using the validated methods 110886. R106583 was also analyzed using the validated method 110938.

Results

- Recruitment/ Number analysed

In total, 33 patients were enrolled in the study. 24 patients entered Part A, and 18 patients entered Part B. 9 patients in Part B had previously participated in Part A. A total of 29 patients were treated during the entire planned treatment period. There were 4 drop-outs: In Part A, 1 patient withdrew consent and 2 patients discontinued the study prior to their third single dose due to Sponsor decision since there were already sufficient data collected in Part A. In Part B, 1 patient discontinued the study after Visit 204 due to Sponsor decision because the patient was not able to complete Visit 205 within the time frame specified in the protocol.

- Baseline data

Patient demographics were similar in Part A and Part B. Overall, in Study TACX, 57.6% of patients were female; 97.0% were Black or African American and 3.0% were Native Hawaiian or other Pacific Islander; 90.9% had HbSS and 9.1% had HbS β0-thalassemia. Body weight ranged from 14.4 to 80.1 kg. The mean age was 10.58 years (range 4.3-17.9 years).

The majority of patients had a history of acute chest syndrome (72.7%) and vaso-occlusive crisis (72.7%). Thirteen patients (39.4%) had at least 1 pre-existing condition other than sickle cell disease, the most common being asthma (n=9; 27.3%).

Twenty-three patients (95.8%) in Part A and 18 patients (100.0%) in Part B were taking at least 1 prior or concomitant medication. Hydroxyurea was the most common type of medication reported in both Part A (n=15; 62.5%) and Part B (n=13; 72.2 %) One patient (4.2%) received concomitant treatment with ketorolac during Part A, and no patients received ketorolac during Part B.

- Efficacy results

PK-PD: There was minimal platelet inhibition following single doses of prasugrel up to approximately 0.25 mg/kg in pediatric patients with SCD. PD response increased with single doses above 0.25 mg/kg. Exposure to Pras-AM increased with increasing single doses. The single 0.60 mg/kg dose produced >50% inhibition by both VN and VASP assays. Greater variability in exposure and in PD response was seen at higher doses.

Steady-state platelet aggregation was reduced following daily prasugrel doses of 0.06 mg/kg, 0.08 mg/kg, and 0.12 mg/kg in pediatric patients with SCD. In general, individual patient response increased with an increase in daily dose. No patient had a steady-state platelet inhibition below 30% at the 0.12 mg/kg dose, and only 1 patient had a steady state platelet inhibition above 60% on the lowest dose of 0.06 mg/kg. VN derived platelet inhibition was significantly higher and PRU was significantly lower in patients given 0.12 mg/kg compared to 0.06 or 0.08 mg/kg. These results suggest that with daily prasugrel doses of 0.06 mg/kg, 0.08 mg/kg, and 0.12 mg/kg, a majority of

pediatric patients with SCD can be titrated to a dose that produces 30 to 60% platelet inhibition at steady state.

Efficacy: There was little change from baseline in the number of patients reporting sickle cell pain, use of analgesics, and missing school as a result of sickle cell pain following two weeks of prasugrel treatment compared to baseline. However, the study was neither powered nor designed to provide to evaluate efficacy, so no conclusion can be made based on these results.

- Safety results

Safety: No deaths were reported during the study and there were no AEs leading to study drug discontinuation. In Part A, there were no hemorrhagic AEs or AEs considered to be related to 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. The 3 events were considered mild in severity. There were 3 hemorrhagic events in 3 patients that occurred in Part B. All three of these events were mild in severity and none required medical intervention.

A total of 3 SAEs occurred during Part A of the study and 3 SAEs occurred in Part B. All of these events were related to the underlying medical condition of SCD and none were deemed to be related to study drug by the site investigator. All patients recovered with the exception of the single patient in Part A (age 17) who experienced severe sickle cell anemia with crisis. This patient did recover outside the reporting period for this study.

1. Discussion on clinical aspects

The primary aim of Study TACX was to characterize the relationships among prasugrel dose, exposure to prasugrel active metabolite (Pras-AM), and platelet inhibition in paediatric patients with sickle cell disease (SCD) in order to identify a dose of prasugrel that produces a 30 to 50% platelet inhibition in this population. This range of platelet inhibition was selected because it corresponds to the range produced by the ticlopidine 500 mg daily dose (Thebault et al 1999) which was studied previously in adults with SCD (Cabannes et al 1984) as well as to the range produced by the clopidogrel 0.2 mg/kg daily dose that was well tolerated in infants and young children with congenital heart disease (Li et al 2008, Wessel et al 2010).

In Part A, single escalating doses resulted in increased exposure and significantly correlated with the PD response. Variability in exposure was higher at higher single doses than at lower doses, whereas variability in PD response tended to increase with increasing dose to a point, and then decreased as platelet inhibition approached its maximum effect.

In Part B, dose-dependent increases in exposure were observed at the three fixed doses administered. Steady-state PD showed considerable inter-patient variability. Following the starting dose of 0.08 mg/kg, steady state platelet inhibition ranged from 0 to 79%, with only 3 patients (16.7%) achieving the target range of 30 to 50% steady state platelet inhibition. Dose increases to 0.12 mg/kg or decreases to 0.06 mg/kg, as appropriate, brought more patients within the target range of platelet inhibition. No patient failed to meet the minimum PD response of 30% on the 0.12 mg/kg dose, while 3 of 8 patients (37.5%) exceeded 50% platelet inhibition on the lowest dose of 0.06 mg/kg dose. The platelet inhibition levels for 2 of these 3 patients were only slightly above the maximum level at 52% and 54%. Only 1 patient exceeded a 60% platelet inhibition on the 0.06 mg/kg prasugrel dose. These results suggest that with prasugrel doses of 0.06 mg/kg, 0.08 mg/kg, or 0.12 mg/kg, the target level of steady state platelet inhibition can be achieved for most pediatric patients with SCD. Furthermore,

PD measurements at post-treatment follow up visits suggest that, for each of the doses studied, platelet function began to approach baseline levels within 96 hours of the last dose of study drug.

The variability in steady state platelet inhibition seen in Study TACX precludes identification of a single mg/kg prasugrel dose to produce steady state platelet inhibition within the target range of 30 to 50% in all patients. A dose titration strategy may be appropriate in future studies to safely identify an appropriate dose to achieve targeted platelet inhibition for each individual patient.

Prasugrel appeared to be safe and well tolerated in paediatric patients with SCD at all 3 daily doses administered during this study. No deaths were reported during the study and no AEs led to study drug discontinuation. There were 3 SAEs in Part A and 3 SAEs in Part B, all of which were related to the underlying medical condition of SCD. In Part A, no haemorrhagic events occurred. In Part B, 3 haemorrhagic events occurred in 3 patients. None of these haemorrhagic events required medical intervention. Two of these events were considered related to study drug by the Study Investigator. Both events were classified as mild and the patients recovered.

Study TACX was not designed to assess efficacy, and due to the short study period and limited sample size, no conclusions could be drawn from the pain questionnaire.

In summary, results of Study TACX indicate that in paediatric patients with SCD:

- Increasing weight-based doses of prasugrel lead to increasing exposures to Pras-AM that, in turn, results in increased platelet inhibition.
- With a dose-titration strategy, daily dosing at 0.06 mg/kg, 0.08 mg/kg, or 0.12 mg/kg prasugrel leads to clinically relevant platelet inhibition at steady state.
- Prasugrel appears to be safe and well tolerated at the single and multiple daily doses administered.

Rapporteur's overall conclusion and recommendation

The intention of this study was to assess whether titration of prasugrel to 30-50% platelet inhibition in as measured by the VerifyNow® P2Y12 (VN) analysis. The rationale behind this is that during veno-occlusive crisis (VOC) experienced by sickle cell disease patients an increase in platelet activation is seen, and consequently inhibition of platelet activation might contribute to limiting or alleviating VOC.

In addition, the current treatment of sickle cell disease in adults consists of hydroxyurea which is less attractive in children due to concerns regarding possible genotoxicity and carcinogenesis. The results of this study will inform dosing decisions in future studies of prasugrel in pediatric populations including an ongoing Phase 3 study of prasugrel vs. placebo. The rationale of the present study is considered justified.

The primary objective was to characterize the relationship between prasugrel dose, exposure to prasugrel active metabolite (Pras-AM), and platelet inhibition in pediatric patients with sickle cell disease. Secondary objectives were to evaluate the adequacy of a correlation model to estimate the Pras-AM concentration from the measured concentration(s) of its inactive metabolite(s) and to address the short-term efficacy, safety and tolerability of prasugrel in pediatric patients with sickle cell disease. The study was not powered to evaluate efficacy so this part of the study was of exploratory interest only. The study objectives are regarded relevant as they will contribute valuable knowledge when designing future studies of prasugrel in children with sickle cell disease.

The study was a Phase 2 study and it was designed as an open-label adaptive-design trial. During Part A, single-escalating doses of prasugrel were analysed in the VN analysis, and PK/PD analyses were performed. During Part B it was assessed whether maintenance doses titrated to the individual patient could keep a steady degree of platelet inhibition of between 30-50%. It is considered justified to use a non-randomized, open-label design as the efficacy assessments were of exploratory interest only. Since it is well known that patients display large inter-patients variability in response to prasugrel it is equally considered justified to assess whether a steady degree of platelet inhibition can be maintained in the individual patient when titrated to an individual dose since intra-patient variability might also be an issue of concern.

A total of 33 patients entered the trial (24 in Part A, 18 in Part B) and 29 completed corresponding to a drop-out rate of approximately 12%. 2 of the 4 drop-outs discontinued due to a Sponsor decision as sufficient data had already been gathered. The drop-out rate is considered sufficiently low to preserve credibility of the study results.

The prasugrel concentrations used in the respective treatment regimens in this study correspond approximately to the recommended maintenance dose of prasugrel in adult patients in relation to PCI treatment (0.12 mg/kg) or are lower. The dose titration to the individual patient is based on analysis of platelet inhibition in the VN analysis which is considered justified.

In the study, 57.6% of patients were female; 97.0% were Black or African American and 3.0% were Native Hawaiian or other Pacific Islander; 90.9% had HbSS (homozygous sickle cell) and 9.1% had HbS β0-thalassemia. Body weight ranged from 14.4 to 80.1 kg. The mean age was 10.58 years (range 4.3-17.9 years). The majority of patients had a history of acute chest syndrome (72.7%) and vaso-occlusive crisis (72.7%). Thirteen patients (39.4%) had at least 1 pre-existing condition other than sickle cell disease, the most common being asthma (n=9; 27.3%). Twenty-three patients (95.8%) in Part A and 18 patients (100.0%) in Part B were taking at least 1 prior or concomitant medication. Hydroxyurea was the most common type of medication reported in both Part A (n=15; 62.5%) and Part B (n=13; 72.2 %). The study population is considered representative of children with sickle cell disease and it is regarded justified that the results may be extrapolated to other children with sickle cell disease.

PK/PD:

Regarding PK/PD the study finds minimal platelet inhibition following single doses of prasugrel up to approximately 0.25 mg/kg in pediatric patients with SCD while PD response increased with single doses above 0.25 mg/kg. Exposure to Pras-AM increased with increasing single doses. The single 0.60 mg/kg dose produced >50% inhibition by both VN and VASP assays. Greater variability in exposure and in PD response was seen at higher doses. These findings are considered plausible and the greater variability in exposure and in PD response seen at higher doses is in line with expectations.

In general, a dose-response relationship in reduction of platelet aggregation was observed with increasing doses of prasugrel. No patient had a steady-state platelet inhibition below 30% at the 0.12 mg/kg dose, and only 1 patient had a steady state platelet inhibition above 60% on the lowest dose of 0.06 mg/kg. VN derived platelet inhibition was significantly higher and PRU was significantly lower in patients given 0.12 mg/kg compared to 0.06 or 0.08 mg/kg. The investigators conclude that these results suggest that daily prasugrel doses of 0.06 mg/kg, 0.08 mg/kg, and 0.12 mg/kg, a majority of pediatric patients with SCD can be titrated to a dose that produces 30 to 60% platelet inhibition at steady state and this is considered reasonable.

Efficacy:

Regarding efficacy, only little change from baseline in the number of patients reporting sickle cell pain, use of analgesics, and missing school as a result of sickle cell pain following two weeks of prasugrel treatment compared to baseline was reported. The investigators state, however, that since the study was neither powered nor designed to provide to evaluate efficacy, no conclusion can be made based on these results. This conclusion is regarded acceptable.

Safety:

No deaths occurred during the study.

Regarding AEs, no AEs led to study drug discontinuation. In Part A, the rate of AEs was low and they were considered mild. In Part B, there were 3 AEs (epistaxis, eyelid bleeding, and middle ear effusion) in 3 patients that were possibly related to study drug. The 3 events were considered mild in severity. There were 3 hemorrhagic events in 3 patients that occurred in Part B. All three of these events were mild in severity and none required medical intervention.

Regarding SAEs, a total of 3 SAEs occurred during Part A of the study and 3 SAEs occurred in Part B. All of these events were related to the underlying medical condition of SCD and none were deemed to be related to study drug by the site investigator.

In general, the rate, nature and degree of AEs and SAEs are considered acceptably low.

Overall conclusion

The investigators conclude that overall the results of the present study indicate that in paediatric patients with SCD:

- Increasing weight-based doses of prasugrel lead to increasing exposures to Pras-AM that, in turn, results in increased platelet inhibition.
- With a dose-titration strategy, daily dosing at 0.06 mg/kg, 0.08 mg/kg, or 0.12 mg/kg prasugrel leads to clinically relevant platelet inhibition at steady state.
- Prasugrel appears to be safe and well tolerated at the single and multiple daily doses administered.

These conclusions are considered acceptable and justified. The possible therapeutic impact of these results must be evaluated in future studies addressing the clinical efficacy of prasugrel in children with sickle cell disease.

Recommendation

☒ **Fulfilled**

No regulatory action required

☐ **Not fulfilled**

Additional clarifications requested

Not applicable