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Ticagrelor versus placebo for the reduction of vaso-occlusive crises in pediatric sickle cell disease: Rationale and design of a randomized, double-blind, parallel-group, multicenter phase 3 study (HESTIA3)☆

Matthew M. Heeney[a,*], Miguel R. Abboud[b], Carl Amilon[c], Marielle Andersson[c], Jessie Githanga[d], Baba Inusa[e], Julie Kanter[f], Maria Leonsson-Zachrisson[c], Alan D. Michelson[g], Anders R. Berggren[c], on behalf of the HESTIA3 study investigators

[a] Division of Hematology/Oncology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, USA
[b] American University of Beirut Medical Center, Cairo Street, Beirut, Lebanon
[c] BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Pepparedsleden 1, Mölndal 431 83, Sweden
[d] Hematology and Blood Transfusion Unit, Department of Human Pathology, University of Nairobi, P. O. Box 19676, Nairobi 00202, Kenya
[e] Paediatric Hematology, Guy's and St Thomas' NHS Trust, Evelina London Children's Hospital, Westminster Bridge Rd, Lambeth, London SE1 7EH, UK
[f] Hematology-Oncology, Department of Medicine, University of Alabama at Birmingham, 2000 6th Avenue S, Birmingham, AL 35233, USA
[g] Center for Platelet Research Studies, Division of Hematology/Oncology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Karp 08213, Boston, MA 02115, USA

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ABSTRACT

Background: An unmet need for therapies exists to reduce sickle cell disease (SCD) complications in pediatric patients. Activated platelets contribute to the formation of cellular aggregates during sickling and vaso-occlusive crises (VOCs). Ticagrelor is an oral, direct-acting, and reversible adenosine diphosphate $P2Y_{12}$ receptor antagonist that inhibits platelet activation and aggregation. Although ticagrelor was well tolerated in two phase 2 studies in children and young adults with SCD, larger and longer-term treatment studies are needed to assess ticagrelor's efficacy to reduce VOCs. HESTIA3 will evaluate the efficacy, safety, and tolerability of ticagrelor versus placebo over a minimum of 1 year (maximum 2 years) in pediatric patients with SCD.

Methods: Approximately 180 patients (aged ≥ 2 to < 18 years) with SCD (≥ 2 VOCs in the prior year) from 18 countries will be randomized 1:1 to ticagrelor or placebo. Primary endpoint: number of VOCs (a composite endpoint of painful crises and/or acute chest syndrome); key secondary endpoints: hospitalizations, pain intensity and analgesic use during VOCs, acceptability of formulation, and health-related quality of life. The weight-based doses of ticagrelor are set by modeling and simulation. Platelet inhibition data, measured by the vasodilator-stimulated phosphoprotein assay, will be collected for exploratory purposes.

Conclusions: HESTIA3 aims to demonstrate that using greater target platelet inhibition than previous studies on SCD, ticagrelor will decrease the frequency of VOC in pediatric patients.

Trial Identifier: NCT03615924; EudraCT2017-002421-38.

Abbreviations key

ACS	acute chest syndrome
ADP	adenosine diphosphate
AE	adverse event
BID	twice daily
DOVE	Determining Effects of Platelet Inhibition on Vaso-Occlusive Events
eDevice	electronic device
eNOS	endothelial nitric oxide synthase
Hb	hemoglobin

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* Corresponding author at: Division of Hematology/Oncology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, USA.
E-mail addresses: matthew.heeney@childrens.harvard.edu (M.M. Heeney), ma56@aub.edu.lb (M.R. Abboud), carl.amilon@astrazeneca.com (C. Amilon), Marielle.Andersson@astrazeneca.com (M. Andersson), jessie.githanga@uonbi.ac.ke (J. Githanga), Baba.Inusa@gstt.nhs.uk (B. Inusa), kanter@musc.edu (J. Kanter), Maria.Leonsson-Zachrisson@astrazeneca.com (M. Leonsson-Zachrisson), Alan.Michelson@childrens.harvard.edu (A.D. Michelson), anders.r.berggren@astrazeneca.com (A.R. Berggren).

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HbS	hemoglobin S
HESTIA	tHE Sickle cell program with TIcAgrelor
MI	myocardial infarction
NO	nitric oxide
PedsQL™	Pediatric Quality of Life Inventory
PD	pharmacodynamic
PK	pharmacokinetic
PRU	$P2Y_{12}$ reaction units
RBC	red blood cell
SCD	sickle cell disease
US	United States
VOC	vaso-occlusive crisis

1. Introduction

Sickle cell disease (SCD) is a monogenic, autosomal recessive, hemoglobinopathy characterized by sickling due to hemoglobin S (HbS) [1–3]. SCD manifests as hemolytic anemia and episodic vaso-occlusive crisis (VOC) often marked by severe pain or acute chest syndrome (ACS) when pulmonary vasculature is affected [4]. SCD pathophysiology extends beyond the red blood cells involving leukocytes, platelets, and the endothelium [5–9]. Platelet activation increases during painful episodes [5] promoting adherence of sickle cells to vascular endothelium and consequent vaso-occlusion (Fig. 1A). Platelets also cause neutrophil adhesion during a VOC [6].

Until recently, hydroxyurea was the only approved treatment for reducing VOC frequency in pediatric patients aged ≥ 2 years in USA and Europe [10–12]. Studies evaluating new therapies involving endothelial blockers, cGMP modifiers, and anti-inflammatory agents are ongoing. Data on the role of platelet inhibition in preventing and treating VOCs remain limited. Biomarkers of platelet activation are elevated in SCD [13–18], making platelets potential targets for reducing VOC frequency (Fig. 1A). Effects of aspirin and ticlopidine in SCD have been tested [19,20]. Prasugrel, an irreversible $P2Y_{12}$ antagonist (Fig. 1B) investigated in the DOVE study [21] in children (2–17 years) with SCD, showed a nonsignificant reduction in the number of VOCs despite low platelet inhibition levels [21]. Newer studies evaluating the use of higher levels of platelet inhibition are needed to better understand their potential efficacy in VOC reduction.

Ticagrelor—an oral, direct-acting, reversible adenosine diphosphate (ADP) $P2Y_{12}$ receptor antagonist that inhibits platelet activation and aggregation (Fig. 1A and B) [22]—reduces cardiovascular death, myocardial infarction (MI), and stroke rates in patients with acute coronary syndrome (90 mg BID) and a history of MI (60 mg BID) [23]. The most commonly reported adverse reactions in adult patients with cardiovascular disease are bleeding and dyspnea, more rare events include reversible creatine and uric acid increases and bradycardia [23]. Ticagrelor also inhibits cellular adenosine uptake by inhibiting the equilibrative nucleoside transporter 1 (Fig. 1C) [24,25] and may contribute to the vasodilation observed in patients with acute coronary syndrome [26,27]. Vasodilation may increase oxygen supply to ischemic tissues during a VOC in SCD and limit the degree of vaso-occlusion.

Upregulation of the adhesion molecule P-selectin on endothelial cells and platelets contributes to cell-cell interactions in VOCs (Fig. 1A) [28]. A study of crizanlizumab, a P-selectin inhibitor, showed a significantly lower rate of sickle cell–related pain crises versus placebo, with a low incidence of adverse events (AEs) [28]. Ticagrelor also significantly decreased P-selectin expression (Fig. 1A) [29,30] compared with prasugrel [31], suggesting additional potential benefits of decreased platelet-leukocyte aggregates for individuals with SCD [28].

Ticagrelor may prevent VOC in SCD by several mechanisms—decreasing platelet activation, platelet-leukocyte interaction, and inflammation, while increasing nitric oxide (NO) production and vasodilation. Bioavailability of endothelial NO synthase (eNOS) generated NO is decreased in SCD by extracellular hemoglobin which scavenges NO [32,33]. Ticagrelor had positive effects on eNOS activity in endothelial cells [34–36]. Adenosine A_{2A} receptor agonists decreased hypoxia/reoxygenation-induced tissue inflammation in a mouse model and in patients with SCD [37,38]. Ticagrelor also showed stronger anti-inflammatory effects in a human model versus the $P2Y_{12}$ inhibitor clopidogrel [39] further emphasizing the importance of assessing ticagrelor's role in SCD.

1.1. The HESTIA program

The HESTIA (t**HE** **S**ickle cell program with **TIcA**grelor) program has been designed to assess the potential therapeutic benefits of ticagrelor in reducing the rate of VOCs in pediatric patients with SCD. HESTIA1 was a two-part, phase 2 study investigating the pharmacokinetics (PK), pharmacodynamics (PD), and safety of ticagrelor in 45 patients aged 2–17 years [40]. HESTIA1 was the first study to determine the dose-exposure-platelet inhibition response relationship for ticagrelor using four doses of ticagrelor (0.125, 0.563, 0.75, and 2.25 mg/kg) in children with SCD. All four doses of ticagrelor were well tolerated with no safety concerns. There were no discontinuations due to AEs, and reported AEs were mainly due to SCD and not treatment-related [40]. The HESTIA2 study randomized 87 young adults (aged 18–30 years) with SCD in a 1:1:1 ratio to ticagrelor 10 mg, ticagrelor 45 mg, or placebo BID [41]. Patients reported daily pain and analgesic use in an electronic device (eDevice) during the 4-week single-blind run-in placebo period, as well as during the 12-week randomized treatment period. Decreases in the mean proportion of days with patient-reported pain, intensity of pain, and analgesic use were similar in all three groups. Both doses of ticagrelor were well tolerated with no increase in bleeding compared to placebo. The proportion of patients experiencing AEs was similar across the groups, with no relation to the ticagrelor dose. HESTIA1 and HESTIA2 found that ticagrelor was well tolerated with a low bleeding risk. The AE profile was in keeping with what are common medical issues in patients with SCD. The phase 2 studies were not designed to evaluate the effect on VOC rate, but with the safety and PK/PD data collected, these studies underpin the rationale and design of the HESTIA3 study.

The presently described phase 3 HESTIA3 study will evaluate the efficacy, safety, and tolerability of ticagrelor versus placebo in pediatric patients in preventing vaso-occlusive pain crisis.

2. Methods

2.1. Study design and population

HESTIA3 is an international, multicenter, double-blind, randomized, parallel-group, placebo-controlled, phase 3 study to evaluate the efficacy and safety of ticagrelor versus placebo in reducing the rate of VOCs, which is the composite endpoint of painful crises and/or ACS in pediatric patients with SCD.

Approximately 180 patients with SCD (confirmed for homozygous sickle cell or sickle beta zero thalassemia) aged ≥ 2 to < 18 years and with ≥ 2 VOCs in the year prior to screening will be randomized 1:1 to ticagrelor or placebo (Fig. 2). At least 50 evaluable patients will be recruited in each of the age groups, ≥ 2 to < 12 years and ≥ 12 to < 18 years. The age of enrolled patients will be monitored during the study and the recruitment of a certain age category will be capped, if required, to ensure at least 50 evaluable patients in each category. The study will be conducted across 18 countries worldwide, including Belgium, Brazil, Canada, Egypt, Ghana, Greece, India, Italy, Kenya, Lebanon, South Africa, Saudi Arabia, Spain, Tanzania, Turkey, Uganda, the US, and the United Kingdom, at approximately 85 centers (Fig. 3). The inclusion and exclusion criteria are listed in brief in Table 1 and extensively in Supplementary Table 1.

The study will be conducted in accordance with ethical principles consistent with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and other local applicable regulatory requirements.

2.2. Study treatment protocol and follow-up

The study will comprise a screening period of 7–28 days, followed

by randomization of eligible patients to double-blind treatment with either ticagrelor or matching placebo for a period of 12–24 months using an Interactive Voice/Web Response System. Body-weight adjusted ticagrelor doses (15 mg: ≥ 12 to ≤ 24 kg body weight, 30 mg: > 24 to ≤ 48 kg body weight, or 45 mg: > 48 kg body weight BID) have been identified based on PK/PD modeling and simulation of phase 2 data (HESTIA1 and HESTIA2) [40,41]. For any patient with weight gain during the study period exceeding the upper weight-limit bands of ≥ 27 kg or ≥ 54 kg, treatment dose will be increased according to the next higher weight band. The ticagrelor formulation and matching placebo will be given as tablets, which can either be swallowed whole or dispersed in a small amount of fluid before drinking depending on the patients' age and/or preferences. The ticagrelor formulation used in HESTIA3 is exclusive to this study and the same formulation can be used in a wide range of pediatric ages.

The selected ticagrelor doses are projected to achieve greater platelet inhibition than those observed in the earlier efficacy trial of platelet inhibition in pediatric patients with SCD [21]. The predicted level of platelet inhibition with the selected doses in HESTIA3 will be 35%–80% platelet inhibition from baseline (corresponding to 180 and 55, respectively, in absolute $P2Y_{12}$ reaction units [PRU] levels assuming a baseline of 280). The platelet inhibition range is based on population PK/PD modeling analyses based on the HESTIA1 and HESTIA2 studies [40,41]. The encouraging trend in efficacy reported for prasugrel, despite a modest platelet inhibition level (mean PRU of 207 corresponding to ~20% reduction from baseline) [24], motivated the inclusion of a greater level of inhibition in HESTIA3.

Other concomitant treatments that may be used in SCD (e.g., hydroxyurea and L-glutamine) during the study will not be withheld from the study participants, which is important considering the use of a placebo-controlled group. The body weight–adjusted doses of hydroxyurea should be stable for 3 months prior to enrollment. L-glutamine may be given at the investigator's discretion.

Patients will be followed up until a common study end date is reached, which is defined as 12 months after the last patient is randomized, but no longer than 24 months. Monthly telephone calls will take place between the on-site visits, involving the study investigator at the site and the patient's caregiver. AEs will be collected from the time of randomization and throughout the study, including the follow-up period (Fig. 2).

2.3. Study endpoints and assessments

2.3.1. Efficacy

The primary objective of HESTIA3 will be to compare the efficacy of ticagrelor versus placebo in reducing the number of VOCs (composite of a painful crisis and/or an ACS event) in pediatric patients aged ≥ 2 to < 18 years with SCD. In comparison to previous trials, patients will not record pain levels daily. Instead, patients will utilize an event diary to record pain that occurs due to a VOC on a handheld electronic device (eDevice). For this study, a painful crisis is defined as an onset or worsening of pain that lasts ≥ 2 h, for which there is no explanation other than vaso-occlusion, and requires therapy with oral or parenteral opioids, parenteral nonsteroidal anti-inflammatory drugs, or other analgesics prescribed by a health care provider in a medical setting (e.g., hospital, clinic, or emergency room visit) or at home. ACS is defined by a new pulmonary infiltrate on chest X-ray with an acute illness characterized by fever and/or respiratory symptoms [4]. All potential pain crises or ACS events will be recorded as judged by the investigator to fulfill the definition of the primary endpoint.

The secondary and exploratory outcome measures are listed in Table 2. Pain intensity during a suspected VOC event will be recorded using the Face, Legs, Activity, Cry, Consolability Scale (Fig. S1) [42] and the Faces Pain Scale-Revised (Fig. S2) [43] assessment tools by caregivers for patients aged 2–4 years and by the patients themselves for those aged ≥ 5 years daily during the VOC event, respectively [42,43]. A body outline diagram will be presented, and the patient/caregiver will be asked to indicate the location(s) of pain (Fig. S3). Details of analgesic use during the event will be collected.

Health-related quality of life will be measured by the Pediatric Quality of Life Inventory™ (PedsQL™) SCD module and fatigue total score and by dimension using the PedsQL™ Multidimensional Fatigue Scale [44]. The SCD module consists of 43 items and measures problems with the patients' pain (severity, impact, and management/control), worry, emotions, treatment, and communication, whereas the Multidimensional Fatigue Scale consists of 18 items measuring problems with general, sleep/rest, and cognitive fatigue. Both tools have been developed in age-specific versions—patient-reported for ages 5–18 years and parent-reported for ages 2–4 years—with good clinical utility [45,46]. In this study, the patient-reported versions will be used for patients aged 5–7, 8–12, and 13–18 years, whereas the parent-reported version will be used for ages 2–4 years and be reported by a caregiver.

Absence from school/work due to SCD will be recorded weekly by patients with the help of caregiver, if needed.

Palatability and swallowability of the study medication will be assessed in patients aged ≥ 5 years after taking the study medication, dispersed or whole, using the Facial Hedonic Scale (Fig. S4) [47] and in patients aged < 5 years by observer assessment. Platelet inhibition measured by the vasodilator-stimulated phosphoprotein assay, and PK samples will be collected at selected visits for exploratory purposes.

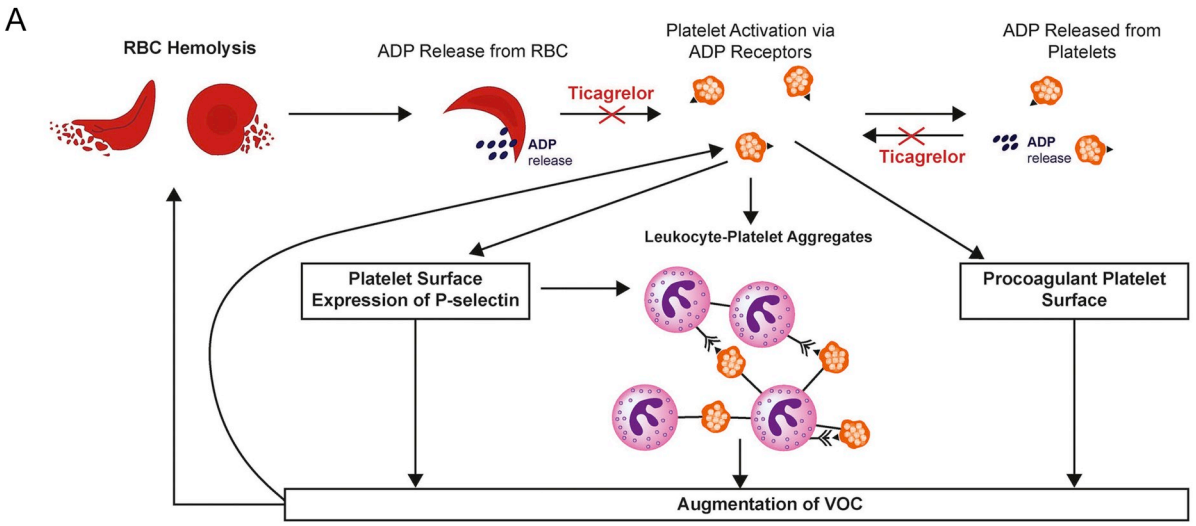
2.3.2. Safety

AEs will be recorded from the time of randomization and throughout the study, including follow-up period. Bleeding and dyspnea are the most common adverse reactions observed with ticagrelor [23]. Any events of dyspnea will be collected as part of the standard AE recording. Any bleeding will be collected in a more detailed way, where investigators are to classify each bleeding event into one of three categories (definitions are included in Supplementary Table 2): major bleeding; clinically relevant non-major bleeding; or minor bleeding [48]. Safety laboratory assessments at study start and during treatment will include collection of blood and urine samples for determination of clinical chemistry, hematology, virology, coagulation, and urinalysis. Local clinical routine procedures to reduce pain and discomfort from blood sampling in children will be followed (e.g., offering topical anesthesia, coordinated sampling to avoid repeated punctures, and use of in-dwelling catheters) as appropriate in accordance with the ethical and instructional guidelines for pediatric blood sampling. Urine pregnancy test will be taken at all visits for females of child-bearing potential. Safety assessments will also include physical examinations, electrocardiogram recordings, and monitoring of vital signs, body weight, and height during the study. Safety will be judged by the investigator and by laboratory assessments. An independent Data and Safety Monitoring Board will review the unblinded study results during the trial with increased attention on bleeding events.

2.4. Statistical analyses

The sample size of ~180 patients randomized in a 1:1 ratio to ticagrelor or placebo, assuming a reduction of 50% in the ticagrelor group will provide approximately 90% power for a two-sided test of the mean number of crises between the treatment groups, at a 5% significance level with a negative binomial regression model. The assumption on effect size is based on earlier studies with other ADP inhibitors or agents acting on similar pathways [19,21,28,49]. The calculations are based on simulations, assuming that the number of VOCs have a negative binomial distribution with a shape parameter of 0.8 mean number of VOCs per year in the placebo group is 2, and average follow-up is of 18 months with 15% dropouts.

The primary analysis will be based on the intent-to-treat principle. Ticagrelor data will be pooled and analyzed irrespective of the body



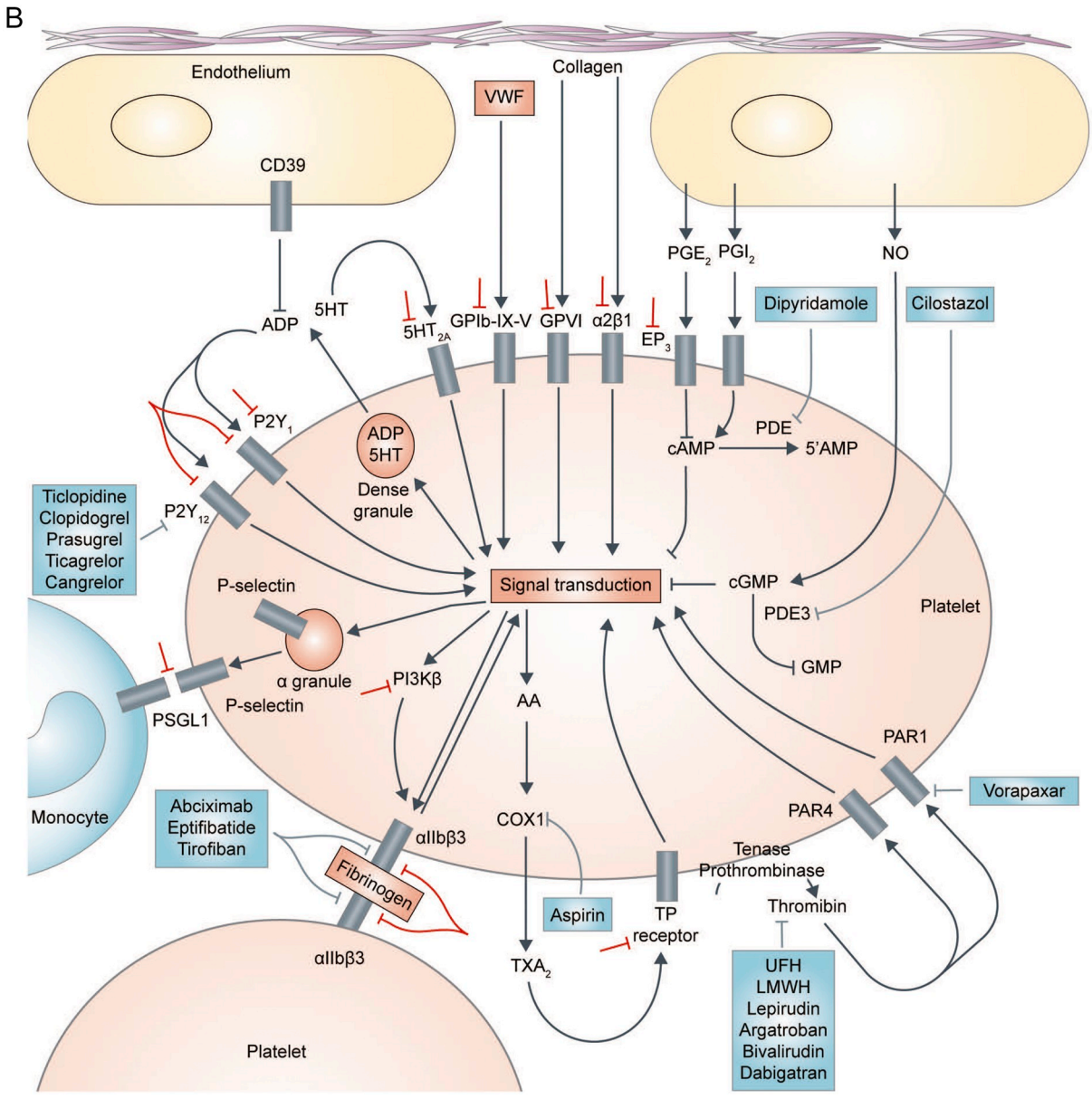


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Fig. 1. Mechanisms of action of ticagrelor in platelet inhibition. (A) Pathophysiology and role of platelet activation in SCD. The red arrows indicate the inhibitory effects of ticagrelor. (B) Antiplatelet agents and their platelet inhibition pathway. The primary mechanism of action of ticagrelor is reversible antagonism of the $P2Y_{12}$ receptor, which results in inhibition of ADP-mediated platelet activation and aggregation. The US Food and Drug Administration-approved antiplatelet agents are shown in blue boxes. Novel antiplatelet agents in development are shown by red bars. Modified with permission from Michelson AD. Nat Rev. Drug Discovery 2010; 9:154–169. (C) Antiplatelet effect of ticagrelor: dual pathway. Schematic representation of the dual mode of platelet aggregation inhibition by ticagrelor. Ticagrelor inhibits platelet aggregation by antagonizing $P2Y_{12}$, which mediates ADP-induced platelet activation/aggregation (in collaboration with another platelet ADP receptor, $P2Y_1$, not indicated in the figure). In addition, ticagrelor increases extracellular adenosine concentration by inhibiting its cellular uptake through ENT1; extracellular adenosine then activates the platelet A_{2A} receptor, which stimulates the production of cAMP by AC, thereby inhibiting platelet activation/aggregation. In addition, the antagonism of $P2Y_{12}$ (which inhibits AC) by ticagrelor amplifies the inhibitory effect on platelet activation/aggregation of adenosine and other agents that stimulate the production of cAMP by AC. Reproduced with permission from Nylander S et al. [24]. Copyright © 1999–2018 John Wiley & Sons, Inc. All rights reserved.
Abbreviations: α2β1, integrin collagen receptor; CD, cluster of differentiation; 5HT, 5-hydroxytryptamine; 5HT2A, 5-hydroxytryptamine 2A receptors; AA, arachidonic acid; AC, adenylyl cyclase; ADP, adenosine diphosphate; AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COX1, cyclooxygenase 1; ENT1, equilibrative nucleoside transporter 1; EP3, prostaglandin E2 receptor EP3 subtype; Gi, G inhibitory alpha subunit; GMP, guanosine monophosphate; GPVI, glycoprotein VI; GPIb-IX-V, transmembrane glycoprotein complex; Gs, G stimulatory alpha subunit; LMWH, low-molecular-weight heparin; NO, nitric oxide; PAR1 and PAR4, proteinase-activated receptor 1 and 4; PDE, phosphodiesterase; PG, prostaglandin; PI3Kβ, phosphoinositide 3-kinase β-isoform; PSGL1, P-selectin glycoprotein ligand 1; RBC, red blood cell; TP, thromboxane prostanoid; TXA2; thromboxane A2; UFH, unfractionated heparin; US, United States; VOC, vaso-occlusive crisis; VWF, von Willebrand factor. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

weight–based dose given. The number of VOCs will be analyzed using negative binomial regression. Any VOC event with an onset date within 7 days from a prior event onset date will not be counted as a new episode. As the follow-up time for a patient in the study is expected to differ between 12 and 24 months, patient follow-up time (log-transformed) will be included as an offset in the linear predictor to adjust for patients having different follow-up times. Additional covariates to be adjusted for in the linear predictor will be treatment group (placebo as reference group) and baseline hydroxyurea therapy (yes or no). The consistency of treatment effect on the primary endpoint across different subgroups will be explored, for example, in patient subgroups based on VOC rate in the year prior to enrollment.

Secondary endpoints, including number of painful crises, number of ACSs, duration of painful crises, number of VOCs requiring hospitalization or emergency department visits, number of days hospitalized for VOC and acute SCD complications, number of acute SCD complications, and sickle cell-related red blood cell transfusions, will be evaluated using the same analysis method as that for the primary endpoint.

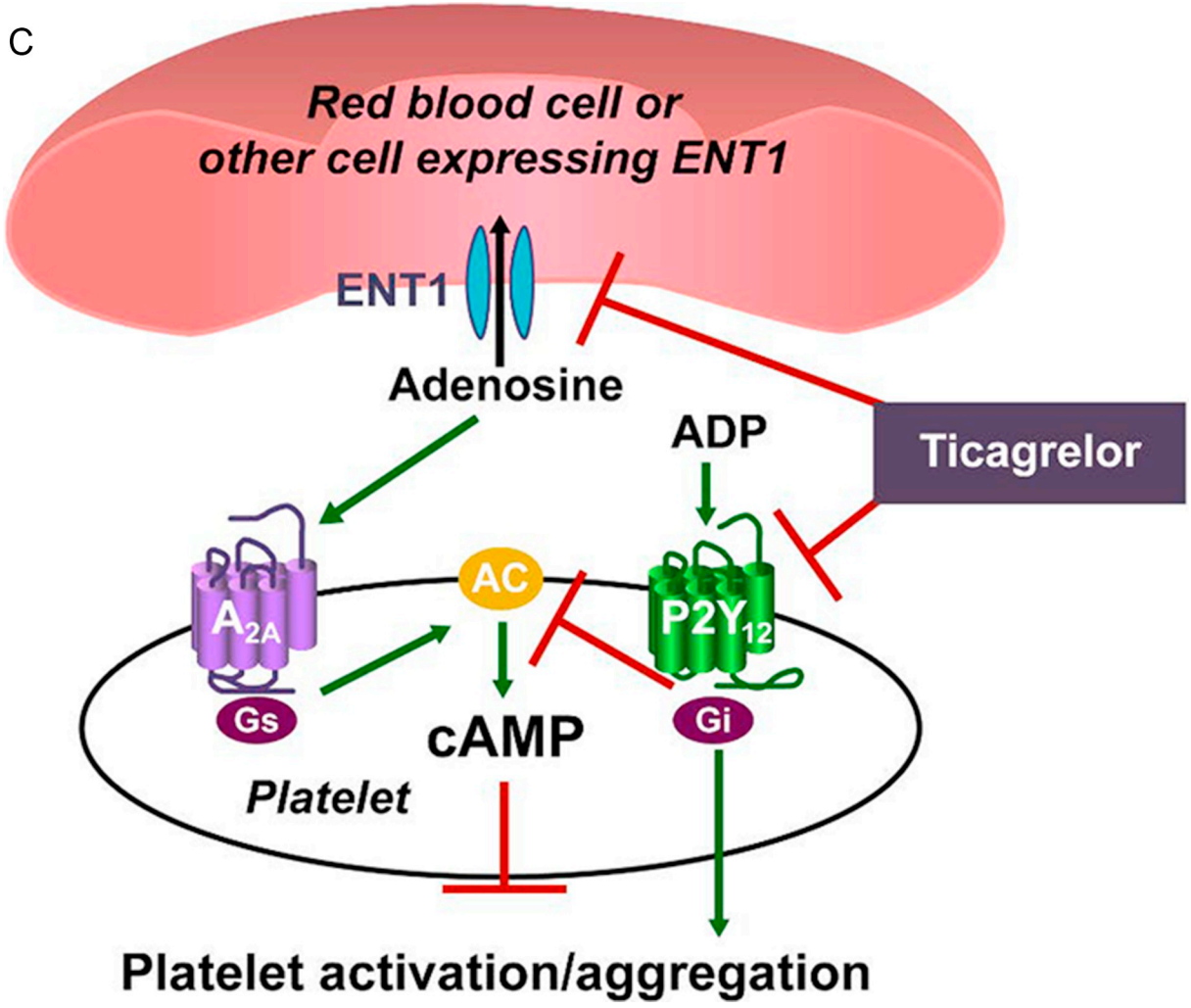

Fig. 1. (*continued*)

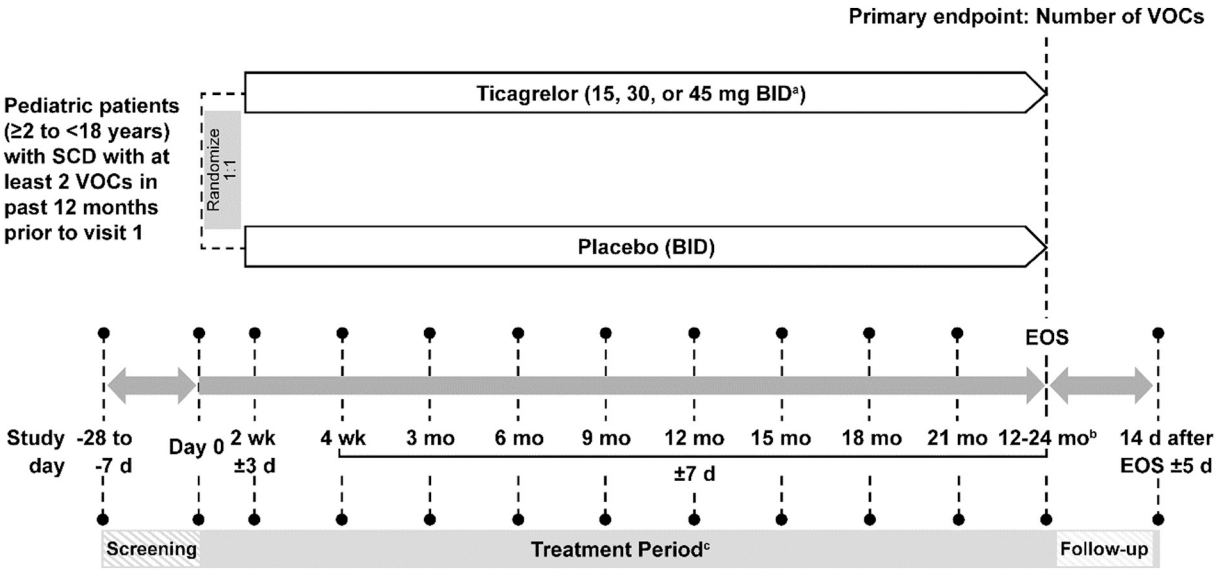

Fig. 2. HESTIA3 study design.
[a]Patients randomized to ticagrelor will receive doses based on body weight band (at screening) as follows: 15 mg: ≥ 12 to ≤24 kg; 30 mg: > 24 to ≤48 kg; 45 mg: > 48 kg.
[b]EOS: all patients will be followed up to common study end date defined as 12 mo after the last patient is randomized or up to approximately 24 mo.
[c]Telephone visits will occur monthly after wk. 4 between site visits.
Abbreviation: BID, twice daily; d, days; EOS, end of study; mo, months; SCD, sickle cell disease; VOC, vaso-occlusive crisis; wk., week.

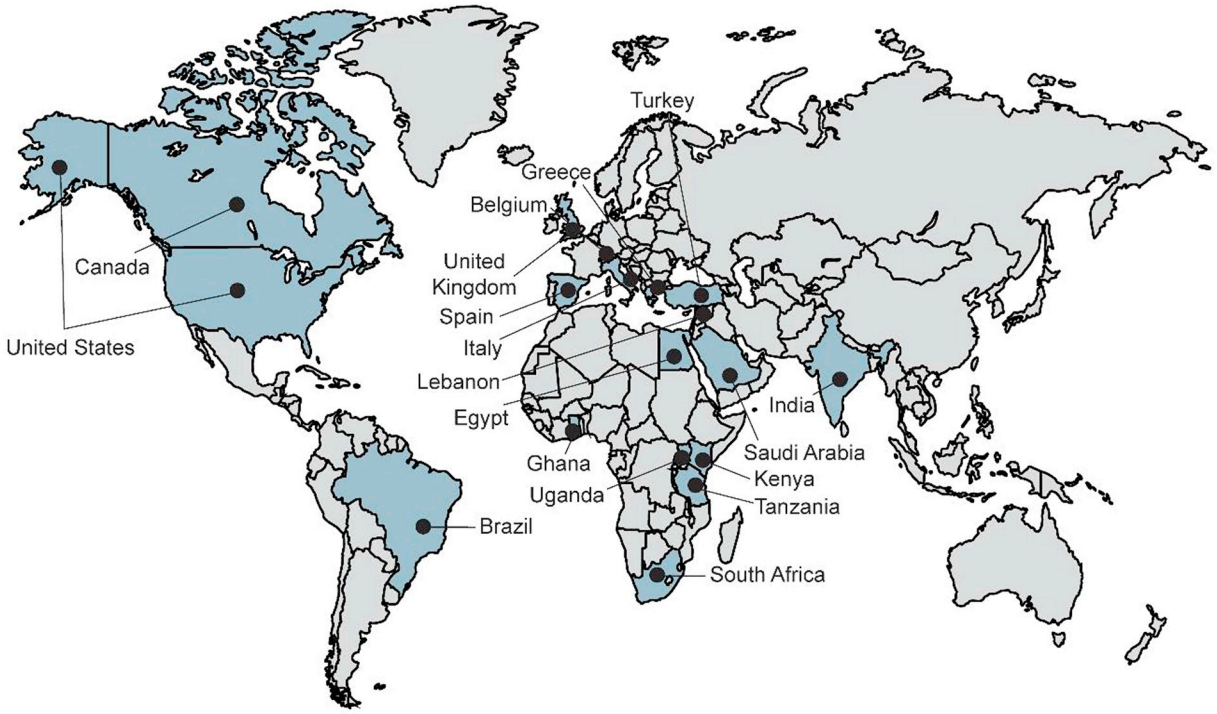

Fig. 3. Countries* where patients are planned to be enrolled in HESTIA3.
*Subject to regulatory and ethics approval for participation in HESTIA3 being received.

Descriptive statistics will be presented for the other secondary endpoints. AEs will be coded using the Medical Dictionary for Regulatory Activities.

3. Importance of the HESTIA3 study

There is an immediate need for effective and well-tolerated therapies for the prevention of SCD complications that can be universally employed. Considering the unmet need for new therapies in SCD, further studies evaluating platelet inhibition in patients with SCD are warranted.

Previous studies have investigated the efficacy of other platelet inhibitors including aspirin, ticlopidine, and prasugrel [19,20,49,50]. However, due to the study design, inability to achieve the primary endpoint or concern for serious AE, these studies were not successful [21,51]. The current study is novel in both therapeutic and trial design

Table 1
Summary of key inclusion and exclusion criteria.

Inclusion criteria
- Male/female pediatric patients aged ≥ 2 to < 18 years, with body weight of ≥ 12 kg (at screening) and diagnosed with HbSS or HbS/β^0.
- ≥ 2 VOCs[a] (painful crisis and/or ACS) in the year prior to screening.
- TCD within the last year for patients ≤16 years of age prior to screening.
- Sexually active female patients of child-bearing potential who agree to a reliable form of birth control. Female patients of child-bearing potential should test negative for pregnancy at screening (Visit 1) and at Visit 2.
- The body weight–adjusted dose for patients treated with hydroxyurea should be stable for 3 months before screening.
- Normal fundoscopy for patients ≥ 10 years within a year prior to screening.

Exclusion criteria
- History of transient ischemic attack or ischemic or hemorrhagic stroke, severe head trauma, intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy.
- Patients at increased risk of bleeding complications or with a history of bleeding disorder.
- Hb < 6 g/dL and platelets < 100×10^9/L at screening.
- Patients with conditional TAMMV values or higher (≥ 153 cm/s TCDi which corresponds to ≥170 cm/s by the nonimaging technique). Any criteria that would locally be considered as TCD indications for chronic transfusion.
- Patients undergoing treatment with chronic RBC transfusion therapy
- Patients continuously using NSAIDs > 3 days/week, or receiving chronic treatment with anticoagulants or antiplatelet drugs.
- Moderate or severe hepatic impairment; renal failure requiring dialysis.
- Concomitant oral or intravenous therapy with strong or moderate CYP3A4 inhibitors, CYP3A4 substrates with narrow therapeutic indices, or strong CYP3A4 inducers that cannot be stopped at least 5 half-lives before randomization.
- Patients having active untreated malaria.

ACS, acute coronary syndrome; CYP, cytochrome P450; Hb, hemoglobin; HbSS, homozygous sickle cell; HbS/β^0, sickle beta zero thalassemia; NSAID, non-steroidal anti-inflammatory drug; RBC, red blood cell; TAMMV, time averaged mean of the maximum velocity; TCD, transcranial doppler; TCDi, transcranial doppler imaging technique; VOC, vaso-occlusive crisis.

[a] VOCs, which can include events treated at home, need to be documented in the patient's medical records or in other documents that can be reconciled.

Table 2
Secondary and exploratory endpoints.

Secondary endpoints
- Number of VOCs requiring hospitalization or emergency department visits.
- Number and duration of painful crises.
- Number of ACSs.
- Number of days hospitalized for VOC.
- Number of acute SCD complications.
- Number of days hospitalized for acute SCD complications.
- Number of sickle cell-related RBC transfusions.
- HRQoL measured by using PedsQL™ SCD module and fatigue total score and by dimension using the PedsQL™ Multidimensional Fatigue Scale (age appropriate versions).
- Proportion of days of absence from school or work (only if going to school or work at randomization).
- Intensity of the worst pain experienced daily during VOC.
  - For patients aged 2–4 years, observer-reported using the FLACC scale.
  - For patients aged 5–18 years, self-reported using FPS-R.
- Type of analgesic (opioid and non-opioid) used during VOC.
- Palatability and swallowability of the formulation.
  - For patients 2–4 years of age taking the tablet dispersed or whole, an observer assessment of palatability and swallowability will be undertaken.
  - For patients ≥ 5 years of age taking the tablet dispersed or whole, palatability will be assessed and categorized using FHS.

Safety endpoints
- AEs/SAEs, including bleeding
- Vital signs and laboratory safety variables.

Exploratory endpoints
- Duration of ACS.
- Population PK parameters, such as oral clearance (CL/F) and ticagrelor exposure (AUC).
- Observed plasma concentrations of ticagrelor and the active metabolite AR-C124910XX.
- PRI measured by VASP assay.

Acute SCD complications will be defined as the composite of individual complications and evaluated as secondary endpoints: TIA/ischemic stroke, hepatic sequestration and splenic sequestration, priapism, and dactylitis. If the frequency allows, the individual components can be assessed as exploratory endpoints.

ACS, acute chest syndrome; AE, adverse event; AUC, area under the curve; FHS, Facial Hedonic Scale; FLACC, Face, Legs, Activity, Cry, Consolability; FPS-R, Faces Pain Scale-Revised; HRQoL, health related quality of life; PedsQL™, Pediatric Quality of Life Inventory™; PK, pharmacokinetics; PRI, platelet reactivity index; RBC, red blood cell; SAE, serious adverse event; SCD, sickle cell disease; TIA, transient ischemic attack; VASP, vasodilator-stimulated phosphoprotein; VOC, vaso-occlusive crisis.

due to a higher target platelet inhibition and the use of an event diary in place of a daily pain report.

The doses of ticagrelor to be used in the HESTIA3 study will result in greater platelet inhibition (35%–80%) than the doses of prasugrel used in the DOVE study achieving around 20% inhibition [21,49]. The HESTIA3 study will study the effects of ticagrelor over a minimum of 12 months (maximum 24 months) compared with the DOVE study that studied the effects of prasugrel for a minimum of 9 months (maximum 24 months) [21].

The HESTIA3 study that will evaluate the efficacy, safety, and tolerability of ticagrelor versus placebo in pediatric patients with SCD has several differentiating attributes. The primary endpoint also includes VOCs managed outside a medical facility to ensure VOC occurring both at home and in the hospital are accounted. HESTIA3 will allow us to expand the utility of the study findings by capturing important information about VOCs on a much larger outpatient scale rather than restricting the findings to purely in-facility management. This global study will be the first to recruit patients across four continents and the first to include India where SCD is one of the common genetic hemoglobinopathies [52–54], thereby capturing a wider population and diverse ethnicities compared with previous studies [19–21,49]. Further, the HESTIA3 study will aim to address the gaps in the DOVE study [21]. HESTIA3 will target a greater level of platelet inhibition and longer treatment exposure with ticagrelor than that achieved in any other multicenter antiplatelet trial in SCD, to date [19–21,28]. The dosing of ticagrelor is simplified and based on body weight groups/bands and not on individual titration of the dose based on platelet inhibition testing which simplifies the dosage schedule and potentially improves patient compliance. The ticagrelor formulation used in HESTIA3 is unique, allowing the same formulation to be used in a wide pediatric age range, allowing the patient to choose between swallowing the tablets whole or by dispersing them in a small amount of fluid before drinking.

The HESTIA3 study will definitively assess the role of antiplatelet drugs in the treatment paradigm for children < 18 years of age with sickle cell anemia. This study will provide data for a full 12 months on the effects of ticagrelor in the prevention of VOCs in pediatric patients with SCD. The eDevice should prove useful for the identification and assessment of potential VOC events. The planned greater platelet inhibition and longer exposure to antiplatelet drug compared with previous studies is expected to definitively clarify the role of platelet inhibition for improved clinical outcomes in affected children.

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Declaration of Competing Interest

Amilon C, Andersson M, Leonsson-Zachrisson M, and Berggren AR are employees of AstraZeneca. Heeney MM is a consultant with AstraZeneca, Sancilio/Micelle Biopharma and Novartis, and is a member of the HESTIA3, SCOT trial, and SEG101 pediatric trial steering committees. Abboud MR receives honorarium from Novartis and research funding from Eli Lilly and Mast Therapeutics, is in the

advisory boards for GBT, and is a consultant for CRSPR and Vertex. Githanga J is a member of the HESTIA3 and HESTIA4 steering committees. Inusa B is a member of the AstraZeneca HESTIA3 and HESTIA4 steering committees, and has received educational grants from Pfizer and Global Therapeutics. Kanter J has worked as a consultant for Bluebird Bio and Novartis; is in the steering committee for AstraZeneca and Novartis, as well as in the advisory boards of Imara, GBT, Modus and Editas. Michelson AD is a member of the AstraZeneca HESTIA3 steering committee and a member of scientific advisory boards for Chiesi and Janssen.

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Author contributions

All authors have contributed to the conception and design of the HESTIA3 study, critical review of the important intellectual content of the article, and provided final approval of the version submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2019.105835.

References

[1] K. Paradowski, Pathophysiology and perioperative management of sickle cell disease, J. Perioper. Pract. 25 (6) (2015) 101–104.
[2] M.A. Bender, Sickle cell disease, GeneReviews®, 2003 https://www.ncbi.nlm.nih.gov/books/NBK1377/ (accessed 12 June 2019).
[3] D.C. Rees, T.N. Williams, M.T. Gladwin, Sickle-cell disease, Lancet 376 (9757) (2010) 2018–2031.
[4] J. Howard, N. Hart, M. Roberts-Harewood, M. Cummins, M. Awogbade, B. Davis, B.C.S.H. Committee, Guideline on the management of acute chest syndrome in sickle cell disease, Br. J. Haematol. 169 (4) (2015) 492–505.
[5] K.I. Ataga, J.E. Brittain, P. Desai, et al., Association of coagulation activation with clinical complications in sickle cell disease, PLoS One 7 (1) (2012) e29786.
[6] D. Zhang, C. Xu, D. Manwani, P.S. Frenette, Neutrophils, platelets, and inflammatory pathways at the nexus of sickle cell disease pathophysiology, Blood 127 (7) (2016) 801–809.
[7] A. Owusu-Ansah, C.A. Ihunnah, A.L. Walker, S.F. Ofori-Acquah, Inflammatory targets of therapy in sickle cell disease, Transl. Res. 167 (1) (2016) 281–297.
[8] E. Sparkenbaugh, R. Pawlinski, Prothrombotic aspects of sickle cell disease, J. Thromb. Haemost. 15 (7) (2017) 1307–1316.
[9] J. Ansari, Y.E. Moufarrej, R. Pawlinski, F.N.E. Gavins, Sickle cell disease: a malady beyond a hemoglobin defect in cerebrovascular disease, Expert. Rev. Hematol. 11 (1) (2018) 45–55.
[10] U.S. Food & Drug Adminstration, FDA Approves Hydroxyurea for Treatment of Pediatric Patients with Sickle Cell Anemia, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm590096.htm, (2017) (accessed 12 June 2019).
[11] European Medicines Agency, Siklos, http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000689/human_med_001050.jsp&mid=WC0b01ac058001d124, (2007) (accessed 12 June 2019).
[12] S.J. Nevitt, A.P. Jones, J. Howard, Hydroxyurea (hydroxycarbamide) for sickle cell disease, Cochrane Database Syst. Rev. (4) (2017) CD002202.
[13] A.L. Frelinger 3rd, J.A. Jakubowski, J.K. Brooks, et al., Platelet activation and inhibition in sickle cell disease (PAINS) study, Platelets 25 (1) (2014) 27–35.
[14] D.P. Inwald, F.J. Kirkham, M.J. Peters, et al., Platelet and leucocyte activation in childhood sickle cell disease: association with nocturnal hypoxaemia, Br. J. Haematol. 111 (2) (2000) 474–481.
[15] J. Villagra, S. Shiva, L.A. Hunter, R.F. Machado, M.T. Gladwin, G.J. Kato, Platelet activation in patients with sickle disease, hemolysis-associated pulmonary hypertension, and nitric oxide scavenging by cell-free hemoglobin, Blood 110 (6) (2007) 2166–2172.
[16] J.A. Jakubowski, C. Zhou, K.J. Winters, et al., The effect of prasugrel on ADP-stimulated markers of platelet activation in patients with sickle cell disease, Platelets 26 (5) (2015) 474–479.
[17] J.A. Jakubowski, C. Zhou, S. Jurcevic, et al., A phase 1 study of prasugrel in patients with sickle cell disease: effects on biomarkers of platelet activation and coagulation, Thromb. Res. 133 (2) (2014) 190–195.
[18] J.A. Jakubowski, C. Zhou, D.S. Small, et al., A phase 1 study of prasugrel in patients with sickle cell disease: pharmacokinetics and effects on ex vivo platelet reactivity, Br. J. Clin. Pharmacol. 75 (6) (2013) 1433–1444.
[19] R. Cabannes, J. Lonsdorfer, J.P. Castaigne, A. Ondo, A. Plassard, I. Zohoun, Clinical and biological double-blind-study of ticlopidine in preventive treatment of sickle-cell disease crises, Agents Actions Suppl. 15 (1984) 199–212.
[20] J. Greenberg, K. Ohene-Frempong, J. Halus, C. Way, E. Schwartz, Trial of low doses of aspirin as prophylaxis in sickle cell disease, J. Pediatr. 102 (5) (1983) 781–784.
[21] M.M. Heeney, C.C. Hoppe, M.R. Abboud, et al., A multinational trial of prasugrel for sickle cell vaso-occlusive events, N. Engl. J. Med. 374 (7) (2016) 625–635.
[22] S. Husted, J.J. van Giezen, Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist, Cardiovasc. Ther. 27 (4) (2009) 259–274.
[23] U.S. Food & Drug Adminstration, BRILINTA Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022433s020lbl.pdf, (2011) (accessed 12 June 2019).
[24] S. Nylander, E.A. Femia, M. Scavone, et al., Ticagrelor inhibits human platelet aggregation via adenosine in addition to P2Y12 antagonism, J. Thromb. Haemost. 11 (10) (2013) 1867–1876.
[25] D. Armstrong, C. Summers, L. Ewart, S. Nylander, J.E. Sidaway, J.J. van Giezen, Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1, J. Cardiovasc. Pharmacol. Ther. 19 (2) (2014) 209–219.
[26] D. Alexopoulos, A. Moulias, N. Koutsogiannis, et al., Differential effect of ticagrelor versus prasugrel on coronary blood flow velocity in patients with non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention: an exploratory study, Circ. Cardiovasc. Interv. 6 (3) (2013) 277–283.
[27] A. Wittfeldt, H. Emanuelsson, G. Brandrup-Wognsen, et al., Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans, J. Am. Coll. Cardiol. 61 (7) (2013) 723–727.
[28] K.I. Ataga, A. Kutlar, J. Kanter, et al., Crizanlizumab for the prevention of pain crises in sickle cell disease, N. Engl. J. Med. 376 (5) (2017) 429–439.
[29] S.B. Patil, L.E. Jackman, S.E. Francis, H.M. Judge, S. Nylander, R.F. Storey, Ticagrelor effectively and reversibly blocks murine platelet $P2Y_{12}$-mediated thrombosis and demonstrates a requirement for sustained $P2Y_{12}$ inhibition to prevent subsequent neointima, Arterioscler. Thromb. Vasc. Biol. 30 (12) (2010) 2385–2391.
[30] G. Yao, C. Zou, F. Liu, P. Wang, Q. Li, G. Su, Effects of oral ticagrelor or clopidogrel before emergent PCI on the inflammatory mediators and endotheliocyte functions in STEMI patients, Int. J. Clin. Exp. Med. 11 (4) (2018) 4064–4071.
[31] I. Bernlochner, A. Goedel, C. Plischke, et al., Impact of immature platelets on platelet response to ticagrelor and prasugrel in patients with acute coronary syndrome, Eur. Heart J. 36 (45) (2015) 3202–3210.
[32] R.C. Jin, J. Loscalzo, Vascular nitric oxide: formation and function, J. Blood Med. 2010 (1) (2010) 147–162.
[33] N. Wajih, S. Basu, A. Jailwala, et al., Potential therapeutic action of nitrite in sickle cell disease, Redox Biol. 12 (2017) 1026–1039.
[34] F. Vieceli Dalla Sega, F. Fortini, G. Aquila, et al., Ticagrelor improves endothelial function by decreasing circulating epidermal growth factor (EGF), Front. Physiol. 9 (2018) 337.
[35] G. Vilahur, M. Gutiérrez, L. Casani, et al., Protective effects of ticagrelor on myocardial injury after infarction, Circulation 134 (22) (2016) 1708–1719.
[36] M.K. Nanhwan, S. Ling, M. Kodakandla, S. Nylander, Y. Ye, Y. Birnbaum, Chronic treatment with ticagrelor limits myocardial infarct size: an adenosine and cyclooxygenase-2-dependent effect, Arterioscler. Thromb. Vasc. Biol. 34 (9) (2014) 2078–2085.
[37] J.J. Field, D.G. Nathan, J. Linden, The role of adenosine signaling in sickle cell therapeutics, Hematol. Oncol. Clin. North Am. 28 (2) (2014) 287–299.
[38] J.J. Field, E. Majerus, V.R. Gordeuk, et al., Randomized phase 2 trial of regadenoson for treatment of acute vaso-occlusive crises in sickle cell disease [published correction appears in *Blood Adv* 2017;1(23):2058], Blood Adv. 1 (20) (2017) 1645–1649.
[39] M.R. Thomas, S.N. Outteridge, R.A. Ajjan, et al., Platelet P2Y12 inhibitors reduce systemic inflammation and its prothrombotic effects in an experimental human model, Arterioscler. Thromb. Vasc. Biol. 35 (12) (2015) 2562–2570.
[40] L.L. Hsu, S. Sarnaik, S. Williams, C. Amilon, J. Wissmar, A. Berggren, HESTIA1 Investigators, A dose-ranging study of ticagrelor in children aged 3-17 years with sickle cell disease: a 2-part phase 2 study, Am. J. Hematol. 93 (12) (2018) 1493–1500.
[41] J. Kanter, M.R. Abboud, B. Kaya, et al., Ticagrelor does not impact patient-reported pain in young adults with sickle cell disease: a multicentre, randomised phase IIb study, Br. J. Haematol. 184 (2) (2019) 269–278.
[42] T. Voepel-Lewis, J. Zanotti, J.A. Dammeyer, S. Merkel, Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients, Am. J. Crit. Care 19 (1) (2010) 55–61.
[43] C.L. Hicks, C.L. von Baeyer, P.A. Spafford, I. van Korlaar, B. Goodenough, The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement, Pain 93 (2) (2001) 173–183.
[44] PedsQL™, The PedsQL™ Measurement Model for the Pediatric Quality of Life Inventory™, http://www.pedsql.org/about_pedsql.html, (2018) (accessed 12 June 2019).
[45] J.A. Panepinto, S. Torres, C.B. Bendo, et al., PedsQL™ sickle cell disease module: feasibility, reliability, and validity, Pediatr. Blood Cancer 60 (8) (2013) 1338–1344.
[46] J.A. Panepinto, S. Torres, C.B. Bendo, et al., PedsQL™ Multidimensional Fatigue Scale in sickle cell disease: feasibility, reliability, and validity, Pediatr. Blood Cancer 61 (1) (2014) 171–177.

[47] E.H. Davies, C. Tuleu, Medicines for children: a matter of taste, J. Pediatr. 153 (5) (2008) 599–604.
[48] L.G. Mitchell, N.A. Goldenberg, C. Male, G. Kenet, P. Monagle, U. Nowak-Göttl, Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary embolism in children, J. Thromb. Haemost. 9 (2011) 1856–1858.
[49] J.A. Jakubowski, C.C. Hoppe, C. Zhou, et al., Real-time dose adjustment using point-of-care platelet reactivity testing in a double-blind study of prasugrel in children with sickle cell anaemia, Thromb. Haemost. 117 (3) (2017) 580–588.
[50] N.O. Osamo, D.P. Photiades, A.A. Famodu, Therapeutic effect of aspirin in sickle cell anaemia, Acta Haematol. 66 (2) (1981) 102–107.
[51] U.S. Food & Drug Adminstration, Drugs@FDA: FDA Approved Drug Products, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019979, (2001) (accessed 12 June 2019).
[52] S. Panigrahi, P.K. Patra, P.K. Khodiar, Neonatal screening of sickle cell anemia: a preliminary report, Ind. J. Pediatr. 79 (6) (2012) 747–750.
[53] D.L. Jain, V. Sarathi, D. Upadhye, et al., Newborn screening shows a high incidence of sickle cell anemia in Central India, Hemoglobin 36 (4) (2012) 316–322.
[54] D.S. Upadhye, D.L. Jain, Y.L. Trivedi, et al., Neonatal screening and the clinical outcome in children with sickle cell disease in Central India, PLoS One 11 (1) (2016) e0147081.