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Human Medicines Evaluation Division

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

Brilique

ticagrelor

Procedure no: EMEA/H/C/001241/P46/023

Note

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

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Table of contents

List of abbreviations:

AE	Adverse event
AUC	Area under the plasma concentration-time curve
CL/F	Oral clearance
C_{max}	Maximum plasma concentration
CSP	Clinical study protocol
H	Hour
N	Number of patients in each treatment group
n	Number of patients in category or analysis
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamic
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PRO	Patient reported outcome
PRU	$P2Y_{12}$ reaction units
PT	Preferred term
R	Randomisation
RBC	Red blood cells
SAE	Serious adverse event
SCD	Sickle cell disease
SD	Standard deviation
SOC	System organ class
TAMMV	Time averaged mean of the maximum velocity
TCD	Transcranial Doppler
TCDi	Imaging Transcranial Doppler
V	Visit
VOCs	Vaso-occlusive crises

1. Introduction

On 18 December 2017, the MAH submitted a completed paediatric study results (study D5136C00007) for ticagrelor (Brilique) to assess the potential therapeutic benefits of ticagrelor in reduction of the occurrence of vaso-occlusive crises (VOCs) in children with sickle cell disease (SCD) aged ≥2 years to <18 years, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study D5136C00007 is part of the Paediatric Investigation Plan (PIP) (PIP number: EMEA-000480-PIP01-08-M10) for ticagrelor, Brilique for sickle cell disease. The PIP comprises 11 studies (three quality studies, four nonclinical studies and four clinical trials) and is scheduled to be completed after December 2019. Study D5136C00007 (Study 12) is the first of the 4 planned paediatric clinical trials to be completed. This study investigates the dosing and tolerability and PK of ticagrelor at doses up to 2.25 mg/kg in children with sickle cell disease (aged ≥2 to <18 years) to support dose selection for Phase III.

These data are also submitted as part of the post-authorisation measures PIP (EMEA-000480-PIP01-08-M10). A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study D5136C00007 is part of a clinical development program for Brilique. The variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted after December 2019. A line listing of all the concerned studies is attached. (Table 1 & Annex).

Table 1. Overview of planned and completed paediatric clinical trials

Study number	Study title	Type of study	Timing
Study 1	Development of a granule for oral suspension to support Study 12 (patients aged 2 to 17 years)	Quality	Completed
Study 11	Development of an age-appropriate tablet formulation for paediatric patients aged from 2 to 17 years	Quality	Not started
Study 16	Development of an age-appropriate formulation for the 0 to 24 month age group, either granule for oral suspension or paediatric tablet to be dispersed	Quality	Not started
AA93000	Ticagrelor: Dose-range-finding neonatal toxicity study following daily oral (gavage) administration for 19 days in the Han Wister rat	Non-clinical	Completed June 2010
AA93001	Ticagrelor: Neonatal toxicity study following daily oral (gavage) administration for 19 days in the Han Wistar rat followed by an 8-week treatment-free period.	Non-clinical	Completed October 2010
2885LR	Ticagrelor: 5-Week Oral Toxicity Study with Assessment of Recovery in the Weanling Rat	Non-clinical	Completed March 2011
3233SR	Ticagrelor: Respiratory Effects in the Suckling Han Wistar Rat following Single Oral Administration	Non-clinical	Completed July 2011
Study 12 (D5136C00007)	Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a single-blind, randomised, parallel group, placebo-controlled 4 weeks extension phase in paediatric	Clinical	Completed February 2017

	patients with sickle cell disease		
Study 15 (D5136C00011)	Open-label, randomised, 4-period, 4-treatment, crossover, single-dose study to assess relative bioavailability of ticagrelor granule for oral suspension and paediatric ticagrelor tablet to commercial ticagrelor tablet in healthy subjects	Clinical	Completed July 2017
Study 13 (D5136C00009)	A Randomized, Double-blind, Parallel-group, Multicenter, Phase III study to Evaluate the Effect of Ticagrelor Versus Placebo in Reducing the Rate of VOCs in Paediatric Patients with Sickle Cell Disease	Clinical	Not started
Study 14 (D5136C00010)	A Multi-centre, Phase I, Open-label, Single-dose Study to Investigate Pharmacokinetics (PK) of Ticagrelor in Infants and Toddlers, Aged 0 to less than 24 Months, with Sickle Cell Disease (HESTIA4)	Clinical	Not started

2.2. Information on the pharmaceutical formulation used in the study

For the paediatric study D5136C00007, 10 and 45 mg granules for oral suspension suspended in water were used. Before each dosing occasion the granules were constituted with 10 mL of purified water to form a homogenous suspension suitable for oral dosing. Dosing was weight based and a suitable volume of suspension was to be withdrawn from the bottle using a syringe suitable for oral dosing. All patients received a handling instruction together with the study drug at each visit starting at Visit 3.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• Study 12 (D5136C00007), a multicentered, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a single-blind, randomised, parallel group, placebo-controlled 4 weeks extension phase in paediatric patients (aged ≥2 to <18 years) with sickle cell disease.

Ticagrelor is an oral, direct-acting, selective, reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated platelet activation and aggregation. It does not prevent ADP binding, but when bound to the $P2Y_{12}$ receptor, ticagrelor prevents ADP-induced signal transduction.

During clinical development in adults, a dose rage of 0.1 to 1260 mg ticagrelor has been evaluated in clinical studies as single dose and 50 to 300 mg twice daily ticagrelor has been evaluated in clinical studies as repeated dose for 16 days. Over a dose range of 10–500 mg single dose and 50-300 mg twice daily (multiple dose) ticagrelor, C_{max} and AUC values increased in an approximately dose-proportional manner.

The pharmacokinetics of ticagrelor have been extensively characterised in healthy volunteers and patients. Ticagrelor can be given with or without food.

Absorption of ticagrelor is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2.5 hours. Based on a population pharmacokinetic analysis of the PEGASUS study, for ticagrelor 60 mg, the median ticagrelor C_{max} was 391 ng/ml and AUC was 3801 ng × h/mL at steady state. For ticagrelor 90 mg, C_{max} was 627 ng/ml and AUC was 6255 ng × h/mL at steady state. The mean absolute bioavailability of ticagrelor was estimated to be 36%.

The steady state volume of distribution of ticagrelor is 87.5 L. Ticagrelor and the active metabolite is extensively bound to human plasma protein (>99.0%).

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite. The systemic exposure of AR-C124910XX is approximately 30-40% of that obtained for ticagrelor. Ticagrelor as well as AR-C124910XX are P-glycoprotein substrates. Ticagrelor is a mild inhibitor of CYP3A4 and a weak P-glycoprotein inhibitor.

The primary route of ticagrelor elimination is via hepatic metabolism. Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is most likely via biliary secretion. When radiolabelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). The mean $t_{1/2}$ was approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

Ticagrelor (Brilique), co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

The approved dose regimen in adults with ACS consists of a loading dose of 180 mg followed by 90 mg bid for up to 1 year. In adult patients with prior myocardial infarction, a dose of 60 mg bid was approved.

Inhibition of platelet activation has been proposed as a therapeutic option in the treatment of children and adults with SCD. Activated platelets promote the adherence of sickle cells to endothelial cells and participate in the vaso-occlusive process.

Dose selection for study D5136C00007 was based on PK-PD modelling and simulation from adult coronary patients. The initial dose was a 0.125 mg/kg (weight-based dose equivalent to 10 mg in adults), which is 11% of the approved dose for adults with ACS. The second dose of ticagrelor was 0.375 mg/kg or 0.563 mg/kg (weight-based dose equivalent to 30 or 45 mg in adults).

2.3.2. Clinical study

Description

This multicentered, open-label, randomised, PK and PD dose-ranging Phase II paediatric study of ticagrelor was conducted to determine appropriate dosing and tolerability in patients with SCD in preparation for a subsequent paediatric Phase III study. In addition, the study collected data on clinical manifestations such as pain and analgesic use to inform the choice of clinical outcome measures in the subsequent study and for exploratory efficacy.

Methods

Objectives

Primary objective:

- To characterise the relationship between ticagrelor dose and inhibition of platelet aggregation in paediatric patients with SCD, using PK/PD modelling, to support dose selection for Phase III.

Secondary objectives:

- To determine the PK properties of ticagrelor and its active metabolite in paediatric patients with SCD and to assess impact of weight, age and other demographics on the ticagrelor PK.
- Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:
  - Number of vaso-occlusive crises (VOC). VOC was defined as a painful sickle cell crisis requiring medical intervention including any of the following: (1) hospitalisation (2) emergency department or clinic visit (3) medically supervised outpatient treatment with escalated doses of drugs for management of painful crisis (could include oral or parenteral opioids or non-steroidal anti-inflammatory drugs (NSAIDs)).
  - Number of VOC requiring hospitalisation or emergency department visits
  - Days hospitalised for VOC or other complications of SCD
  - Days with pain (ages ≥4 years only)
  - Intensity of pain (ages ≥4 years only)
  - Days of analgesic use (ages ≥4 years only)
  - Days of opioid analgesic use
  - Days of absence from school or work (ages ≥6 years only)

Safety objectives:

- To assess safety and tolerability of single and multiple doses of ticagrelor in paediatric patients with SCD.
- To determine the percent of patients with haemorrhagic events requiring medical intervention. A haemorrhagic event was defined as bleeding prompting an unscheduled visit or call to a medical provider and resulting in therapy or further investigation.

Exploratory objectives:

- Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing:
  - Days with pain (ages <4 years only)
  - Intensity of pain (ages <4 years only)

Study design

This study consisted of 2 parts: a multicentre, open-label, dose-ranging study of ticagrelor (Part A) followed by an optional double-blind, placebo-controlled extension phase (Part B) in paediatric patients with SCD (Figure 1).

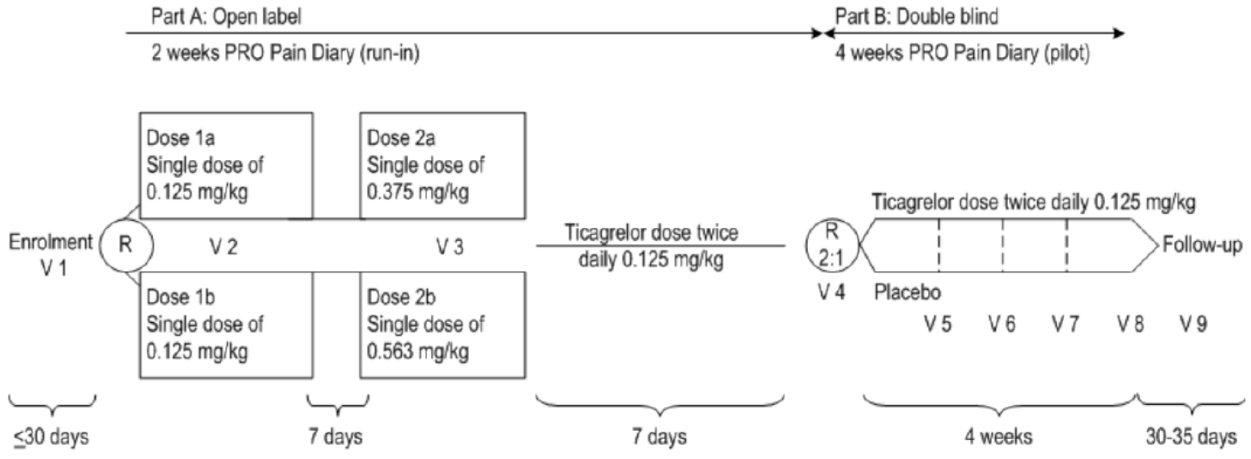


Figure 1. Study design (initial protocol)

Assessment of the first 12 randomised patients indicated that higher doses were needed in order to accomplish the primary study objective of characterising the relationship between ticagrelor dose and inhibition of platelet aggregation to support dose selection for Phase III. The mean $P2Y_{12}$ reaction units (PRU) reduction 2 hours post-dose at Visit 4 was <20%, and plasma ticagrelor concentrations were lower than expected. Therefore, the CSP was amended (Figure 2). Detailed protocol amendments and other significant changes to study conduct are shown in the clinical study report.

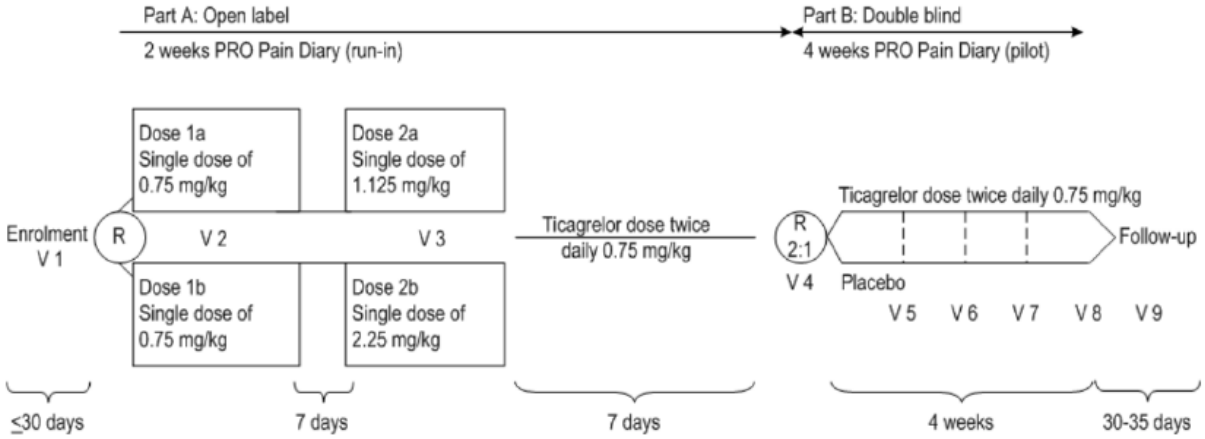


Figure 2. Study design (after CSP Amendment 3)

In Kenya and Lebanon, patients were not randomised to Part B, due to issues with study drug supply and availability. The patients finished the study drug after 1 week open-label treatment and visited the study centre 30 to 35 days after treatment was stopped for follow-up (Figure 3).

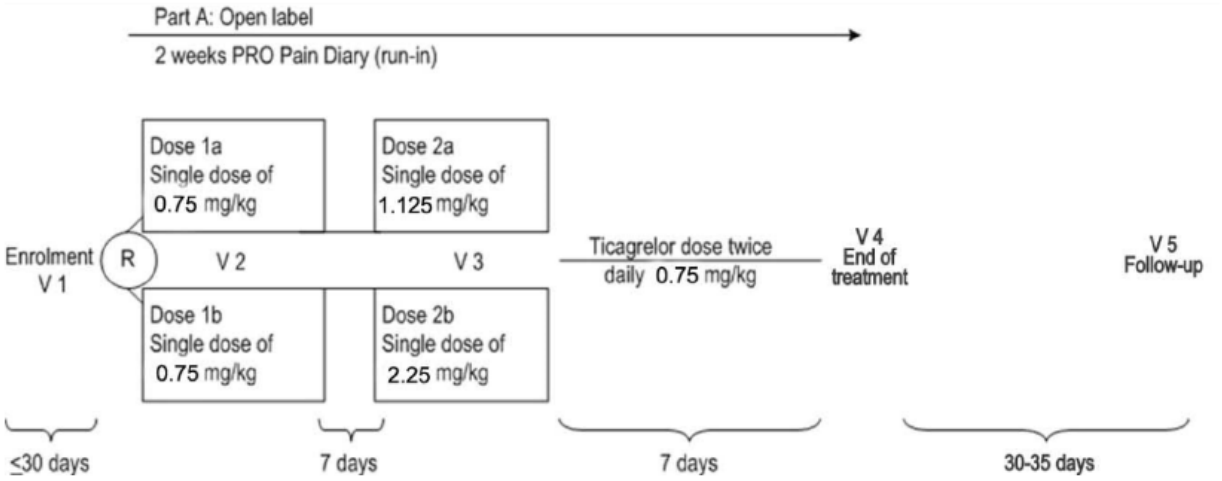


Figure 3. Study design (local amendments in Kenya and Lebanon)

For safety reasons the dosing schedule was modified for individual patients based on their PRU at Visits 2, 3 and 4. The dose modifications could occur at Visit 2, 3 and 4 (see “treatment” for further details).

Duration of treatment

In Part A, the treatment period consisted of 2 single doses (separated by at least 7 days) followed by 7 days open-label ticagrelor treatment bid. In Part B, patients were randomised to 4 weeks bid treatment with 0.75mg/kg ticagrelor or placebo. The total expected study duration for an individual patient participating in both Parts A and B was approximately 3 months (including 30 days follow-up after last dose) and approximately 2 months for an individual patient participating in only Part A (including 30 days follow-up after last dose).

Study population /Sample size

A minimum of 36 patients and a maximum of 50 patients were to be randomised in the study, in order to ensure 36 evaluable patients completing 2 single doses in Part A. A patient was considered evaluable if he/she had provided data up to and including Visit 3. Of these 36 evaluable patients, at least 12 patients were to be 2 to 11 years of age and 12 patients were to be 12 to 18 years. In addition, a minimum of 12 evaluable patients were to complete Part B (through Visit 8).

The key inclusion criteria were:

1. Children aged ≥2 to <18 years (age from birth to Visit 1) of age and body weight >16 kg diagnosed with homozygous sickle cell or sickle beta-zero-thalassaemia.
2. If ≤16 years, had transcranial Doppler (TCD) within the past year prior to Visit 1.
3. If this was not the case, a TCD examination was to be done before proceeding in the study.
4. If ≥6 years old, had an ophthalmological examination within the past year prior to Visit 1. If this was not the case, the patient was to be examined by an ophthalmologist before proceeding in the study.
5. If treated with an anti-sickling agent such as hydroxyurea, the weight-adjusted dose was to be stable for 1 month before enrolment.
6. Suitable venous access for the study-related blood sampling.
7. Provision of signed and dated written informed consent prior to any study-specific procedures not part of standard medical care, (local regulations and international guidelines are to be followed in determining the assent/consent requirements for children).

CHMP comment:

The inclusion criteria are acceptable and reflect the general paediatric population with SCD. In small children (<16 kg) it is not possible to draw sufficient blood for evaluation. (RSI 6)

Furthermore, the inclusion criterion "*on a stable dose of anti-sickling agent such as hydroxyurea for 1 month before enrolment*" is considered relatively short. However, considering that this is a PK/PD dose ranging study this is acceptable.

The key exclusion criteria were:

1. Previous history of transient ischaemic attack or clinically overt cerebrovascular accident (ischaemic or haemorrhagic), severe head trauma, intracranial haemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy.
2. Findings on TCD: Current or previous values for time averaged mean of the maximum velocity (TAMMV) that were Conditional or Abnormal.
   Conditional TAMMV values were ≥153 cm/sec using imaging TCD (TCDi) technique (corresponding to ≥170 cm/sec by the non-imaging technique). Both the middle cerebral

artery and the internal carotid artery were to be considered. Abnormal TAMMV values were ≥180 cm/sec using TCDi (corresponding to ≥200 cm/sec by the non-imaging technique) and were an indication for chronic transfusions because of a high stroke risk. Any other criteria that would locally be considered as TCD indications for chronic transfusion would also have excluded the patient.

3. Undergoing treatment with chronic RBC transfusion therapy.
4. Use of NSAIDs >3 days per week.
5. Received chronic treatment with anticoagulants or antiplatelet drugs that could not be discontinued.
6. Moderate or severe hepatic impairment, defined as Child-Pugh Class B or C or renal failure requiring dialysis.
7. Active pathological bleeding or increased risk of bleeding complications according to Principal Investigator.
8. Patient considered to be at risk of bradycardic events (e.g., known sick sinus syndrome or second or third degree atrioventricular block) unless already treated with a permanent pacemaker.
9. Concomitant oral or intravenous therapy with strong Cytochrome P450 (CYP) 3A4 inhibitors, CYP3A4 substrates with narrow therapeutic indices, or strong CYP3A4 inducers, which could not be stopped at least 5 half-lives, but not shorter than 10 days, before enrolment.
10. Surgical procedure planned to occur during the study.
11. Patients who were currently pregnant or breastfeeding, or planning to become pregnant during the study.
12. Females (if after menarche) who were not willing to use a highly effective method of contraception which resulted in a low failure rate (i.e., less than 1% per year).
13. Known hypersensitivity or contraindication to ticagrelor.
14. Concern for the inability of the patient or parents to comply with study procedures and/or follow-up.
15. Any condition which, in the opinion of the Principal Investigator, would make it unsafe or unsuitable for the patient to participate in this study.
16. Previous enrolment in the present study.
17. Participation in another clinical study with a study drug or device during the last 30 days preceding enrolment.
18. Involvement in the planning and/or conduct of the study

CHMP comment:

The exclusion criteria are appropriate. The contra-indications currently listed for ticagrelor are included as exclusion criteria. Severe patients needing chronic RBC transfusion are not included in the current study.

Treatments

Part A:

Open-label single doses (Visit 2 and 3):

Initially, all patients received oral 0.125 mg/kg as their initial dose, followed 7 days later by 0.375 mg/kg or 0.563 mg/kg.

Patients randomised after Protocol Amendment 3, received oral 0.75 mg/kg as their initial dose, followed 7 days later by 1.125 mg/kg or 2.25 mg/kg.

Repeated dosing (Visit 3-4; twice daily [bid]):

Patients self-administered oral 0.125 mg/kg of open-label ticagrelor for 1 week.

Patients randomised after Protocol Amendment 3, self-administered 0.75 mg/kg of open-label ticagrelor for 1 week.

Part B:

Repeated dosing (Visit 4-8; bid):

Initially, patients self-administered oral 0.125 mg/kg of ticagrelor or placebo for 4 weeks.

Patients randomised after Protocol Amendment 3, self-administered oral 0.75 mg/kg of ticagrelor or placebo for 4 weeks.

For safety reasons the initial dosing schedule was modified for individual patients as follows:

- If PRU at 2 hours following dosing of 0.125 mg/kg was <95, the subsequent maximum dose for this patient was to be 0.0625 mg/kg throughout the study.
- If PRU was <95 on any 2 dosing occasions following dosing of 0.0625 mg/kg, the patient was to be discontinued from further study drug.

For patients randomised after clinical study protocol (CSP) Amendment 3, the dosing schedule was modified for individual patients as follows:

- If PRU at 2 hours following dosing of 0.75 mg/kg was <95, the subsequent maximum dose for this patient was to be 0.563 mg/kg throughout the study.
- If PRU was <95 following dosing of 0.563 mg/kg, the patient was to be discontinued from further study drug.

CHMP comment:

For safety reasons the dosing schedule was modified for individual patients if the PRU was < 95. The cut-off was introduced in the context of much uncertainty (RSI 4, 5). It is not intended to monitor PRU in practice.

Outcomes/endpoints

The primary endpoint for this study is the dose relationship between ticagrelor dose and inhibition of platelet aggregation in paediatric patients aged ≥2 years to <18 years with SCD. This is measured by: $P2Y_{12}$ reaction units (PRU), maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC).

Secondary endpoints are shown in

Table 2, safety and exploratory endpoints in Table 3.

Table 2. Primary and secondary outcomes

Objective			
Priority	**Type**	**Description**	**Description**
Primary	PK/PD	To characterise the relationship between ticagrelor dose and inhibition of platelet aggregation in paediatric patients with SCD, using PKPD modelling, to support dose selection for Phase III	PRU, C_{max} and AUC
Secondary	PK	To determine the PK properties of ticagrelor and its active metabolite in paediatric patients with SCD and to assess impact of weight, age and other demographics on the ticagrelor PK	Concentrations of ticagrelor and its active metabolite. Population PK parameters (CL/F and AUC)
Secondary	Efficacy	Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing - see Variable column:	– Number of VOC* – Number of VOC requiring hospitalisation or emergency department visits – Days hospitalised for VOC or other complications of SCD – Days with pain (ages ≥4 years only) – Intensity of pain (ages ≥4 years only) – Days of analgesic use (ages ≥4 years only) – Days of opioid analgesic use – Days of absence from school or work (ages ≥6 years only) – Palatability

* VOC was defined as a painful sickle cell crisis requiring medical intervention including any of the following (1) hospitalisation (2) emergency department or clinic visit (3) medically supervised outpatient treatment with escalated doses of drugs for management of painful crisis (could include oral or parenteral opioids or non-steroidal anti-inflammatory drugs).

Table 3. Safety and exploratory outcomes

Objective			
Priority	**Type**	**Description**	**Description**
Safety	Safety/Tolerability	To assess safety and tolerability of single and multiple doses of ticagrelor in paediatric patients with SCD	AEs/Serious Adverse Events Vital signs, laboratory safety samples
Safety	Safety	To determine the percent of patients with haemorrhagic events requiring medical intervention	Haemorrhagic events**
Exploratory	Exploratory	Investigation of efficacy of ticagrelor vs. placebo in paediatric patients with SCD in reducing - see Variable column:	– Days with pain (ages <4 years only) – Intensity of pain (ages <4 years only)

CHMP comment:

The primary endpoint for this study is the dose relationship between ticagrelor dose and inhibition of platelet aggregation. Inhibition of platelet aggregation is measured by the reduction in $P2Y_{12}$ reaction units (PRU), which can be measured reliably but the clinical relevance of PRU in SCD is not established (RSI 3).

The secondary endpoints are considered appropriate.

Statistical Methods

The primary variables are summarised using descriptive statistics using the pharmacokinetic-pharmacodynamic (PK-PD) analysis sets for Part A and Part B.

Samples for determination of drug concentration in plasma were analysed by Covance, using a validated LC-MS/MS method. The lower limit of quantification of ticagrelor and its active metabolite in plasma is 1.00 and 2.50 ng/mL, respectively. The upper limit of quantification was 2000 ng/mL for ticagrelor and 1000 ng/mL for the metabolite. [D-7]AZD6140 was used as internal standard. Precision and accuracy were ≤15% for ticagrelor (inter-run precision ranged from 4.3 to 8.9% and inter-run accuracy from100.7 to 101.8%) and also for AR-C124910XX (inter-run precision ranged from 5.5 to 8.1% and inter-run accuracy from 99.0 to 101.1%). All samples were analysed within 536 days of collection following storage at -10 to -30°C which is within the 60 months of established long-term stability. Two samples for ticagrelor and 6 samples for AR-C124910XX were re-assayed due to high internal standard or low internal standard. There were 54 samples included in the incurred sample reanalysis. Of the incurred samples, 92.6% and 94.4% of the repeat results and original results for ticagrelor and AR-C124910XX, respectively, were within 20% of the mean of the two values; this is within the acceptance criteria.

SAS version 9.1.3 or later were used for all statistical analyses. All population pharmacokinetics analyses were performed using NONMEM software (see Beal et al 2011) (v. VII, level 3.0, Globomax, USA).

Summaries of absolute value and change from baseline of $P2Y_{12}$ reaction units (PRU) by dose/treatment group and visit/timepoint for Part A and Part B are provided. Plots for individual and mean PRU levels and PK values over time are provided for Part A and Part B.

Secondary efficacy variables in Part A are summarised descriptively using the safety analysis set and actual treatment. For vaso-occlusive crisis (VOC) in Part A, summary statistics are provided for all VOC. Palatability measures for Part A are summarised descriptively and listed for all patients for whom the assessment was performed.

Efficacy variables in Part B are summarised descriptively using the efficacy analysis set (EAS) and planned treatment.

Independent sample t-tests were planned but since the EAS contained less than 30 patients they were not performed.

Sample collection

Blood sampling in subjects >21 kg was done at 1, 2, 4 and 6 hours post-dose on Visit 2 and 3, at 2 hours on Visit 4 and at 1, 2 and 4 hours at Visit 8. For subjects between 16 and 21 kg, blood samples were drawn at 1,2, 4 and 6 hours post-dose at Visit 2 and 3 and at 1 and 2 hours post-dose at Visit 4. Blood was collected in tubes containing lithium heparin as anticoagulant and stored at -10 to 30°C.

Results

Recruitment / Number analysed

The study was conducted at 24 centres, in 6 countries. Seventy-three patients were screened and enrolled into Part A of the study.

Forty-six patients were randomised into Part A of the study and 45 patients received study drug. One patient did not receive study drug due to insufficient venous access during the pre-dose sampling period. Seven patients were withdrawn from this part of the study, 4 (8.7%) patients due to development of study-specific withdrawal criteria, 2 (4.3%) patients due to patient decision and 1 (2.2%) patient due to other (drop in PRU)(Table 4).

During Part A, patients received single doses at Visit 2 and Visit 3. Fourteen patients received a 0.125 mg/kg ticagrelor dose (at Visit 2), 31 patients received a 0.75 mg/kg ticagrelor dose (at Visit 2).

Seven patients received a 0.375 mg/kg ticagrelor dose (at Visit 3), 18 patients received a 0.563 mg/kg ticagrelor dose (at Visit 3), 10 patients received a 1.125 mg/kg ticagrelor dose (at Visit 3) and 9 patients receiving a 2.25 mg/kg ticagrelor dose (at Visit 3).

Table 4. Patient disposition by randomised treatment group - Part A

	Number (%) of patients treated with ticagrelor				
	0.125 mg/kg + 0.375 mg/kg + 0.125 mg/kg bid for 1 week (N=7)	0.125 mg/kg + 0.563 mg/kg + 0.125 mg/kg bid for 1 week (N=8)	0.75 mg/kg + 1.125 mg/kg + 0.75 mg/kg bid for 1 week (N=16)	0.75 mg/kg + 2.25 mg/kg + 0.75 mg/kg bid for 1 week (N=15)	Total (N=46)
Patients enrolled[a]					73
Patients randomised	7 (100)	8 (100)	16 (100)	15 (100)	46 (100)
Patients who were not randomised					27
Lost to follow-up	-	-	-	-	1
Screen failure	-	-	-	-	13
Withdrawal by sponsor	-	-	-	-	10
Withdrawal by parent/guardian	-	-	-	-	2
Withdrawal by patient	-	-	-	-	1
Patients who received treatment	7 (100)	7 (87.5)	16 (100)	15 (100)	45 (97.8)
Patients who did not receive treatment	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (2.2)
Patients who completed Part A	**7 (100)**	**7 (87.5)**	**12 (75.0)**	**13 (86.7)**	**39 (84.8)**
Patients discontinued from Part A	0 (0.0)	1 (12.5)	4 (25.0)	2 (13.3)	7 (15.2)
Patient decision	0 (0.0)	1 (12.5)	1 (6.3)	0 (0.0)	2 (4.3)
Development of study-specific withdrawal criteria[b]	0 (0.0)	0 (0.0)	3 (18.8)	1 (6.7)	4 (8.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (2.2)

[a] Informed consent received
[b] Out of the 4 patients who discontinued due to development of study-specific withdrawal criteria, 2 patients did nevertheless complete the study part

Twenty-five patients were randomised into Part B of the study and 23 patients received study drug. Two patients had PRU <95 on 2 dosing occasions in Part A, and thus did not receive study drug (Table 5). Four patients were withdrawn from this part of the study, 2 (8.0%) patients due to development of study-specific withdrawal criteria, 1 (4.0%) patient due to patient decision and 1 (4.0%) patient due to being lost to follow-up.

Table 5. Patient disposition by randomised treatment group - Part B

	Number (%) of patients		
	Ticagrelor (N=17)	Placebo (N=8)	Total (N=25)
Patients randomised to Part B	17 (100)	8 (100)	25 (100)
Patients with PRU <95 on 2 dosing occasions	2 (11.8)	0 (0.0)	2 (8.0)
Patients who received treatment	15 (88.2)	8 (100)	23 (92.0)
Patients who did not receive treatment	2 (11.8)	0 (0.0)	2 (8.0)
Patients who completed Part B	**14 (82.4)**	**7 (87.5)**	**21 (84.0)**
Patients discontinued from Part B	3 (17.6)	1 (12.5)	4 (16.0)
Patient decision	1 (5.9)	0 (0.0)	1 (4.0)
Development of study-specific withdrawal criteria	2 (11.8)	0 (0.0)	2 (8.0)
Patient lost to follow-up[a]	0 (0.0)	1 (12.5)	1 (4.0)

In Part A, the safety analysis set (SAS) included 45 ticagrelor patients. In Part B, the SAS included 16 ticagrelor and 7 placebo patients (23 patients total).

Baseline data

The mean age of patients included in part A was 11.2 years (ranging between 3 and 17 years) in the overall trial population, this resulted in no major difference between the age of the treatment groups in part B (Table 6).

Table 6. Demographic characteristics (safety analysis set)

	Part A	Part B		
Demographic characteristic	**Ticagrelor (N=45)**	**Ticagrelor (N=16)**	**Placebo (N=7)**	**Total (N=23)**
Age (years)				
n	45	16	7	23
Mean (SD)	11.2 (3.34)	10.2 (3.73)	9.7 (3.35)	10.0 (3.55)
Minimum, Maximum	3, 17	3, 17	4, 14	3, 17
Age category (n [%])				
2-11 years	24 (53.3)	12 (75.0)	5 (71.4)	17 (73.9)
12-18 years	21 (46.7)	4 (25.0)	2 (28.6)	6 (26.1)
Sex (n [%])				
Male	21 (46.7)	7 (43.8)	5 (71.4)	12 (52.2)
Female	24 (53.3)	9 (56.3)	2 (28.6)	11 (47.8)
Race (n [%])				
White	10 (22.2)	1 (6.3)	0 (0.0)	1 (4.3)
Black or African American	35 (77.8)	15 (93.8)	7 (100)	22 (95.7)
Any past SCD complication (n [%])				
Yes	30 (66.7)	10 (62.5)	5 (71.4)	15 (65.2)
No	15 (33.3)	6 (37.5)	2 (28.6)	8 (34.8)

CHMP comment:

In part B, the demographic characteristics are sufficiently well distributed across the two treatment groups, with the exception of the higher percentage of males in the placebo group (71.4%) compared with the ticagrelor group (43.5%). In the adult population, gender differences seem to be not clinically relevant for ticagrelor and no dose adjustment for ticagrelor is required on the basis of gender. It is not likely the imbalance between boys and girls will influence the results of this study.

Up to two-thirds of patients are of black or African American origin, reflecting the prevalence of SCD in this group, which is higher compared to Caucasians.

Table 7. Sickle cell disease characteristics (safety analysis set)

	Number (%) of patients			
	Part A	Part B		
SCD characteristic	Ticagrelor (N=45)	Ticagrelor (N=16)	Placebo (N=7)	Total (N=23)
Any past SCD complication	30 (66.7)	10 (62.5)	5 (71.4)	15 (65.2)
Dactylitis or hand-foot syndrome	8 (17.8)	2 (12.5)	2 (28.6)	4 (17.4)
Acute chest syndrome	16 (35.6)	6 (37.5)	1 (14.3)	7 (30.4)
Hepatic sequestration	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Splenic sequestration	7 (15.6)	2 (12.5)	0 (0.0)	2 (8.7)
Bone necrosis	2 (4.4)	1 (6.3)	0 (0.0)	1 (4.3)
Priapism	1 (2.2)	0 (0.0)	1 (14.3)	1 (4.3)
Cholelithiasis	8 (17.8)	4 (25.0)	3 (42.9)	7 (30.4)
Joint necrosis	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	13 (28.9)	3 (18.8)	3 (42.9)	6 (26.1)

Table 8. Vaso-occlusive crises past 12 months (safety analysis set)

	Number (%) of patients			
	Part A	Part B		
VOC history	Ticagrelor (N=45)	Ticagrelor (N=16)	Placebo (N=7)	Total (N=23)
Any VOC history	34 (75.6)	13 (81.3)	6 (85.7)	19 (82.6)
Number of VOC within prior 12 months				
1	8 (17.8)	2 (12.5)	1 (14.3)	3 (13.0)
2	13 (28.9)	6 (37.5)	2 (28.6)	8 (34.8)
3	5 (11.1)	3 (18.8)	1 (14.3)	4 (17.4)
4	5 (11.1)	2 (12.5)	1 (14.3)	3 (13.0)
5	1 (2.2)	0 (0.0)	1 (14.3)	1 (4.3)
6	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
9	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Primary setting[b]				
In-patient hospitalisation	23 (51.1)	8 (50.0)	5 (71.4)	13 (56.5)
Emergency department	5 (11.1)	1 (6.3)	1 (14.3)	2 (8.7)
Short-stay outpatient unit	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)
Medical clinic outpatient (unscheduled visit)	8 (17.8)	5 (31.3)	0 (0.0)	5 (21.7)
Medically supervised outpatient treatment with escalated pain medication	3 (6.7)	1 (6.3)	1 (14.3)	2 (8.7)
Self-treated (no consultation with medical personnel prior to escalation of pain medication)	5 (11.1)	2 (12.5)	0 (0.0)	2 (8.7)
Other	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)

CHMP comment:

Imbalances in several SCD complications have been observed, e.g. ACS was more common in the ticagrelor group compared to the placebo group (37.5% versus 14.3%). These imbalances might influence the secondary endpoints. Nevertheless, the number of patients included in part B of the trial was too limited (n=23) to draw firm conclusion on these secondary endpoints (see below).

	Number (%) of patients			
	Part A	Part B		
VOC history	Ticagrelor (N=45)	Ticagrelor (N=16)	Placebo (N=7)	Total (N=23)
Treatments administered[b]				
Non-narcotic pain medications[a]	28 (62.2)	11 (68.8)	5 (71.4)	16 (69.6)
Oral narcotics[a]	19 (42.2)	9 (56.3)	4 (57.1)	13 (56.5)
Parenteral narcotics[a]	17 (37.8)	8 (50.0)	3 (42.9)	11 (47.8)

CHMP comment:

The pre-trial use of pain medication was similar between the ticagrelor and placebo group.

Pharmacokinetics

A summary of the results is shown below (Table 9, Figure 4 and Figure 5). Following single doses at visits 2 and 3, ticagrelor was well absorbed with the C_{max} observed within the first 2 hours post-dose, in the majority of patients. As the numbers of PK blood samples were limited after 1-week bid doses of ticagrelor 0.125 mg/kg, 0.563 mg/kg and 0.75 mg/kg at visit 4, a firm interpretation of plasma concentration time profiles could not be made. Mean concentrations at each visit were lower for the active metabolite (AR-C124910XX) than for ticagrelor (Figure 6). The observed C_{max} values of AR-C124910XX 2 hours post-dose were, on average, approximately 1/3 of ticagrelor concentrations. Ticagrelor exposure appeared to increase approximately proportionally to increasing weight-based doses after both single and repeated dosing of ticagrelor in paediatric SCD patients aged 2 years to <18 years. Overall, geometric mean (SD) CL/F was 22.50 ± 7.53 L/h.

Table 9. Summary of pharmacokinetic parameters for ticagrelor by actual treatment/ dose and visit – Part A (pharmacokinetic analysis set)

Visit	Actual treatment/dose	Summary statistic	AUC (ng.h/mL)	C_{max} (ng/mL)	CL/F (L/h)
Overall	N=45	n	-	-	45
		Geometric mean	-	-	22.50
		Arithmetic mean (SD)	-	-	23.67 (7.531)
		Median	-	-	23.70
		Min, Max	-	-	11.9, 45.8
Visit 2	0.125 mg/kg (N=14)	n	14	14	-
		Geometric mean	161.9	15.240	-
		Arithmetic mean (SD)	174.6 (72.24)	18.584 (15.2709)	-
		Median	160.5	12.850	-
		Min, Max	80, 337	5.27, 66.90	-
Visit 2	0.75 mg/kg (N=31)	n	31	31	-
		Geometric mean	1151.9	162.961	-
		Arithmetic mean (SD)	1190.1 (308.39)	180.577 (84.9230)	-
		Median	1189.3	164.000	-
		Min, Max	665, 1899	60.90, 429.00	-
Visit 3	0.375 mg/kg (N=7)	n	7	7	-
		Geometric mean	437.5	52.069	-
		Arithmetic mean (SD)	488.4 (262.24)	59.900 (34.4115)	-
		Median	423.0	50.900	-
		Min, Max	241, 1009	24.70, 124.00	-
Visit 3	0.563 mg/kg (N=18)	n	18	18	-
		Geometric mean	879.3	96.031	-
		Arithmetic mean (SD)	904.9 (236.12)	105.544 (51.4902)	-
		Median	860.3	96.450	-
		Min, Max	579, 1514	40.30, 256.00	-
Visit 3	1.125 mg/kg bid (N=10)	n	10	10	-
		Geometric mean	1638.7	269.174	-
		Arithmetic mean (SD)	1709.6 (521.80)	304.400 (162.2147)	-
		Median	1628.0	257.500	-
		Min, Max	1067, 2494	132.00, 625.00	-
Visit 3	2.25 mg/kg bid (N=9)	n	9	9	-
		Geometric mean	2850.9	566.550	-
		Arithmetic mean (SD)	3050.1 (1277.39)	600.667 (225.9447)	-
		Median	2545.1	613.000	-
		Min, Max	1773, 5886	356.00, 1080.00	-
Visit 4	0.125 mg/kg bid (N=14)	n	14	14	-
		Geometric mean	161.9	13.973	-
		Arithmetic mean (SD)	174.6 (72.24)	18.104 (15.3652)	-
		Median	160.5	13.550	-
		Min, Max	80, 337	4.68, 61.60	-
Visit 4	0.563 mg/kg bid (N=9)	n	9	9	-
		Geometric mean	913.5	111.367	-
		Arithmetic mean (SD)	932.5 (208.82)	133.700 (81.1597)	-
		Median	951.4	126.000	-
		Min, Max	654, 1397	44.80, 260.00	-
Visit 4	0.75 mg/kg bid (N=17)	n	17	17	-
		Geometric mean	1022.4	157.216	-
		Arithmetic mean (SD)	1056.5 (287.32)	194.176 (114.8138)	-
		Median	1033.7	200.000	-
		Min, Max	665, 1663	23.70, 474.00	-

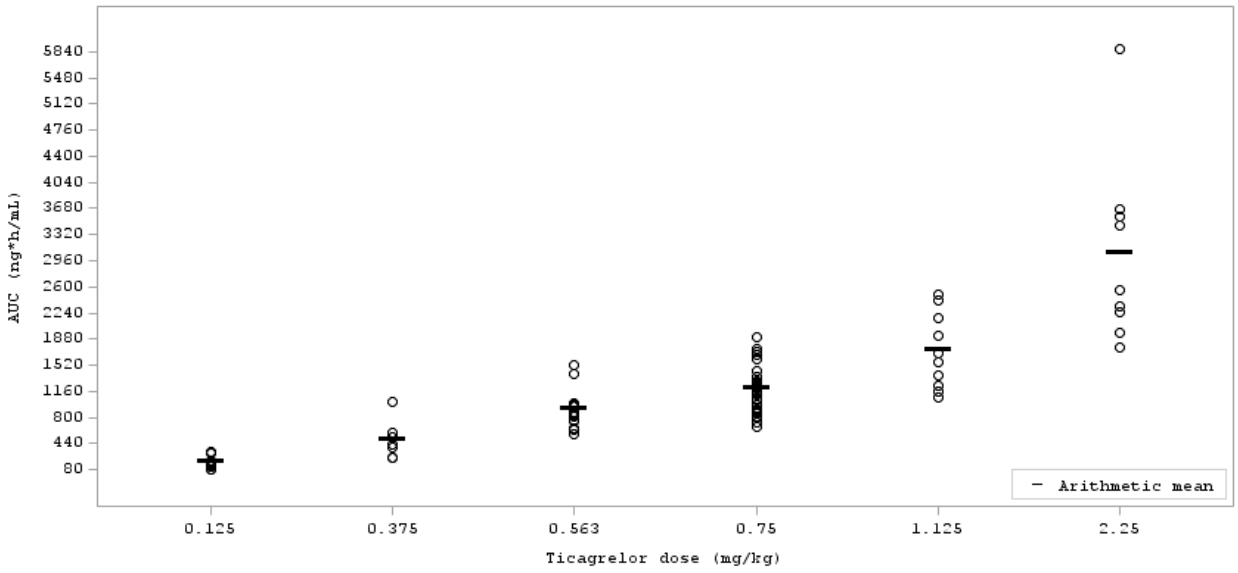


Figure 4. Plot of individual area under the plasma concentration time curve by dose, Visits 2 and 3: ticagrelor (pharmacokinetic analysis set)

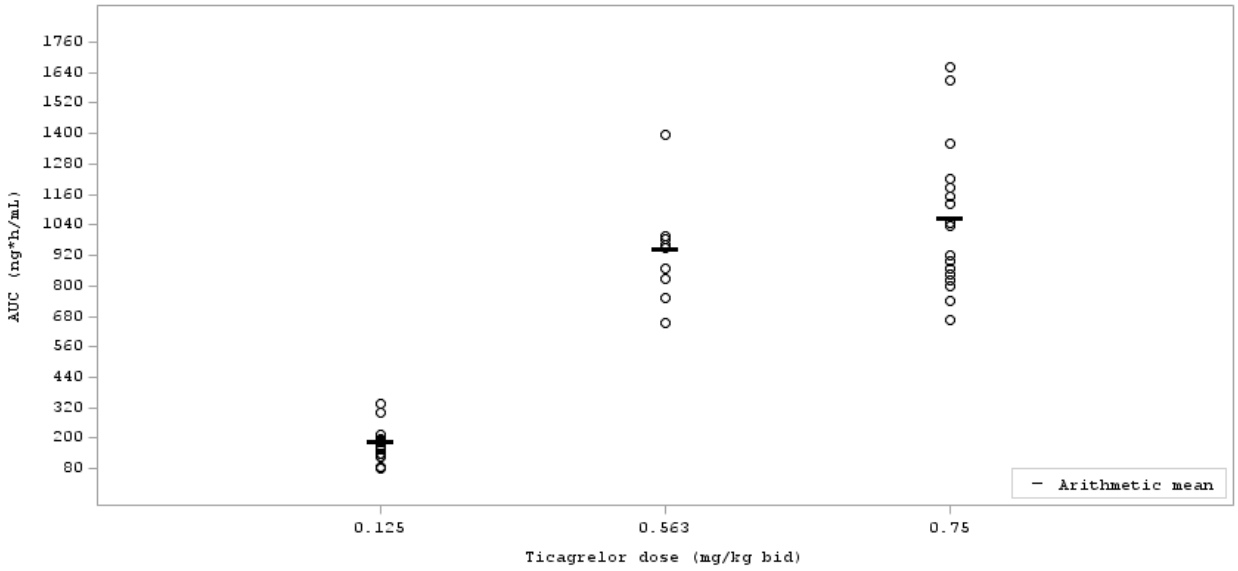


Figure 5. Plot of individual area under the plasma concentration time curve by dose, Visit 4: ticagrelor (pharmacokinetic analysis set)

A **B**

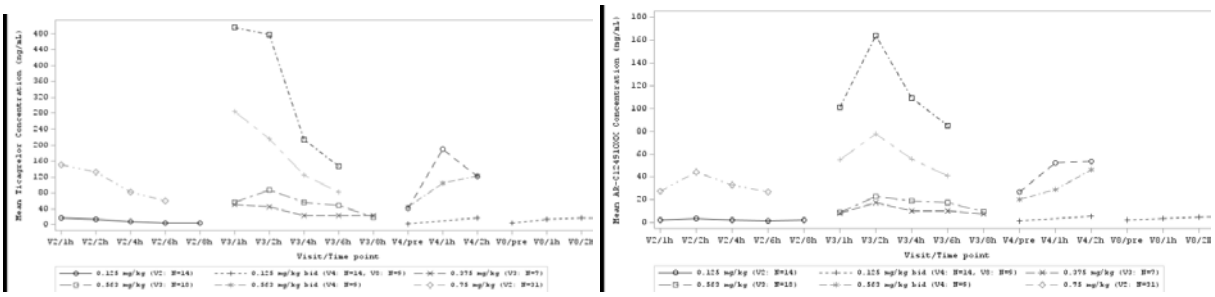


Figure 6. Plot of mean plasma concentration values over time of ticagrelor (A) and AR-C124910XX (B)

At Visit 8, following 4-week repeated twice daily dosing of ticagrelor 0.125 mg/kg, mean concentrations increased from pre-dose to 1 hour and 2 hours post-dose, and decreased slightly at 4 hours post-dose. Mean concentrations at Visit 8 were lower for AR-C124910XX than for ticagrelor. Plasma concentration data for ticagrelor and AR-C124910XX were available from 9 patients. The mean observed C_{max} and AUC values for both ticagrelor and AR-C124910XX were comparable to the corresponding dose in Part A. Overall geometric mean (SD) CL/F was 19.15 ± 6.67 L/h (Table 10).

Table 10. Summary of pharmacokinetic parameters for ticagrelor by actual dose and visit – Part B (pharmacokinetic analysis set)

Visit	Treatment group	Actual dose	Summary statistic	AUC (ng.h/mL)	C_{max} (ng/mL)	CL/F (L/h)
Visit 8	Ticagrelor	0.125 mg/kg bid (N=9)	n	9	9	9
			Geometric mean	160.6	16.394	19.15
			Arithmetic mean (SD)	178.8 (88.58)	20.300 (13.3671)	20.15 (6.673)
			Median	154.3	16.400	21.10
			Min, Max	80, 337	4.68, 45.10	11.9, 30.8

Pharmacodynamics

Following single ticagrelor doses of 0.125 mg/kg to 2.25 mg/kg at Visits 2 and 3, mean (standard deviation) decrease in PRU from baseline to 2 hours post-dose ranged from 6.01% (21.42) for ticagrelor 0.125 mg/kg to 72.84% (19.83) for ticagrelor 2.25 mg/kg.

Following repeated bid ticagrelor doses of 0.125 mg/kg, 0.563 mg/kg and 0.75 mg/kg at Visit 4, mean (SD) decrease in PRU from baseline to 2 hours post-dose ranged from 11.12% (21.76) for ticagrelor 0.125 mg/kg to 57.97% (29.18) for ticagrelor 0.563 mg/kg (Table 11).

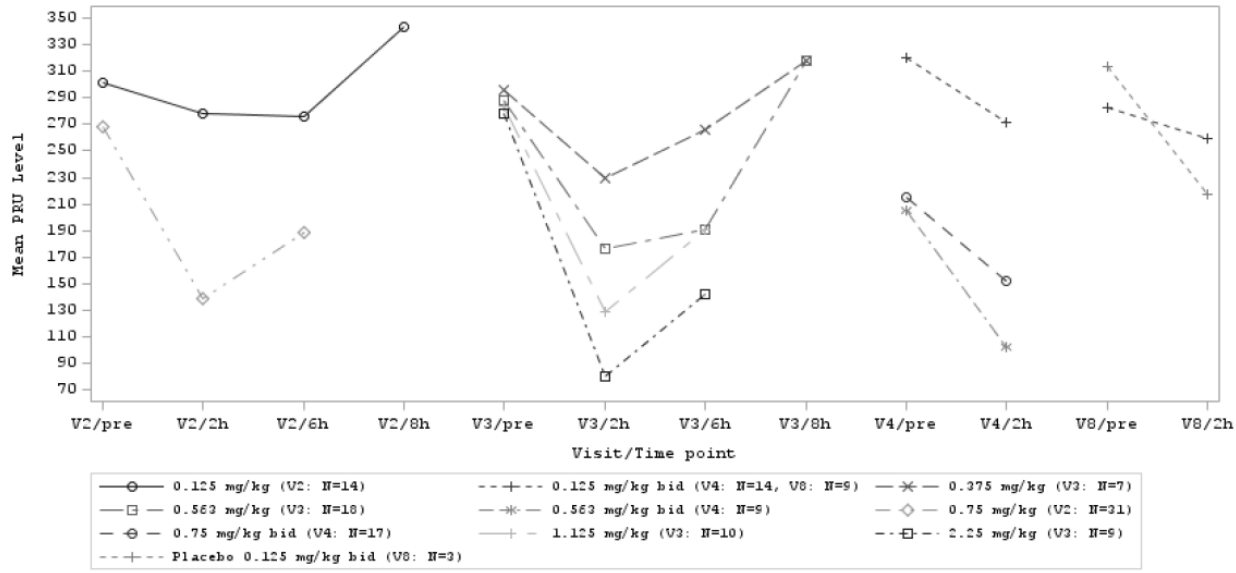


Figure 7. Plot of mean PRU levels over time (pharmacodynamic analysis set)

Table 11. Absolute value and percent change from baseline of PRU by actual treatment / dose and visit / timepoint – Part A

			Result			Percent change from baseline[a]		
Visit	**Actual treatment/dose**	**Timepoint**	**n**	**Mean (SD)**	**Min, Max**	**n**	**Mean (SD)**	**Min, Max**
Visit 2	0.125 mg/kg (N=14)	Pre-dose	14	301.6 (46.55)	231, 372	-	-	-
		2 hr	14	278.2 (47.20)	172, 330	14	-6.01 (21.416)	-38.8, 42.0
		6 hr	5	276.0 (75.43)	156, 358	5	3.53 (28.432)	-44.5, 29.7
		8 hr	5	343.0 (38.13)	288, 372	5	0.29 (13.429)	-13.6, 21.6
Visit 2	0.75 mg/kg (N=31)	Pre-dose	30	268.0 (35.95)	212, 331	-	-	-
		2 hr	31	138.4 (70.68)	22, 269	30	-49.54 (26.030)	-90.4, 8.1
		6 hr	28	189.0 (69.84)	14, 298	27	-31.66 (23.581)	-93.5, 3.8
Visit 3	0.375 mg/kg (N=7)	Pre-dose	7	295.4 (42.30)	215, 349	7	-1.59 (24.089)	-42.2, 25.5
		2 hr	7	229.0 (64.22)	131, 317	7	-25.30 (21.665)	-47.8, 3.6
		6 hr	2	266.0 (57.98)	225, 307	2	-2.76 (16.989)	-14.8, 9.3
		8 hr	3	318.3 (66.43)	263, 392	3	-8.37 (17.841)	-28.5, 5.4
Visit 3	0.563 mg/kg (N=18)	Pre-dose	17	287.7 (34.35)	232, 358	17	9.88 (16.060)	-13.1, 37.1
		2 hr	18	176.2 (79.53)	27, 332	18	-32.88 (31.625)	-87.6, 20.3
		6 hr	14	190.4 (47.78)	112, 276	14	-24.74 (21.529)	-58.2, 10.8
		8 hr	1	318.0 (-)	318, 318	1	-11.91 (-)	-11.9, -11.9
Visit 3	1.125 mg/kg (N=10)	Pre-dose	10	283.7 (36.88)	230, 341	10	0.59 (13.219)	-22.1, 25.1
		2 hr	10	128.9 (37.68)	58, 203	10	-53.64 (17.159)	-79.5, -12.5
		6 hr	9	191.2 (57.59)	77, 287	9	-33.36 (21.544)	-72.8, 0.7

			Result			Percent change from baseline[a]		
Visit	**Actual treatment/dose**	**Timepoint**	**n**	**Mean (SD)**	**Min, Max**	**n**	**Mean (SD)**	**Min, Max**
Visit 3	2.25 mg/kg (N=9)	Pre-dose	9	277.7 (39.36)	229, 352	8	-4.54 (5.740)	-10.5, 4.4
		2 hr	9	79.9 (47.74)	7, 164	8	-72.84 (19.830)	-97.7, -29.9
		6 hr	9	141.7 (69.58)	14, 234	8	-50.27 (29.786)	-95.5, -7.9
Visit 4	0.125 mg/kg bid (N=14)	Pre-dose	1	320.0 (-)	320, 320	1	-8.83 (-)	-8.8, -8.8
		2 hr	13	271.2 (70.35)	177, 391	13	-11.12 (21.760)	-48.1, 27.8
Visit 4	0.563 mg/kg bid (N=9)	Pre-dose	9	205.4 (53.22)	133, 267	9	-15.44 (24.929)	-48.4, 15.6
		2 hr	9	102.0 (72.53)	20, 239	9	-57.97 (29.177)	-92.4, -12.1
Visit 4	0.75 mg/kg bid (N=17)	Pre-dose	16	214.7 (48.71)	106, 283	15	-22.41 (18.548)	-53.5, 15.1
		2 hr	17	152.0 (72.35)	7, 325	16	-45.16 (27.151)	-97.0, 10.9

CHMP comment:

A single dose of ticagrelor of 0.125 mg/kg , 0.375mg/kg, 0.563 mg/kg, 0.75mg/kg, 1.125 mg/kg, and 2.25 mg/kg resulted in a dose-dependent decrease in PRU from baseline to 2 hours post-dose of 6.01%, 25.30%, 32.88%, 49.54%, 54.64%, and 72.84%, respectively. After 7 days open-label ticagrelor twice daily 0.125 mg/kg , 0.563 mg/kg, and 0.75 mg/kg resulted in a decrease of 11.12%, 57.97%, 45.16%, respectively, indicating that the 0.75 mg/kg bid did not show additional PRU reduction compared with the 0.563 mg/kg bid.

PART B

Only PRU results for the dose of 0.125 mg/kg ticagrelor were available from Visit 8, since PD sampling was removed from this visit in CSP Amendment 3.

To reduce burden on patients and families the amended protocol allowed for patients to opt out of participation in Part B. The PK/PD determinations previously scheduled for Visit 8 were moved to Visit 4 in order to assure that steady state PK/PD was obtained in all study patients

Most of the remaining patients declined participation in Part B, as a result selection bias can have occurred, therefore only descriptive statistics were used.

Table 12. Absolute value and percent change from baseline of PRU by actual dose and visit / timepoint – Part B

				Result			Percent change from baseline[a]		
Visit	Treatment group	Actual dose	Timepoint	n	Mean (SD)	Min, Max	n	Mean (SD)	Min, Max
Visit 2	Ticagrelor	0.125 mg/kg bid (N=9)	Pre-dose	9	297.6 (47.37)	231, 372	-	-	-
	Placebo	0.125 mg/kg bid (N=3)	Pre-dose	3	277.7 (34.53)	249, 316	-	-	-
Visit 8	Ticagrelor	0.125 mg/kg bid (N=9)	Pre-dose	8	282.8 (19.26)	260, 315	8	-3.89 (17.719)	-27.7, 32.0
			2 hr	9	259.6 (61.95)	125, 338	9	-10.92 (25.507)	-55.5, 31.6
	Placebo	0.125 mg/kg bid (N=3)	Pre-dose	3	313.3 (20.13)	292, 332	3	13.72 (12.330)	0.0, 23.9
			2 hr	3	217.3 (78.34)	132, 286	3	-23.06 (20.787)	-47.0, -9.5

CHMP comment:

With respect to part B, considering that the placebo group showed a higher percent change from baseline of PRU (-23.06%) compared with 0.125mg/kg bid ticagrelor (-10.92%) due to too low doses of ticagrelor, no conclusions can be drawn.

Pharmacokinetic - pharmacodynamic evaluation

The relationship between ticagrelor dose, exposure and platelet inhibition (PRU response), were analysed using a PK/PD model. Population PK and PKPD analyses were performed on ticagrelor and AR-C124910XX plasma concentration and platelet inhibition data.

In brief, a 2-compartment PK model with first-order absorption and elimination processes was used to describe ticagrelor and AR-C124910XX plasma concentration-time profiles and a sigmoid E_{max} model with individual predicted ticagrelor concentrations was used to characterise the relationship between ticagrelor concentration and platelet inhibition response over time (see Figure 8 below). The population PK dataset contained 878 ticagrelor and AR-C124910XX plasma concentration samples available from both single dose and steady-state conditions. The population PKPD analysis was based on 341 PRU measurements which were time-matched to PK sampling and included also baseline samples taken prior to administration of ticagrelor. The model results showed that PK of ticagrelor and its active metabolite (AR-C124910XX) appeared to be predictable.

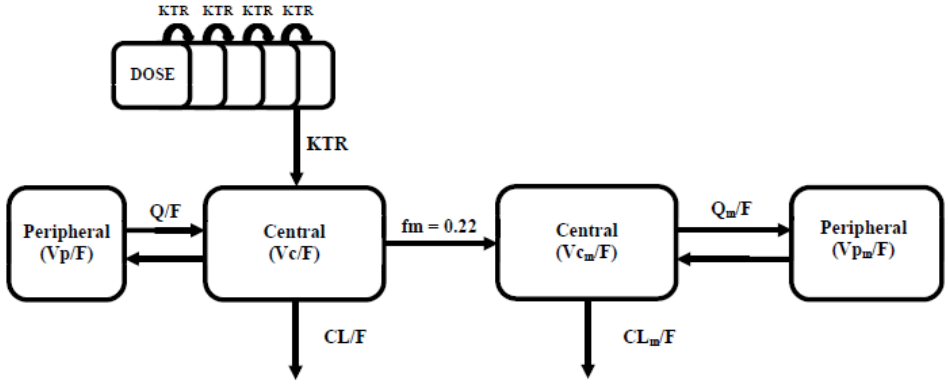


Figure 8. PK model

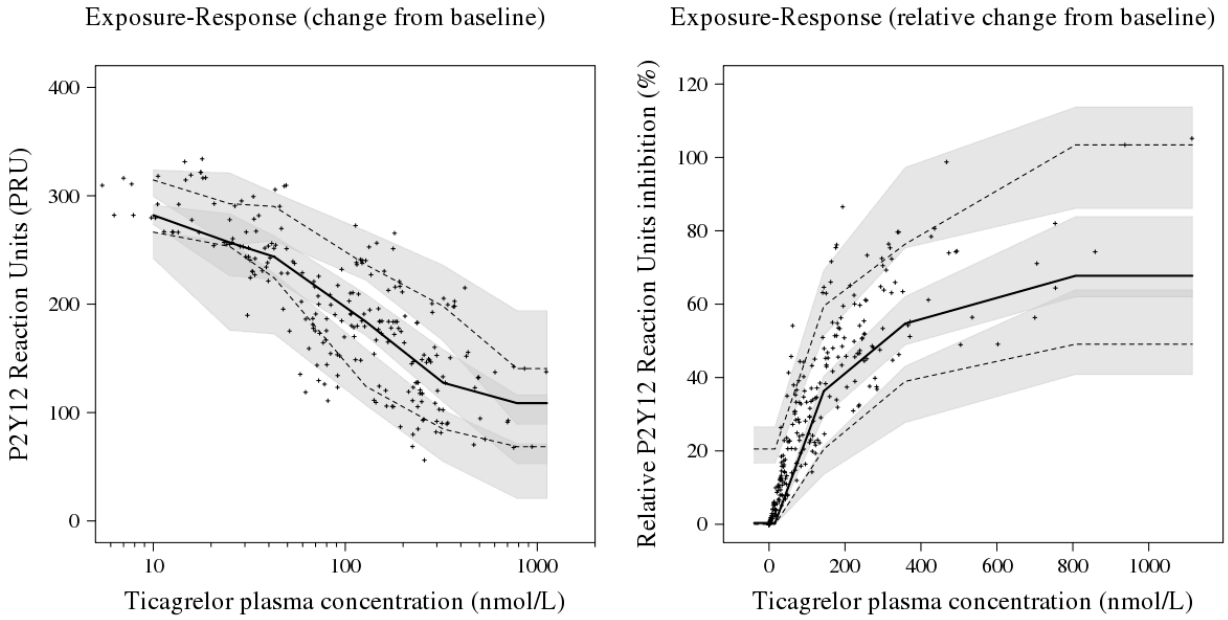


Figure 9. VPCs of the final model absolute and relative PRU response

The relationship between ticagrelor plasma concentrations and PRU is presented in the Figure 1010.

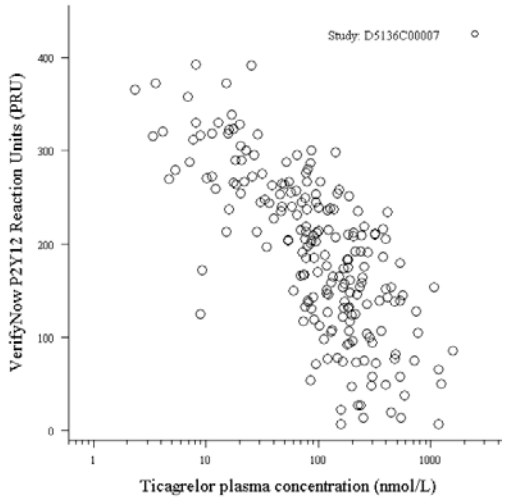


Figure 10. Individual ticagrelor plasma concentrations versus $P2Y_{12}$ reaction units in paediatric sickle cell disease patients ≥2 to <18 years (study D5136C0000)

A wide ticagrelor exposure range was observed in the study, with platelet inhibition (PRU) ranging from baseline to near full PRU inhibition. PRU levels were reflective of the exposure, with maximum PRU inhibition close to the observed C_{max} and with a return towards baseline values with the decline of ticagrelor concentrations. Overall the ticagrelor exposure – platelet inhibition response relationship was adequately described by the PKPD model and was in line with the relationship previously reported in young adult (18 to 30 years) SCD patients and adult coronary patients.

Secondary efficacy variables: VOC

PART A

Table 13. Number of vaso-occlusive crises – Part A (safety analysis set)

Treatment group	n	Group total number of VOCs	Mean (SD)	Min, Max
Ticagrelor (N=45)	45	27	0.6 (1.19)	0, 5

PART B

Table 14. Number of vaso-occlusive crises – Part B (efficacy analysis set)

Treatment group	n	Group total number of VOCs	Mean (SD)	Min, Max
Ticagrelor (N=15)	15	15	1.0 (2.00)	0, 8
Placebo (N=8)	8	5	0.6 (0.74)	0, 2

The number of VOC requiring hospitalisation or emergency department visits in the ticagrelor group was 3, compared to 1 VOC in the placebo group. No patient had more than 1 VOC in either treatment group. Mean percentage of days hospitalised was 4.52% and 1.34% in the ticagrelor and placebo group, respectively.

CHMP comment:

At baseline, 34 out of 45 patients had a vaso-occlusive crisis (VOC) history (75.6%) (Part A). In part B of the trial, this was 81.3% for the ticagrelor group and 85.7% for the placebo group respectively. During treatment with ticagrelor (Part B), the number of VOC was higher in the ticagrelor group (1 crisis per patient) compared with placebo (0.6 crisis per patient), however the numbers are too low to draw firm conclusions.

Secondary efficacy variables: pain

PART A

Patients aged ≥4 years in Part A, experienced pain for a mean (SD) of 25.07% (31.07) of days. Overall mean (SD) intensity of pain in patients ≥4 years, was 0.85 (1.27). Mean intensity of pain decreased from the first week (mean [SD] 1.02 [1.53]) to the second week (mean [SD] 0.62 [0.98]).

Patients aged ≥4 years in Part A used analgesics for a mean (SD) of 14.52% (22.00) of days.

Patients aged ≥4 years in Part A, used opioid analgesics for a mean (SD) of 6.24% (17.96) of days.

A small percentage of days of absence from school or work was reported in patients ≥6 years, with a mean (SD) of 3.22% (7.29).

PART B

Patients aged ≥4 years in Part B experienced pain for a mean (SD) of 27.01% (34.07) and 31.78% (23.73) of days, in the ticagrelor and placebo groups, respectively. Overall mean (SD) intensity of pain in patients ≥4 years was 1.40 (2.03) in the ticagrelor group compared to 0.87 (0.49) in the placebo group. In the ticagrelor group, mean intensity of pain decreased from the first week (mean [SD] 1.64 [2.60]) to the second (mean [SD] 1.11 [2.24]) and third weeks (mean [SD] 1.06 [1.88]), but increased at the fourth week (mean [SD] 1.46 [2.62]).

The placebo group showed similar results - mean intensity of pain decreased from the first week (mean [SD] 1.36 [0.83]) to the second week (mean [SD] 0.38 [0.53]), but increased at the third week (mean [SD] 0.67 [1.12]) and fourth week (mean [SD] 0.83 [0.90]).

Patients aged ≥4 years in Part B used analgesics for a mean (SD) of 16.79% (20.84) and 18.56% (19.11) of days, in the ticagrelor and placebo groups, respectively. Patients aged ≥4 years in Part B, used opioid analgesics for a mean (SD) of 12.46% (22.50) and 0.54% (1.54) of days, in the ticagrelor and placebo groups, respectively.

Patients aged ≥6 years in Part B, were absent from school or work for a mean (SD) of 4.86% (10.87) and 5.95% (9.49) of days, in the ticagrelor and placebo groups, respectively.

CHMP comment:

Inconsistent results on intensity of pain have been reported. No conclusions can be drawn on clinical efficacy with respect to pain due to the limited number of patients.

Safety results

Exposure

PART A

Forty-five patients received at least 1 dose of randomised study drug (ticagrelor). Mean (SD) study drug exposure (number of days in Part A where study drug had been taken) was 9.5 days (3.38).

PART B

Twenty-three patients received at least 1 dose of randomised study drug (ticagrelor/placebo). Mean (SD) study drug exposure (number of days in Part B where study drug had been taken) was 29.4 days (3.41) in the placebo group and 27.4 days (6.39) in the ticagrelor group.

Adverse events

PART A

Overall, 30 (66.7%) patients experienced at least 1 adverse event (AE). No patients experienced an AE that led to death, and 5 (11.1%) patients experienced at least 1 serious AE (SAE). No patient experienced an AE that led to discontinuation of the study drug or from the study. One (2.2%) patient experienced an AE that led to dose interruption (Table 15).

The most commonly reported AEs by PT were sickle cell anaemia with crisis (9 [20.0%] patients), abdominal pain (6 [13.3%] patients) and arthralgia and pain in extremity (5 [11.1%] patients each) (Table 16).

Most AEs were mild or moderate in intensity, but 3 patients (6.7%) experienced AEs of severe intensity. AEs that were considered related to study drug were reported by 2 (4.4%) patients. The AEs considered related to study drug were abdominal pain, headache and jaundice.

SAEs were experienced by 5 (11.1%) patients (sickle cell anaemia with crisis [n=3], gastroenteritis viral [n=1], and acute chest syndrome [n=1]). None of the SAEs were related to study drug.

There were no patients who discontinued study drug due to an AE, however, one patient had a dose interruption due to sickle cell anaemia with crisis.

Additionally, for two patients, results for PRU at Visit 4 revealed a drop in PRU < 95 while already being on the reduced dose of 0.563 mg/kg. This led to the discontinuation of further treatment for both patients. Both patients were excluded from the EAS, and hence from all related analyses.

Overall, there were no clinically important changes in mean or median values of any laboratory parameters over time. No bleeding events were reported during Part A.

Table 15. Adverse events – Part A (safety analysis set)

AE category	Number (%) of patients treated with ticagrelor[a] Total (N=45)
Any AE	30 (66.7)
Any AE leading to death	0 (0.0)
Any SAE (including events leading to death)	5 (11.1)
Any AE leading to discontinuation of study drug	0 (0.0)
Any AE leading to dose interruption	1 (2.2)
Any AE leading to dose reduction	0 (0.0)
Any AE leading to withdrawal from study	0 (0.0)

Table 16. Adverse events (≥2 patients), by system organ class and preferred term – Part A (safety analysis set)

SOC/MedDRA PT[c]	Number (%) of patients treated with ticagrelor[a] Total (N=45)
Patients with any AE[b]	30 (66.7)
Blood and lymphatic system disorders	10 (22.2)
Sickle cell anaemia with crisis	9 (20.0)
Gastrointestinal disorders	7 (15.6)
Abdominal pain	6 (13.3)
General disorders and administration site conditions	6 (13.3)
Facial pain	2 (4.4)
Non-cardiac chest pain	2 (4.4)
Musculoskeletal and connective tissue disorders	11 (24.4)
Arthralgia	5 (11.1)
Pain in extremity	5 (11.1)
Back pain	3 (6.7)
Nervous system disorders	5 (11.1)
Headache	4 (8.9)

PART B

Twenty-three patients received at least 1 dose of randomised study drug (ticagrelor/placebo). Mean (SD) study drug exposure (number of days in Part B where study drug had been taken) was 29.4 days (3.41) in the placebo group and 27.4 days (6.39) in the ticagrelor group. Overall, 19 (82.6%) patients experienced at least 1 AE (13 [81.3%] patients in the ticagrelor group and 6 [85.7%] patients in the placebo group). Overall, no patients experienced an AE that led to death, and 5 (21.7%) patients experienced at least 1 SAE (4 [25.0%] patients in the ticagrelor group and 1 [14.3%] patient in the placebo group). No patient experienced an AE that led to discontinuation of the study drug or from the study. Two (8.7%) patients experienced an AE that led to dose interruption (1 [6.3%] patient in the ticagrelor group and 1 [14.3%] patient in the placebo group) (Table 17).

The most commonly reported AEs by PT were sickle cell anaemia with crisis and arthralgia (6 [26.1%] patients each; 4 [25.0%] patients in the ticagrelor group and 2 [28.6%] patients in the placebo group) and abdominal pain and pain in extremity (5 [21.7%] patients each; 3 [18.7%] patients in the ticagrelor group and 2 [28.6%] patients in the placebo group) (Table 18).

Most AEs during Part B were mild or moderate in intensity. During Part B, 3 (13.0%) patients experienced AEs of severe intensity, all in the ticagrelor group. No AEs during Part B were considered related to study drug.

SAEs were experienced by 5 (21.7%) patients (sickle cell anaemia with crisis [n=4] and acute chest syndrome [n=1]). None of the SAEs were related to study drug and all were considered recovered/resolved.

There were no patients who discontinued study drug due to an AE, however, 2 patients had a dose interruption due to an AE. One patient had a dose interruption due to abdominal pain, musculoskeletal pain, pain in extremity and sickle cell anaemia with crisis and another patient had a dose interruption due to sickle cell anaemia with crisis.

Overall, there were no clinically important changes in mean or median values of any laboratory parameters over time. No bleeding events were reported during Part B.

Table 17. Adverse events – Part B (safety analysis set)

	Number (%) of patients[a]		
AE category	**Ticagrelor (N=16)**	**Placebo (N=7)**	**Total (N=23)**
Any AE	13 (81.3)	6 (85.7)	19 (82.6)
Any AE leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events leading to death)	4 (25.0)	1 (14.3)	5 (21.7)
Any AE leading to discontinuation of study drug	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to dose interruption	1 (6.3)	1 (14.3)	2 (8.7)
Any AE leading to dose reduction	0 (0.0)	0 (0.0)	0 (0.0)
Any AE leading to withdrawal from study	0 (0.0)	0 (0.0)	0 (0.0)

Table 168. Adverse events (≥2 patients in any treatment group), by system organ class and preferred term – Part B (safety analysis set)

	Number (%) of patients[a]		
SOC/MedDRA PT[c]	**Ticagrelor (N=16)**	**Placebo (N=7)**	**Total (N=23)**
Patients with any AE[b]	13 (81.3)	6 (85.7)	19 (82.6)
Blood and lymphatic system disorders	4 (25.0)	2 (28.6)	6 (26.1)
Sickle cell anaemia with crisis	4 (25.0)	2 (28.6)	6 (26.1)
Gastrointestinal disorders	7 (43.8)	3 (42.9)	10 (43.5)
Abdominal pain	3 (18.8)	2 (28.6)	5 (21.7)
Vomiting	3 (18.8)	0 (0.0)	3 (13.0)
Abdominal pain upper	2 (12.5)	0 (0.0)	2 (8.7)
General disorders and administration site conditions	4 (25.0)	1 (14.3)	5 (21.7)
Pyrexia	2 (12.5)	0 (0.0)	2 (8.7)
Musculoskeletal and connective tissue disorders	9 (56.3)	3 (42.9)	12 (52.2)
Arthralgia	4 (25.0)	2 (28.6)	6 (26.1)
Pain in extremity	3 (18.8)	2 (28.6)	5 (21.7)
Back pain	2 (12.5)	1 (14.3)	3 (13.0)
Musculoskeletal pain	2 (12.5)	1 (14.3)	3 (13.0)
Nervous system disorders	1 (6.3)	2 (28.6)	3 (13.0)
Headache	0 (0.0)	2 (28.6)	2 (8.7)
Respiratory, thoracic and mediastinal disorders	5 (31.3)	0 (0.0)	5 (21.7)
Oropharyngeal pain	3 (18.8)	0 (0.0)	3 (13.0)
Cough	2 (12.5)	0 (0.0)	2 (8.7)

CHMP comment:

In part B, 30 patients (66.7%) experienced at least 1 AE. The most common adverse events were sickle cell anaemia with crisis (9 [20.0%] patients), abdominal pain (6 [13.3%] patients) and arthralgia and pain in extremity (5 [11.1%] patients each). AEs that were considered by the investigator related to study drug were experienced by 2 patients (abdominal pain, headache, and jaundice). SAEs were reported in 5 patients, however none were related to study drug.

In Part B, the percentage of patients experiencing at least one AE was lower in the ticagrelor group (81.3%) compared with the placebo group. (85.7%). The most commonly reported AEs were sickle cell anaemia with crisis (25% vs 28.6% for the ticagrelor and placebo group, respectively), arthralgia (25.0% vs 28.6%), abdominal pain (18.8% vs 28.6%) and pain in extremity (18.8% vs 28.6%). None of the AEs were considered related to study drug. Furthermore, a higher incidence in SAEs were reported in the ticagrelor group (25%) compared with the placebo group (14.3%), however, none were related to study drug.

No bleedings were reported in this study. However, for two patients, results for PRU at Visit 4

revealed a drop in PRU <95 while already being on the reduced dose of 0.563 mg/kg for safety reasons based on the dosing schedule. These patients discontinued from treatment and were excluded from further analysis.

Furthermore, no deaths were reported during of the study.

2.3.3. Discussion on clinical aspects

Because of the remaining additional morbidity and mortality in patients with sickle cell disease (SCD) other new treatments should be considered. Inhibition of platelet activation has been proposed as a therapeutic option in the treatment of children and adults with SCD. Activated platelets promote the adherence of sickle cells to endothelial cells and participate in the vaso-occlusive process.

A dose-ranging Phase II study of ticagrelor followed by a single-blind, randomised, parallel group, placebo-controlled 4 weeks extension phase in paediatric patients (aged ≥2 to <18 years) with SCD was submitted as part of part of the Paediatric Investigation Plan (PIP) (PIP number: EMEA-000480-PIP01-08-M10) for ticagrelor (Brilique).The inclusion criteria were acceptable and reflected the general paediatric population with SCD.

The primary objective was the characterization of the relationship between ticagrelor dose and inhibition of platelet aggregation in paediatric patients with SCD, using PK/PD modelling, to support dose selection for Phase III. Inhibition of platelet aggregation is measured by the reduction in $P2Y_{12}$ reaction units (PRU), which is an acceptable surrogate for platelet aggregation. The relevance of PRU in SCD is still uncertain. For safety reasons the dosing schedule was modified for individual patients if the PRU was < 95 as a conservative choice in the context of uncertainty. The MAH does not intend to monitor PRU in clinical practice. In general, Ticagrelor is to be used without ASA in SCD which reduces the risk of bleeding significantly. (RSI)

In the dose-ranging Part A of the study, 45 patients received study drug of which 39 completed Part A. In the placebo-controlled extension phase (Part B), 23 patients received study drug of which 21 patients completed Part B.

Pharmacokinetics

The MAH did not provide a comparison of the obtained pharmacokinetic data in the paediatric population and the adult population. Only very limited PK data is obtained in the paediatric population (*e.g.* AUC) and is based on limited blood sampling (1, 2 and 4 hours for subjects >21 kg and 1 and 2 hours for subjects <21 kg). Due to the limited blood sampling C_{max} and t_{max} cannot be determined accurately. Furthermore, AUC is based on very limited data and the elimination half-life is not calculated. It is therefore unclear if the pharmacokinetics differs in the paediatric population compared to adults. Based on the data provided by the MAH and the PK parameters in adults from the SmPC and D80 AR, the exposure and clearance appear lower in the paediatric population compared to adults when correcting for differences in dose. The exposure to ticagrelor appears dose proportional over the dose range investigated.

parameter	Adults 60 mg bd[!]	Adults 90 mg bd[#]	Paediatric 0.125 mg/kg bd
C_{max} (ng/mL)	391	627	20.3 ± 13.4

C_{max}/dose	455	486	162
AUC (ng × h/mL)	3801	6255	178.8 ± 88.6
AUC/dose	4420	4849	1430

[!] dose is ~0.86 mg/kg bd based on a body weight of 70 kg; [#] dose is 1.29 mg/kg bd based on a body weight of 70 kg

Pharmacodynamics

A single dose of ticagrelor of 0.125 mg/kg , 0.375mg/kg, 0.563 mg/kg, 0.75mg/kg, 1.125 mg/kg, and 2.25 mg/kg resulted in a dose-dependent decrease in PRU from baseline to 2 hours post-dose of 6.01%, 25.30%, 32.88%, 49.54%, 54.64%, and 72.84% respectively. After 7 days open-label ticagrelor twice daily 0.125 mg/kg , 0.563 mg/kg, and 0.75 mg/kg resulted in a decrease of 11.12%, 57.97%, 45.16%, respectively, indicating that the 0.75 mg/kg bid did not show additional PRU reduction compared with the 0.563 mg/kg bid. With respect to part B, considering that the placebo group showed a higher percent change from baseline of PRU (-23.06%) compared with 0.125mg/kg bid ticagrelor (-10.92%) due to too low doses of ticagrelor, no conclusions can be drawn

PK/PD modelling

The relationship between ticagrelor dose, exposure and platelet inhibition (PRU response), were analysed using a PK/PD model. The PK/PD model appears to adequately describe the ticagrelor exposure – platelet inhibition response relationship. However, only limited PK was obtained in the paediatric population. The PK/PD model needs to be further validated with data from the Phase III clinical study in the paediatric population.

For the planned paediatric trials the MAH is advised to further evaluate the pharmacokinetic and pharmacodynamics parameters in the paediatric population and compare these with adults. Furthermore, there appears to be a PK/PD relationship regarding plasma concentrations and platelet inhibition. However, the data is too limited to make final conclusions.

The dose for the Phase III study is based on an update of the PRU target range is and the (updated) PKPD model (RSI 2).

Secondary efficacy variables

No conclusions can be drawn on clinical efficacy, due to the limited number of patients. The concept of ticagrelor in patients with SCD cannot be considered proven yet (RSI 1).

Safety

No new safety concerns were raised from single and repeated doses of ticagrelor during the study. The most common adverse events were sickle cell anaemia with crisis, arthralgia, abdominal pain and pain in extremity. Adverse events considered related to study drug were reported in only 2 patients. These adverse evets included abdominal pain, headache and jaundice, which are also reported in adult patients. No patients discontinued due to adverse events. Two (8.7%) patients experienced an adverse event that led to dose interruption however, this happened in 1 patient in the ticagrelor group and patient in the placebo group. None SAEs were considered related to study drug. No bleedings were reported in this study. However, for two patients, results for PRU at Visit 4 revealed a drop in PRU <95 in part B while already being on the reduced dose of 0.563 mg/kg. These patients discontinued and were excluded from further analysis. As PRU < 95 is considered to be associated with a higher risk for bleeding, this event should be closely monitored in the planned paediatric studies.

3. CHMP comments overall conclusion and recommendation

Study D5136C00007 was conducted to assess the dosing and tolerability and PK of ticagrelor at doses up to 2.25 mg/kg in children with sickle cell disease (aged ≥2 to <18 years) to support dose selection for Phase III. Only very limited PD and PK data is obtained from the paediatric population and this data is based on limited blood sampling. The PK and PD may differ in the paediatric population compared to adults, also depending on the different indication (RSI 3) and not using ASA in SCD. The dose for the Phase III study has been proposed by the MAH based on (updated) clinical considerations for the PRU target and PK-PD modelling (RSI 2).

There appears to be a PK/PD relationship regarding plasma concentrations and platelet inhibition. However, the PK/PD model needs to be further validated with data from the Phase III clinical study in the paediatric population due to the current limited PK data in the paediatric population.

For the planned paediatric trials the MAH is advised to further evaluate the pharmacokinetic and pharmacodynamics parameters in the paediatric population and compare these with adults. The PK/PD model can be updated with the obtained data from the Phase II study.

Measuring $P2Y_{12}$ reaction units (PRU) as surrogate for platelet aggregation has been validated, but application in patients with SCD is largely uncertain (RSI 3).

No definite conclusions can be drawn on the clinical efficacy and safety in the paediatric population due to the limited number of patients. Moreover, this study did not provide evidence for the proof of concept for ticagrelor in paediatric patients with SCD (RSI 1). The results of the planned paediatric clinical trials have to be waited for, to draw definite conclusions. In general, no new safety concerns were raised and the administered doses of ticagrelor seem to be well tolerated. Additionally, the adverse events are in accordance with adults. However, long-term studies are needed to draw further conclusions on the efficacy and safety of ticagrelor for SCD in children.

The CHMPagrees with the MAH that the benefit-risk balance remains positive and that no amendment to the SmPC is warranted. No concerns are raised in relation to clinical study results from study No. D5136C00007. However, in order to provide items for discussion about the feasibility of the Paediatric Investigation Plan (PIP) for ticagrelor in patients with sickle cell disease, several questions have been discussed in the RSI, highlighting much uncertainty. With the additional information received by the applicant, the issues raised in the RSI have been sufficiently discussed. No further action is required with regards to (alteration of) the PIP.

X Fulfilled

The results from this study are used for a Phase III study in the paediatric population.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Please provide evidence gathered so far for the proof of concept of ticagrelor in patients with sickle cell disease.
2. Please provide information regarding the dose selection for the planned phase III study, since no dose has been proposed by the MAH based on this study.
3. The MAH is requested to provide scientific data in order to justify that $P2Y_{12}$ reaction units (PRU) are predictive for platelet aggregation. Additionally, the MAH is requested to justify that the use of PRU as a surrogate for platelet aggregation is also applicable to patients with sickle cell disease.
4. The MAH is requested to justify the cut-off point of PRU < 95 used in the dosing schedule. Additionally, the MAH is requested to discuss how this should be monitored in clinical practice.
5. The MAH is requested to discuss the risk for major bleeding for patients with PRU < 95.
6. The MAH is requested to justify why children with body weight < 16 kg were excluded from the study.

The timetable is a 30 day response timetable with clock stop.

5. MAH responses to Request for supplementary information

5.1. Question 1

Please provide evidence gathered so far for the proof of concept of ticagrelor in patients with sickle cell disease.

MAH's response

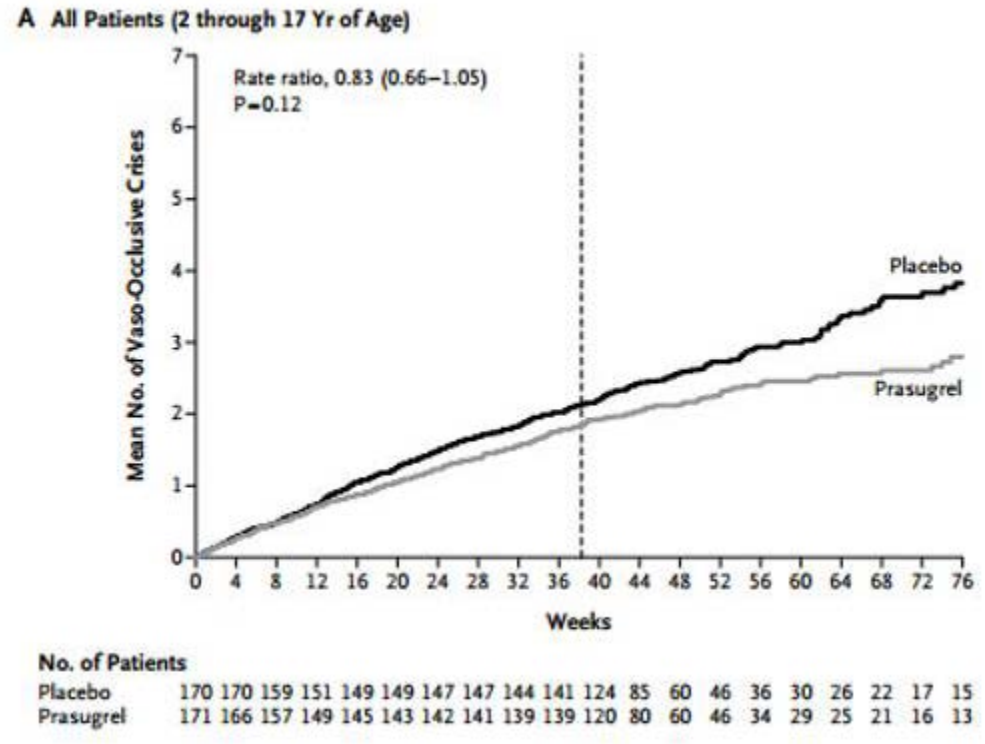
The focus of the ticagrelor clinical development programme has been the treatment of adults with various manifestations of atherosclerotic disease. Thus, the proof of concept for the evaluation of ticagrelor in SCD is based on studies with other antiplatelet therapies.

The rationale for the use of antiplatelet therapy in the management of SCD is based on the evidence that platelets participate in the vaso-occlusive process and that platelet activation correlates with the frequency of pain episodes (Ataga et al 2012). VOCs are initiated and sustained by interactions among sickle cells, endothelial cells, blood cells, and constituents of plasma. Activated platelets participate in VOCs by promoting the adhesion of sickle cells to endothelial cells and through formation of platelet-leukocyte aggregates, which augment the inflammatory state and contribute to vaso-occlusion. In patients with SCD, platelets are activated during the non-crisis "steady state" and are further activated during painful episodes (Lee et al 2006). Ticagrelor is an oral, direct-acting, selective, reversibly-binding P2Y12 receptor antagonist that prevents adenosine diphosphate (ADP)-mediated platelet activation and aggregation. An additional mechanism of action of ticagrelor, increasing local endogenous adenosine levels (Nylander et al 2013), may contribute to a vasodilatory effect observed in healthy subjects and in patients with acute coronary syndromes as measured by coronary blood flow (Alexopoulos et al 2013, Wittfeldt et al 2013), which could help increase oxygen supply to ischaemic tissues during a VOC.

Results of previous studies support the hypothesis that inhibition of platelet activation and/or decreased formation of platelet-leukocyte aggregates are potential therapeutic options in the treatment of children with SCD. The antiplatelet agent ticlopidine was evaluated in a double-blind, randomised, placebo-controlled study in 140 patients aged 15 to 45 years with HbS (Cabannes et al 1984). Patients were randomised to receive 6 months of study treatment. There were 42 painful crises in the 70 patients on ticlopidine, and 125 crises in the 70 patients on placebo, a significant difference. In addition, the painful crises were significantly shorter (3 days on ticlopidine versus 4 days on placebo) and the crises were less severe on ticlopidine.

Prasugrel, like ticagrelor, is a P2Y12 receptor antagonist which has also been studied in patients with SCD. Both ticagrelor and prasugrel act via the P2Y12 receptor, though their binding characteristics differ. In a Phase II study, 62 adults with SCD were randomised to prasugrel or placebo for 30 days (Wun et al 2013). Biomarkers of in vivo platelet activation (platelet surface P-selectin and plasma soluble P-selectin) were significantly reduced in patients on prasugrel. This study was followed by the Phase III DOVE study which randomised 341 children with SCD to receive prasugrel or placebo for 9 to 24 months (Heeney et al 2016). A numerical reduction in the number of patients with VOCs was seen with prasugrel, although the difference versus placebo was not statistically significant. The separation between prasugrel and placebo appears to occur after the first 12 weeks of treatment (Figure 1). The level of platelet inhibition achieved in the prasugrel group was at the lower end of the intended range (<20%, Jakubowski et al 2017), and therefore the dose may have been too low for clinical benefit to be demonstrated in this study. AstraZeneca is aiming for a substantially higher level of platelet inhibition for the ticagrelor Phase III study (see response to Question 2, Section 2.2).

Figure 1 Mean number of VOCs in the prasugrel DOVE study



Vertical dashed line represents 9 months after randomisation. From Heeney et al 2016.

Upregulation of the adhesion molecule P-selectin on endothelial cells and platelets contributes to the cell–cell interactions involved in the pathogenesis of vaso-occlusion and sickle cell-related pain crises.

The P-selectin inhibitor crizanlizumab has been investigated in a Phase II, randomised, double-blind, placebo-controlled study in adults with SCD. Treatment with crizanlizumab resulted in a significantly lower rate of sickle cell–related pain crises than placebo and was associated with a low incidence of adverse events (Ataga et al 2017), suggesting that a decrease in platelet-leucocyte aggregates would be beneficial in SCD treatment. Ticagrelor has been shown to decrease P-selectin expression (Patil et al 2010) and ticagrelor has been shown to significantly decrease P-selectin expression compared to prasugrel (Bernlochner et al 2015).

In addition to the ticagrelor studies included in the PIP, a Phase II ticagrelor study (D5136C00008) has been conducted in young adults (aged 18 to 30 years) with SCD. This study provided additional data to support the paediatric programme. Study D5136C00008 was a randomised, double-blind, parallel-group, multicentre study in which 87 patients were randomised in a 1:1:1 ratio to receive ticagrelor 10 mg twice daily (bd), ticagrelor 45 mg bd, or placebo bd, as oral doses for 12 weeks. The primary endpoint of proportion of days with pain due to SCD, and the secondary endpoints of intensity of pain, and use of analgesics were collected using an electronic Patient-Reported Outcomes instrument, with patients reporting on a daily basis. There were no effects of ticagrelor 10 mg or 45 mg on the primary endpoint of patient-reported pain or the secondary pain-related endpoints as captured in an eDiary during the 12 week study period. However, effects on platelet activity were demonstrated with mean PRU reductions of ~80% and 50% at peak and trough, respectively, for the highest ticagrelor dose (45 mg bd). Treatment with ticagrelor for 12 weeks in the study was considered to be well tolerated. Events of bleeding in the ticagrelor 45 mg group were of the same number and similar to findings in the placebo and the ticagrelor 10 mg bd groups.

The short treatment period in this study, together with the small number of patients, may have limited the ability of the study to show a treatment difference between ticagrelor and placebo. The duration of the Phase III study treatment period will be longer: at least 12 months, with an expected average follow-up of 18 months.

Conclusion

In conclusion, the ticagrelor mechanism of action and the results of previous studies of antiplatelet agents suggesting a potential to reduce VOCs support the continued investigation of the role of antiplatelet therapies in the reduction of VOCs in paediatric patients with SCD.

Assessment of the MAH's response

The use of ticagrelor in SCD is based on multiple potential modes of action:

- preventing ADP mediated platelet activation and aggregation
- vasodilation
- decreasing platelet-leucocyte aggregates by upregulation of adhesion molecule P-selectin

Relevant clinical evidence is based upon three trials:

- Cabannes 1984: ticlopidine: reduction in crises in adults
- Heeney 2016: Prasugrel: positive trend, starting at 12 weeks.
- Ticagrelor Phase 2: not efficacious, well tolerated

Conclusion

The concept of using ticagrelor in SCD has not been proven yet, but the considerations presented support further development. **Issue resolved.**

5.2. Question 2

Please provide information regarding the dose selection for the planned phase III study, since no dose has been proposed by the MAH based on this study.

MAH's response

AstraZeneca has selected the following ticagrelor doses for the planned Phase III study (D5136C00009), based on 3 body weight categories:

- ≥12 kg to ≤24 kg body weight: 15 mg (1 tablet of ticagrelor 15 mg or 1 tablet of placebo to match ticagrelor 15 mg) bd
- >24 kg to ≤48 kg body weight: 30 mg (2 tablets of ticagrelor 15 mg or 2 tablets of placebo to match ticagrelor 15 mg) bd
- >48 kg body weight: 45 mg (3 tablets of ticagrelor 15 mg or 3 tablets of placebo to match ticagrelor 15 mg) bd.

[For any patient having a weight gain during the study period clearly exceeding the upper limit of the band for the first 2 categories (≥27 kg and ≥54 kg, respectively), the dose should be increased according to the next weight band.]

Analysis of the data from Studies D5136C00007 and D5136C00008 [For a description of Study D5136C00008, see the response to Question 1, Section 2.1.] suggested that these doses would provide similar ticagrelor exposure across the weight bands and achieve a level of platelet inhibition that is believed to be clinically relevant. The targeted level of platelet inhibition is 35% to 80%, based on the assumption that the level of inhibition in the prasugrel study was too low. Since the aim is to treat symptoms, it is judged that a complete platelet inhibition (>80%) could potentially increase the risk of bleeding events and should therefore be avoided. Selection of the 3 weight-based doses was based on PKPD modelling and simulation using data from Studies D5136C00007 and D5136C00008, and was guided by the intent to achieve a higher level of platelet inhibition than reported in the prasugrel DOVE study (Heeney et al 2016), balanced against the potentially increased risk of bleeding associated with a high degree of platelet inhibition.

PKPD modelling and simulation

A population PK model of ticagrelor exposure was developed, which described the observed individual plasma concentrations following single and multiple doses in the range 0.125 mg/kg to 2.25 mg/kg, in children <18 years of age, and pooled with data from the study in young adults, who received ticagrelor 10 mg or 45 mg. The PK model was used to evaluate potentially important relationships between exposure and demographic variables (e.g., age, weight, gender) and then to link individual predicted exposures to the observed platelet inhibition in patients in Studies D5136C00007 and D5136C00008. The model confirmed a relationship between body weight and ticagrelor oral clearance. The relationship between exposure and platelet inhibition (PRU) was described using a direct effect PKPD model that linked individual predicted ticagrelor concentrations to the observed PRU as measured

by the VerifyNow assay. Simulations were performed using the developed population PKPD model to evaluate the overall population variability in ticagrelor exposure and platelet inhibition response associated with the proposed dosing algorithm.

Efficacy, PKPD, and safety considerations

The doses for the Phase III study are predicted to result in >35% platelet inhibition in terms of reduction in PRU from baseline. Assuming a mean PRU of 280 at baseline (as seen in Study D5136C00007, and similar to the baseline PRU of 276 in the prasugrel DOVE study), a PRU reduction ≥ 35% would correspond approximately to an absolute PRU level <180. Given the reversible mechanism of action of ticagrelor, the level of P2Y12 inhibition during ticagrelor treatment is expected to vary within a dosing interval and peak ~2 hours post-dose. The predicted level of platelet inhibition in the Phase III study is similar to that observed in the ticagrelor 45 mg bd group in Study D5136C00008, where after 1 week of treatment the mean decrease from baseline PRU was 48% before the morning dose and 81% at 2 hours post-dose. The 45 mg bd dose was well tolerated (see Question 1).

As described in the response to Question 1, results of previous studies with ticlopidine, prasugrel, and crizanlizumab support the continued evaluation of agents that target the role of platelets in vaso-occlusion. The DOVE study showed an encouraging trend towards efficacy on the primary endpoint, with a numerically lower rate of VOCs in the prasugrel group versus placebo, but insufficient efficacy, with differences between treatment groups not statistically significant. The target platelet inhibition range for the study, defined as absolute PRU values of 136 to 231, was met; however, the mean PRU after 9 months of treatment in the fully titrated dose population was 207i.e.ie, only ~20% reduction from baseline) (Jakubowski et al 2017). The lack of therapeutic benefit with prasugrel may have been related to insufficient platelet inhibition (Heeney et al 2016). Consequently, doses for the ticagrelor Phase III study have been selected to achieve a greater level of platelet inhibition. Moreover, the ticlopidine study in adolescents and adults with SCD showed significant reductions in VOCs (Cabannes et al 1984) at doses that generally provide <60% inhibition of platelet aggregation, providing further support for the platelet inhibition level and selected doses for Phase III.

In addition to aiming for a higher level of platelet inhibition in consideration of efficacy, it is necessary to minimise the risk associated with very high levels of platelet inhibition. Inherent to their reduction in platelet reactivity, antiplatelet agents increase the risk of bleeding. The doses selected for Study D5136C00009 are within the range evaluated in Studies D5136C00007 and D5136C00008, in which there was no indication of an increased bleeding risk with ticagrelor. Furthermore, these doses have been selected to result in a less pronounced level of platelet inhibition (~35% to 80%) than is achieved in adults with cardiovascular disease. The approved ticagrelor doses for adults with coronary artery disease (60 mg bd and 90 mg bd) given in combination with ASA achieve platelet inhibition in the range of 80% to 90% across the dosing interval. Ticagrelor will not be combined with ASA in the paediatric Phase III study. Thus, a lower bleeding risk is anticipated in Study D5136C00009 than seen in adult cardiovascular outcome studies.

The DOVE study in children with SCD investigated doses of prasugrel resulting in ~20% platelet inhibition, with no significant difference in the safety endpoints, including the frequency of bleeding events requiring medical intervention, compared with placebo. Although not in children with SCD, the CLARINET study randomised 906 infants aged ≤92 days with congenital heart disease to clopidogrel or placebo for a median of 5.8 months (Wessel et al 2013) using doses shown to give an average platelet inhibition of 45% to 50% (Li et al 2008, Wessel et al 2013). No increased bleeding risk was observed for clopidogrel or prasugrel compared with placebo in these studies.

Assessment of the MAH's response

The targeted level of platelet inhibition is 35% to 80% and PKPD modelling is used to derive a dose to achieve this target. Both the target range (its usefulness) and the PK-PD modelling introduce uncertainties but the presented justification is acceptable. It is important to take into account that combination with ASA is not intended.

Conclusion

Issue resolved.

5.3. Question 3

The MAH is requested to provide scientific data in order to justify that $P2Y_{12}$ reaction units (PRU) are predictive for platelet aggregation. Additionally, the MAH is requested to justify that the use of PRU as a surrogate for platelet aggregation is also applicable to patients with sickle cell disease.

MAH's response

The interaction between ADP and the P2Y12 receptor is an important mechanism in platelet aggregation. The VerifyNow assay measures platelet aggregation in whole blood, using an optical signal reported as P2Y12 reaction units (PRU). The ONSET/OFFSET study used 3 different validated assays for platelet function testing to assess the antiplatelet effects of ticagrelor: light transmittance aggregometry (LTA), the VerifyNow P2Y12 assay, and the vasodilator-stimulated phosphoprotein (VASP) assay (Figure 2, Gurbel et al 2009).

Results of another study (Kerneis et al 2015), comparing the level of platelet inhibition with ticagrelor and prasugrel using these 3 assays, showed variability across the tests, but there was a correlation between the VerifyNow and VASP assay, and between LTA and VerifyNow.

From these studies, it is concluded that platelet aggregation measured as PRU is a good functional variable on a group level for platelet aggregation. It is acknowledged that the individual variability is high and that other mechanisms are involved in the global platelet function. However, more importantly, there is a correlation between PRU and clinical outcome in patients with coronary artery disease. Both the level of platelet inhibition measured as PRU (Stone et al 2013) and the relative change in PRU (Luo et al 2016) have been shown to be related to outcome in patients with acute coronary syndromes. Platelet aggregation measured as PRU has also been shown to correlate with bleeding events (Mangiacapra et al 2012, Tantry et al 2013).

Figure 2 Platelet function testing using light transmission aggregometry, the VerifyNow™ P2Y12 assay, and the VASP assay

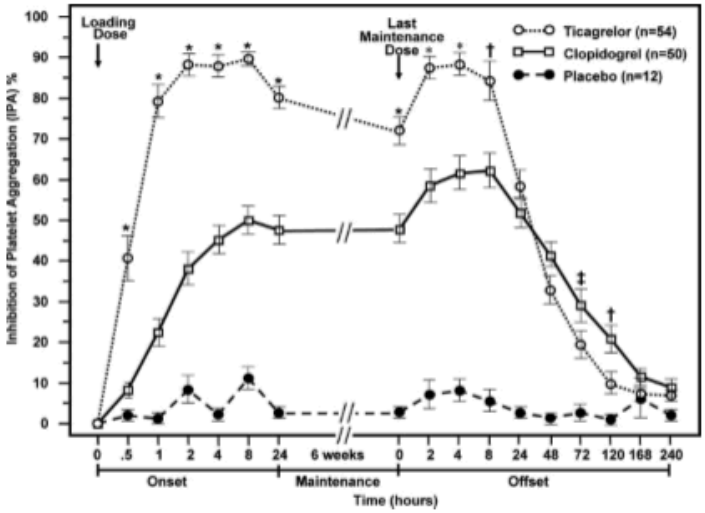


Figure 2. IPA (%; 20 μmol/L ADP, final extent) by protocol time and treatment. Data are expressed as mean±SEM. *$P<0.0001$, †$P<0.005$, ‡$P<0.05$, ticagrelor vs clopidogrel.

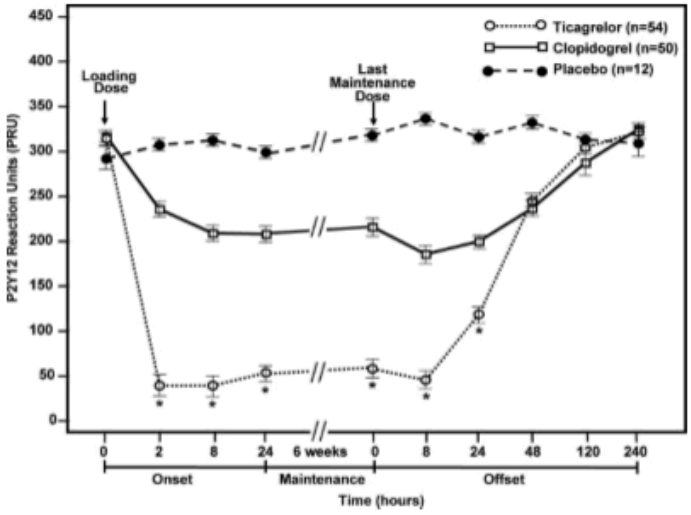


Figure 3. P2Y12 reaction units (PRU) as assessed by the VerifyNow P2Y12 assay by protocol time and treatment. Data are expressed as mean±SEM. *$P<0.0001$, ticagrelor vs clopidogrel.

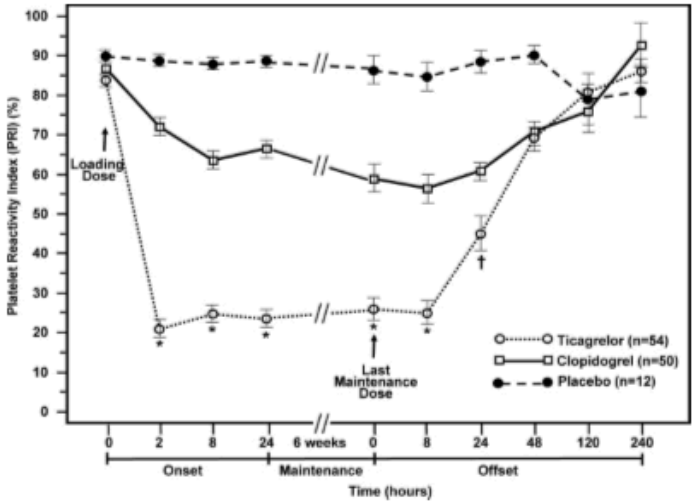


Figure 4. Platelet reactivity index (PRI, %) as assessed by VASP-P by protocol time and treatment. Data are expressed as mean±SEM. *$P<0.0001$, †$P<0.005$, ticagrelor vs clopidogrel.

ADP, Adenosine diphosphate; VASP, Vasodilator-stimulated phosphoprotein assay. From Gurbel et al 2009.

The rationale for the use of antiplatelet therapies in management of SCD is based on the belief that although platelets probably do not initiate VOCs, they play a role in amplifying and maintaining vaso-

occlusion. The spectrum of clinical manifestations in SCD may result in part from recurrent episodes of disseminated microvascular ischaemia-reperfusion injury (Polanowska-Grabowska et al 2010) that triggers vascular inflammation, with platelet monocyte and platelet-neutrophil aggregates as important amplifiers of the process. In theory, antiplatelet therapy could decrease the incidence and severity of VOCs, and has the potential to affect other disease manifestations related to microvascular occlusion.

When comparing PKPD data between different populations, both with regards to SCD and to age, the PRU response was found to be correlated to ticagrelor plasma concentration and PD response. The correlation was in line with that previously seen with ticagrelor in adults with cardiovascular disease. This finding is also consistent with a previous in vitro study (Söderlund et al 2015) in which platelet inhibition was analysed in blood from children and adults spiked with ticagrelor. The study results showed that the in vitro potency of ticagrelor assessed by the VASP test or ADP-induced platelet-rich plasma aggregation was not significantly different in blood from children compared with blood from adults. In addition, the in vitro potency appeared numerically similar across the different age groups studied. The exposure-response and sensitivity to ticagrelor appears similar between adult patients with coronary artery disease and both young adult and paediatric SCD patients. However, there is an observed numerical difference in the IC50 value between the populations with SCD and cardiovascular disease.

A correlation between measurements of platelet aggregation and VOC has not been demonstrated. However, in addition to evaluating the efficacy and safety of ticagrelor in paediatric patients with SCD, Study D5136C00009 will also explore the relationship between platelet inhibition/exposure and efficacy, and between platelet inhibition/exposure and bleeding. In the ticagrelor paediatric SCD studies, measurement of reduction in PRU from baseline will be primarily used as a tool to estimate the effect of ticagrelor in the paediatric population, rather than to predict efficacy relative to VOC.

Assessment of the MAH's response

As a measurement, PRU has been validated to an acceptable level. PRU is related to outcomes in coronary disease and bleedings, but the relation to outcomes in SCD has not been proven. There is an observed numerical difference in the IC50 value between the populations with SCD and cardiovascular disease and in SCD ticagrelor will not be combined with ASA.

Conclusion

Use of PRU to titrate ticagrelor in SCD is associated with much uncertainty.

Issue resolved.

5.4. Question 4

The MAH is requested to justify the cut-off point of PRU < 95 used in the dosing schedule. Additionally, the MAH is requested to discuss how this should be monitored in clinical practice.

MAH's response

Study D5136C00007 was the first study with ticagrelor in patients aged 2 to <18 years. Prior to this, the PKPD relationship had not been explored in this age group or in patients with SCD. Study D5136C00007 was designed to characterise the relationships between ticagrelor dose-exposure and inhibition of platelet aggregation, including the impact of demographic covariates such as age and

weight in paediatric SCD patients. Thus, prior to understanding these relationships, the limit of PRU <95 was chosen to reduce the risk of bleeding, reflecting the caution required in studying a new indication in a different population to the approved adult indication for ticagrelor.

The time course of antiplatelet effect of ticagrelor in adults with coronary artery disease (Gurbel et al 2009) and the relationship between PRU and bleeding risk was previously investigated in an elderly population with ischaemic heart disease (Tantry et al 2013), and in this population a PRU <85 was related to increased risk of bleeding. It is assumed that the bleeding risk is higher in an elderly population with coronary artery disease receiving concomitant ASA, than in young patients with SCD. Although several PRU values <95 were observed during Study D5136C00007, no bleeding events were reported on treatment.

The intent for the Phase III study and future clinical use is that measurement of platelet inhibition will not be needed for dose titration. The Phase III study will establish the safety and efficacy of ticagrelor in paediatric SCD patients without continuous monitoring of platelet inhibition. The bleeding risk in the study will be minimised by excluding patients who may be predisposed to clinically significant bleeding, and through specific discontinuation criteria. The time below an absolute PRU of 85, based on increased risk of bleeding in elderly patients with coronary artery disease (Tantry et al 2013), was considered when selecting the doses, which are predicted to result in ~40% average reduction in PRU at steady state. In ticagrelor-treated adults with cardiovascular disease, the risk for major bleeding appears very low, with ~90% to 100% platelet inhibition through the dosing interval. However, minor bleedings are a common side effect. The bleeding risk in this patient group is balanced by the benefits of reduction in life-threatening cardiovascular events. However, considering the anticipated benefit in paediatric SCD patients is symptom control (reduction of VOC), targeting complete platelet inhibition is not justified.

Assessment of the MAH's response

As discussed in Question 3, the cut-off is used in a context of much uncertainty.

Conclusion

Issue resolved.

5.5. Question 5

The MAH is requested to discuss the risk for major bleeding for patients with PRU < 95.

MAH's response

Bleeding is the most important safety concern for all antiplatelet medications; inherent to their mechanism of action, antiplatelet agents increase the risk of bleeding. Based on previous studies in adults with cardiovascular disease, many of whom were taking dual antiplatelet therapy, there is a risk of bleeding across all degrees of severity, from minimal nuisance bleeding to life-threatening and fatal bleeding that may occur related to surgical or other procedures, as well as during long term out of hospital use. However, data from an adult population in another indication should be interpreted with caution in the context of paediatric SCD. As stated above, the risk of bleeding is still largely unknown in this paediatric SCD population, although based on earlier paediatric studies with antiplatelet agents

(Cabannes et al 1984, Wessel et al 2013, Heeney et al 2016), there were no indications of an increased risk of clinically important bleeding. Ticagrelor at doses of 10 mg bd and 45 mg bd for 12 weeks was well tolerated in young adult patients (18 to 30 years) with SCD in Study D5136C00008, with no increased bleeding risk compared to placebo. The mean platelet inhibition in terms of PRU in that study ranged between ~50% at trough to ~80% at 2 hours post-dose for the 45 mg group. There is no established cut-off for platelet inhibition predicting bleeding risk, although studies in adult patients with ischaemic heart disease being treated with P2Y12 inhibitors in combination with ASA and undergoing coronary artery interventions suggest an increased risk for bleeding events at PRU <85 (Tantry et al 2013). Although these data may be less applicable to children with SCD, in whom ticagrelor will not be administered in combination with ASA, the time and proportion of patients with PRU <85 (corresponding to >70% reduction in PRU) was also taken into account as an extra precaution when selecting doses for the ticagrelor Phase III paediatric study. Based on the limited current knowledge and experience, there are no indications of an increased bleeding risk using ticagrelor in the paediatric SCD population.

Phase III considerations

Considering that the expected benefit in the Phase III study would be symptom reduction, and that patients with SCD suffer from anaemia, the acceptance for bleeding events will be low. It is anticipated that the majority of the Phase III study population will be included within the platelet inhibition range >35% to <80% (corresponding to PRU of ~181 to ~56), although it is acknowledged that some patients may fall outside this range for a limited duration over the dosing interval, owing to fluctuations in exposure and variability in platelet function. In view of the reversible and variable P2Y12 inhibition with ticagrelor, a high degree of platelet inhibition for a limited time is considered acceptable. Simulations suggest that doses higher than those proposed result in a larger proportion of patients attaining <PRU 85 (or well above 70% inhibition) during the majority of the dosing interval. Although the risk for major bleeding appears very low with ~90% to 100% platelet inhibition throughout the dosing interval in ticagrelor-treated patients with cardiovascular disease, minor bleedings are a common side effect. A level of platelet inhibition >80% as targeted in adults with acute coronary syndromes or prior MI (for whom a ticagrelor dose of 90 mg bd or 60 mg bd, respectively, is indicated) would not be appropriate for SCD patients, where the aim of treatment is to control symptoms rather than prevent life-threatening events.

Evaluation of the potential bleeding risk has taken into consideration the published results on previous studies with prasugrel and ticlopidine in patients with SCD and with clopidogrel in a paediatric population, as well as the observations in adult patients with cardiovascular disease during treatment with P2Y12 inhibitors.

Assessment of the MAH's response

Risk of major bleeding is small because ticagrelor is not combined with ASA in SCD. This is independent of the PRU.

Conclusion

Issue resolved.

5.6. Question 6

The MAH is requested to justify why children with body weight < 16 kg were excluded from the study.

MAH's response

The 16 kg body weight cut-off used in Study 12 (D5136C00007) was determined by the blood sampling volumes required by the protocol. Given that the primary endpoint was to evaluate the PK and PD properties of ticagrelor in this patient population to support the Phase III study design, the volume of blood required to be drawn at Visits 2 and 3 coincided with the maximum volume specified by EU guidelines (Ethical considerations paediatric 2008), in which the maximum volume of blood that can be drawn at a single time for the 16 kg cut-off is 1% or 3% over 4 weeks. A 16 kg toddler has 80 mL/kg (1280 mL) of blood, 1% of which is 12.8 mL. Children <16 kg were not eligible for Study 12, since the 1% blood volume limit would have been exceeded.

Assessment of the MAH's response

Small children cannot be adequately assessed in the context of the protocol. This justification is acceptable.

Conclusion

Issue resolved.

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Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Quality

Product Name: Brilique; Active substance: ticagrelor

Study title	Study number	Date of completion	Date of submission of final study report
Development of a granule for oral suspension to support Study 12 (patients aged 2 to 17 years)	Study 1	Completed, date unknown	
Development of an age-appropriate tablet formulation for paediatric patients aged from 2 to 17 years	Study 11	Not started	
Development of an age-appropriate formulation for the 0 to 24 month age group, either granule for oral suspension or paediatric tablet to be dispersed	Study 16	Not started	

Non clinical studies

Product Name: Brilique; Active substance: ticagrelor

Study title	Study number	Date of completion	Date of submission of final study report
Ticagrelor: Dose-range-finding neonatal toxicity study following daily oral (gavage) administration for 19 days in the Han Wister rat	AA93000	June 2010	
Ticagrelor: Neonatal toxicity study following daily oral (gavage) administration for 19 days in the Han Wistar rat followed by an 8-week treatment-free period.	AA93001	October 2010	
Ticagrelor: 5-Week Oral Toxicity Study with Assessment of Recovery in the Weanling Rat	2885LR	March 2011	
Ticagrelor: Respiratory Effects in the Suckling Han Wistar Rat following Single Oral Administration	3233SR	July 2011	

Clinical studies

Product Name: Brilique; Active substance: ticagrelor

Study title	Study number	Date of completion	Date of submission of final study report
Multicenter, open-label, randomised, pharmacokinetic (PK) and pharmacodynamic (PD) dose-ranging Phase II study of ticagrelor followed by a single-blind, randomised, parallel group, placebo-controlled 4 weeks extension phase in paediatric patients with sickle cell disease	Study 12 (D5136C00007)	February 2017	

Open-label, randomised, 4-period, 4-treatment, crossover, single-dose study to assess relative bioavailability of ticagrelor granule for oral suspension and paediatric ticagrelor tablet to commercial ticagrelor tablet in healthy subjects	Study 15 (D5136C00011)	July 2017	
A Randomized, Double-blind, Parallel-group, Multicenter, Phase III study to Evaluate the Effect of Ticagrelor Versus Placebo in Reducing the Rate of VOCs in Paediatric Patients with Sickle Cell Disease	Study 13 (D5136C00009)	Not started	
A Multi-centre, Phase I, Open-label, Single-dose Study to Investigate Pharmacokinetics (PK) of Ticagrelor in Infants and Toddlers, Aged 0 to less than 24 Months, with Sickle Cell Disease (HESTIA4)	Study 14 (D5136C00010)	Not started	