Amsterdam, 30 January 2020
EMA/89357/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Brilique

International non-proprietary name: ticagrelor

Procedure no.: EMEA/H/C/001241/P46/0026

Note

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

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1. Introduction

On September 23, 2019, the MAH submitted a completed paediatric study for Brilique, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study HESTIA4 has been conducted as part of a paediatric program based on an agreed Paediatric Investigational Plan (PIP), (PIP number: EMEA-000480-PIP01-08-M11) which is ongoing 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).

The variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted after March 2021.

A line listing of all the concerned studies is shown in Table 1.

Table 1 Line listing of studies in the development program.

Study number	Study title	Area	Status/Date of completion	Date of submission of final study report
Study 1	Development of a granule for oral suspension to support Study 12 (patients aged 2 to 17 years).	Quality	Completed	NA
Study 11	Development of an age-appropriate tablet formulation for paediatric patients aged from 2 to 17 years.	Quality	Ongoing	NA
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	Ongoing	NA
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	21 October 2014 (submitted with PIP compliance check)
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	21 October 2014 (submitted with PIP compliance check)
2885LR	Ticagrelor: 5-Week Oral Toxicity Study with Assessment of Recovery in the Weanling Rat.	Non-clinical	Completed/March 2011	21 October 2014 (submitted with PIP compliance check)
3233SR	Ticagrelor: Respiratory Effects in the Suckling Han Wistar Rat following Single Oral Administration.	Non-clinical	Completed/July 2011	21 October 2014 (submitted with PIP compliance check)
Study 12 (D5136C00007) (HESTIA 1)	Multicentre, 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.	Clinical	Completed/February 2017 [b]	18 June 2018 (submitted with PIP compliance check)
Study 15 (D5136C00011) (HESTIA BA)	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 [b]	18 June 2018 (submitted with PIP compliance check)
Study 13 (D5136C00009) (HESTIA 3)	A Randomized, Double-blind, Parallel-group, Multicentre, 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	Start Date 15/10-2018 Ongoing Study progressing as planned	NA
Study 14 (D5136C00010) (HESTIA 4)	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.	Clinical	Completed/May 2019 [b]	19 November 2019

a First patient included in study. b Last subject, last visit. NA Not applicable; PD Pharmacodynamics; PK Pharmakokinetics; SCD Sickle cell disease

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in the study was "Granules for oral suspension 10 mg". Treatment consisted of a single oral 0.1 mg/kg dose of ticagrelor for the age group <6 months and a single oral 0.2 mg/kg dose of ticagrelor for the age group ≥6 months. Before administration, ticagrelor granules were constituted with 10 mL of purified water to form a homogenous suspension of 1 mg/mL ticagrelor. Study treatment was provided in glass bottles. Each bottle was labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory guidelines. This formulation is not (yet) authorised.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study 14 - D5136C00010 - HESTIA 4: 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.

2.3.1.1. Regulatory background

According to Article 46 of the Regulation of the European Parliament and of the Council (EC) No. 1901/2006, as amended (Paediatric Regulation, implemented 27 January 2007), the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD[h]) and the European Medicines Agency (EMA) require that for authorised medicinal products, paediatric studies not previously submitted should be submitted to European Health Agencies. The present document constitutes an overview of a paediatric study conducted for ticagrelor, i.e. Study 14, D5136C00010 (a multicentre, 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), which is submitted in accordance with this requirement.

2.3.1.2. Product background

Ticagrelor (BRILIQUE) is an oral, direct-acting, selective, reversibly binding P2Y12 receptor antagonist that prevents adenosine diphosphate (ADP)-mediated platelet activation and aggregation. It does not prevent ADP binding, but when bound to the P2Y12 receptor, ticagrelor prevents ADP-induced signal transduction. Ticagrelor 90 mg twice daily (bd) and co-administered with acetylsalicylic acid, was first approved by the EMA on 3 December 2010 for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS). An extended indication, for ticagrelor 60 mg bd co-administered with acetylsalicylic acid, was approved on 18 February 2016 for the prevention of atherothrombotic events in patients with a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

This Study 14 (D5136C00010) has been conducted as part of a paediatric program based on an agreed Paediatric Investigation Plan (PIP) (PIP number: EMEA-000480-PIP01-08-M11) which is ongoing 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.

2.3.2. Clinical study

2.3.2.1. Results of study D5136C00010

Paediatric patients aged 0 months to <24 months, diagnosed with homozygous SCD (HbSS) or sickle beta-zero-thalassaemia (HbS/β0), as confirmed by high performance liquid chromatography or haemoglobin electrophoresis were enrolled. At least 20 evaluable patients were to be included, with a minimum of 2 evaluable patients aged from birth to <6 months, 3 evaluable patients aged from 6 months to <12 months and a minimum of 5 evaluable patients aged from 12 months to <24 months. All patients who received at least 1 dose of ticagrelor and provided at least 1 post dose analysable plasma sample for PK analysis were included in the PK analysis set. All patients who received at least 1 single dose of ticagrelor, and for whom any post dose data were available, were included in the safety analysis set. The trial enrolled 23 patients and 21 were dosed. Two subjects were aged <6 months, 6 were aged 6 to <12 months and 13 aged 12 to <24 months. The demographic and baseline characteristics of the patients were considered appropriate to achieve the objectives of the study.

No formal sample size calculation was performed. The sample size was selected in agreement with the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) to provide adequate information on the PK properties of ticagrelor in paediatric patients aged 0 months to <24 months with SCD.

Ticagrelor, granules for oral suspension 10 mg, to be taken as a single oral 0.1 mg/kg dose of ticagrelor for the age group <6 months and as a single oral 0.2 mg/kg dose of ticagrelor for the age group ≥6 months. Before administration, ticagrelor granules were constituted with 10 mL of purified water to form a homogenous suspension of 1 mg/mL ticagrelor. In the 19 patients receiving 0.2 mg/kg ticagrelor, the maximum plasma concentration of ticagrelor was generally measured at 1 or 2 hours post dose and the plasma concentrations decreased at the 4- and 6-hours sample timepoints.

The maximum geometric mean plasma concentration of ticagrelor after oral administration of 0.2 mg/kg ticagrelor (21.82 ng/mL) occurred at the 2-hour sample timepoint.

In the 2 patients <6 months old receiving 0.1 mg/kg ticagrelor, there was no 1-hour sample for 1 patient. The maximum plasma concentration of ticagrelor was measured at the first sample timepoint (1 or 2 hours respectively) and plasma concentrations declined at each of the subsequent sample timepoints. At 2 hours post dose ticagrelor plasma concentrations were 17.6 and 28.1 ng/mL. There was no concentration below lower limit of quantification reported (ie, <1.0 ng/mL).

Following administration of 0.2 mg/kg ticagrelor, geometric mean plasma C_{max} and area under the plasma concentration-time curve from zero to 6 hours ($AUC_{0\text{-}6h}$) values were calculated as 34.44 ng/mL and 112.39 ng.h/mL, respectively. Following administration of 0.1 mg/kg ticagrelor, geometric mean plasma C_{max} and $AUC_{0\text{-}6h}$ values were calculated as 23.80 ng/mL and 87.22 ng.h/mL, respectively.

The C_{max} and $AUC_{0\text{-}6h}$ values were similar following administration of 0.2 mg/kg ticagrelor in patients aged 6 months to <12 months and 12 months to <24 months (Cmax: 48.23 ng/mL and 29.48 ng/mL, and $AUC_{0\text{-}6h}$: 141.68 ng.h/mL and 101.00 ng.h/mL, respectively).

In the 19 patients receiving 0.2 mg/kg ticagrelor the plasma concentrations were lower for the active metabolite than for ticagrelor. The maximum plasma concentration of the metabolite was generally measured at the later sample timepoints (4 or 6 hours) compared with the maximum plasma concentration of ticagrelor (1 or 2 hour). The maximum geometric mean plasma concentration of the active metabolite after oral administration of 0.2 mg/kg ticagrelor occurred at the 2-hour (7.4 ng/mL) sample timepoint.

In the 2 patients <6 months old receiving 0.1 mg/kg ticagrelor, there was no 1-hour sample for 1 patient. The maximum plasma concentration of active metabolite occurred at the 2-hour sample for both patients (5.9 ng/mL and 8.1 ng/mL). Following administration of 0.2 mg/kg ticagrelor, geometric mean plasma C_{max} and $AUC_{0\text{-}6h}$ values for the active metabolite were calculated as 9.17 ng/mL and 34.97 ng.h/mL, respectively. Following administration of 0.1 mg/kg ticagrelor, geometric mean plasma C_{max} and $AUC_{0\text{-}6h}$ values were calculated as 6.89 ng/mL and 29.76 ng.h/mL, respectively.

The C_{max} and $AUC_{0\text{-}6h}$ values calculated for active metabolite were similar following administration of 0.2 mg/kg ticagrelor in patients aged 6 months to <12 months and 12 months to <24 months (C_{max}: 11.5 ng/mL and 8.26 ng/mL, and $AUC_{0\text{-}6h}$: 43.66 ng.h/mL and 31.56 ng.h/mL, respectively).

There were 12 adverse events (AEs) reported in 6 (31.6%) patients administered 0.2 mg/kg ticagrelor. Pallor and viral upper respiratory tract infection were each reported in 2 (10.5%) patients; the other AEs reported were: sickle cell anaemia with crisis, splenomegaly, nasal congestion, rash, fall and injury. One serious adverse event (SAE) of bronchiolitis of moderate intensity in association with a viral infection 7 days after dosing was reported. There were no AEs reported in the 2 patients aged <6 months administered 0.1 mg/kg ticagrelor. None of the AEs or the SAE reported in the study were considered by the Investigator to be related to treatment or of severe intensity. There were no clinically relevant changes from baseline to follow-up for the haematology or serum chemistry evaluations including evaluation of the liver chemistry. There were no clinically relevant treatment-related changes in vital sign measurements.

The palatability of the formulation was generally acceptable to the patients. Overall, ticagrelor was well-tolerated by the patients with SCD aged <24 months in this study and no safety concerns were raised.

2.3.2.2. MAH's overall conclusions

In study D5136C00010, 21 patients with SCD aged <24 months received a single oral dose of ticagrelor (0.1 mg/kg ticagrelor in patients aged <6 months and 0.2 mg/kg ticagrelor in patients aged 6 months to <24 months) and all 21 patients had measurable plasma concentrations of ticagrelor. Exposure (C_{max} and $AUC_{0\text{-}6h}$) was similar across all age groups (<6 months, 6 months to <12 months and 12 months to <24 months). The palatability of the formulation was generally acceptable to the patients. Ticagrelor was well-tolerated by the patients with SCD aged <24 months in this study and no safety concerns were raised.

2.3.2.3. MAH's opinion on impact on marketing authorisation and conclusion

The PK results from the submitted study D5136C00010 are in accordance with the previous studies in adults and in children aged 2-18 years. No new safety concerns were raised. The submitted paediatric study does not influence the benefit risk for ticagrelor. Accordingly, it is the MAH's opinion that no amendment to the SmPC is warranted.

2.3.3. Discussion on clinical aspects

2.3.3.1. Summary of the data

The data can be summarised in tables as shown below:

Table 2 Demographics

Age group	Target	Enrolled	Dosed	Dose
0-<24 months	>= 20	23	21	
0-<6 months	>= 2		2	0.1 mg/kg
6-<12 months	>= 3		6	0.2 mg/kg
12-<24 months	>= 5		13	0.2 mg/kg

Table 3 PK Summary

			ticagrelor				active metabolite			
time after dose		h	1	2	4	6	1	2	4	6
Tica 0.1 mg	< 6 mo	min		17.6	9.6	6.7		5.9	4.4	3.6
		max		28.1	16.5	12.2		8.1	7.5	6.3
Tica 0.2 mg	all	geometric mean	18.51	21.82	16.54	10.39	4.65	7.40	7.33	5.89
	6 < 12	geometric mean	13.14	26.03	22.78	14.30	3.57	8.82	9.87	8.30
	12<24	geometric mean	21.68	20.12	14.27	9.19	5.25	6.82	6.38	5.16

Table 4 PK Results

		ticagrelor		active metabolite	
geometric mean		AUC0-6 ng h/mL	C max ng/mL	AUC0-6 ng h/mL	C max ng/mL
Tica 0.1 mg	< 6 mo	87.22	23.80	29.76	6.89
Tica 0.2 mg	all	112.39	34.44	34.97	9.17
	6 < 12	141.68	48.23	43.66	11.50
	12<24	101.00	29.48	31.56	8.26

2.3.3.2. Current paediatric labelling

There are 3 formulations of Brilique currently authorised:

- Brilique 60 mg film-coated tablets
- Brilique 90 mg film-coated tablets
- Brilique 90 mg orodispersible tablets

The granules for oral suspension 10 mg used in the study, are not authorised (yet).

The paediatric information in all formulations is the same:

Section 4.2

The safety and efficacy of ticagrelor in children below the age of 18 years have not been established. No data are available.

Section 5.1

The European Medicines Agency has waived the obligation to submit the results of studies with Brilique in all subsets of the paediatric population in acute coronary syndromes (ACS) and history of myocardial infarction (MI) (see section 4.2 for information on paediatric use).

Section 5.2

Ticagrelor has not been evaluated in a paediatric population (see sections 4.2 and 5.1).

2.3.3.3. Discussion

The study has been completed in line with the agreed PIP. The PK results from the submitted study D5136C00010 are in accordance with the previous studies in adults and in children aged 2-18 years. No new safety concerns were raised. The submitted paediatric study does not influence the benefit risk for ticagrelor in the approved indication.

The current SmPC is not completely accurate, as some PK information is now available. However, the extrapolation of information on the granules to the tablets is questionable. Also, the currently approved indications for ticagrelor are not relevant in the paediatric population and the information on the PIP indication of Sickle Cell Disease does not yet warrant discussion in the SmPC as it is incomplete. Therefore, the MAH proposal not to update the SmPC is agreed.

3. Rapporteur's overall conclusion and recommendation

The study has been completed in line with the agreed PIP. No amendment to the SmPC is warranted. The variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted after March 2021.

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled:

N/A