Clinical Pharmacology Memorandum

NDA number	022433
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Receipt date	11/19/2021
Submission type	Efficacy supplement
Supplement number	34
Brand name	BRILINTA®
Generic name	ticagrelor
Dosage form, route of administration	Oral tablets, granules for suspension
Studied indication	Reduction of vaso-occlusive crises in pediatric patients with sickle cell disease
Applicant	Astra Zeneca
OCP Review Team	Snehal Samant MS, PhD, Jihye Ahn PharmD, Liang Li PhD, Sudharshan Hariharan PhD
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology
OND Division	Division of Non-malignant Hematology

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1. EXECUTIVE SUMMARY

BRILINTA® (ticagrelor) is an oral, direct-acting, selective, and reversibly binding P2Y12 receptor antagonist that prevents adenosine diphosphate-mediated platelet activation and aggregation. Ticagrelor is approved by the FDA for the reduction in the rate of thrombotic cardiovascular events in adult patients with acute coronary syndrome and history of myocardial infarction or coronary artery disease. Ticagrelor is also indicated to reduce the risk of stroke in patients with acute ischemic stroke or high risk transient ischemic attack. The Applicant has submitted this supplemental New Drug Application (sNDA) for BRILINTA to comply with the issued Written Request for studies of ticagrelor in pediatric patients with sickle cell disease (SCD).

This sNDA contains the results for Study D5136C00010 (HESTIA4) and Study D5136C00009 (HESTIA3), as specified in the Written Request Amendment 1 (August 12, 2021). HESTIA4 is a Phase I study which investigated the pharmacokinetic properties of ticagrelor in pediatric patients of age 0 to less than 24 months with sickle cell disease. HESTIA3 is a Phase III study which evaluated the effect of ticagrelor versus placebo in reducing the rate of vaso-occlusive crises (VOCs) in pediatric patients with sickle cell disease. The unfavorable benefit-risk profile (including imbalance in deaths and failure to demonstrate an effect on the primary endpoint) of ticagrelor in pediatric patients (aged ≥2 years to <18 years) with sickle cell disease in HESTIA3 resulted in the termination of this study. This study was modified in the amended Written Request to account for the early termination. The Applicant has proposed an update to the current approved BRILINTA prescribing information Section 8.6 to reflect the negative outcome of HESTIA3 and to avoid potential off-label use.

The Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology (OCP/ DCEP) has reviewed the clinical pharmacology information contained in NDA 022433/ Supplement 34 and finds it acceptable. This memo summarizes the PK-PD results of ticagrelor assessed in studies HESTIA3 and HESTIA4 in pediatric patients with sickle cell disease. No clinical pharmacology related changes are required to the BRILINTA label based on the results of these studies.

2. PK-PD OF TICAGRELOR IN PEDIATRIC PATIENTS WITH SICKLE CELL DISEASE.

2.1 PK of ticagrelor and its active metabolite in pediatric patients with sickle cell disease of age 3 months to < 2 years (HESTIA4)

HESTIA4 (Study D5136C00010) is a multicenter, multinational, single dose, open label, PK study in which 21 pediatric patients with SCD aged <24 months (range: 3 months to 21 months) and body weight ≥ 5 kg at screening. Patients aged below 6 months received ticagrelor 0.1 mg/kg, and patients aged above 6 months received 0.2 mg/kg single oral dose of ticagrelor administered as granules for suspension. Samples for PK assessment were taken at 1-, 2-, 4-, and 6-hours post-dose from each patient. At least 20 evaluable patients (including ≥ 2 evaluable patients aged from birth to < 6 months, 3 evaluable patients aged from 6 months to < 12 months,

and ≥ 5 evaluable patients aged from 12 to < 24 months) were required. In total, 21 patients with SCD (2 patients aged from birth to < 6 months, 6 patients aged 6 to < 12 months, and 13 patients aged 12 to < 24 months) received a single oral dose of ticagrelor (0.1 mg/kg in patients aged < 6 months, and 0.2 mg/kg in patients aged 6 months to < 24 months). Before administration, ticagrelor granules were constituted with 10 mL of purified water to form a homogenous suspension of 1 mg/mL ticagrelor. All patients had measurable plasma concentrations of ticagrelor. The PK properties of ticagrelor following a single oral dose were assessed as the primary endpoint, including observed plasma concentrations, $AUC_{0\text{-}6h}$ and C_{max}. The PK properties of the active metabolite of ticagrelor (ARC124910XX) following a single oral dose were assessed as a secondary endpoint, including observed plasma concentrations, $AUC_{0\text{-}6h}$, and C_{max}.

Table 1. Summary of ticagrelor plasma pharmacokinetic parameters following a single oral dose in pediatric patients with SCD and < 2 years of age (HESTIA4) (Pharmacokinetic Analysis Set)

Dose level	Summary statistic	Ticagrelor		ARC124910XX	
		$AUC_{0\text{-}6h}$ (ng.h/mL)	Cmax (ng/mL)	$AUC_{0\text{-}6h}$ (ng.h/mL)	Cmax (ng/mL)
Ticagrelor 0.1 mg/kg, < 6 months of age (N = 2)	Geometric mean	87.22	23.80	29.76	6.89
	CV (%)	32.72	23.78	22.84	22.55
Ticagrelor 0.2 mg/kg, ≥ 6 months of age (N = 19)	Geometric mean	112.39	34.44	34.97	9.17
	CV (%)	52.21	74.75	58.67	61.25

Patients received a single dose of ticagrelor on Day 1. $AUC_{0\text{-}6h}$, area under the plasma concentration-time curve from zero to 6 hours; CV, coefficient of variation; N, number of patients in treatment and age combination group. Source: Derived from HESTIA4 CSR, Table 11.2.2.1.

The maximum geometric mean plasma concentration of ticagrelor after oral administration of 0.2 mg/kg ticagrelor occurred at 2-hours post-dose. 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. Geometric mean C_{max} and $AUC_{0\text{-}6h}$ values for ticagrelor were 1.6-fold and 1.4-fold higher, respectively, following administration of ticagrelor 0.2 mg/kg in patients aged 6 months to < 12 months compared to 12 months to < 24 months (C_{max}: 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).

Following administration of the 0.2 mg/kg dose in patients ≥ 6 months of age, geometric mean plasma C_{max} and $AUC_{0\text{-}6h}$ were 1.4-fold and 1.3-fold higher, respectively, compared to patients < 6 months of age who were administered 0.1 mg/kg dose. Geometric mean C_{max} and $AUC_{0\text{-}6h}$ values for the active metabolite were 1.4-fold higher following administration of ticagrelor 0.2 mg/kg in patients aged 6 months to < 12 months compared to 12 months to < 24 months (C_{max}:

11.5 ng/mL and 8.26 ng/mL, and $AUC_{0\text{-}6h}$: and 43.66 ng.h/mL and 31.56 ng.h/mL, respectively). Population PK analysis of ticagrelor and AR-C124910XX was performed using plasma concentration and time data from pediatric patients with SCD, based on pooled data from HESTIA1 and HESTIA4. Ticagrelor oral clearance (CL/F) was estimated at 23.3 L/h for a patient with a 35 kg body weight (the median body weight of the HESTIA1 and HESTIA4 population). CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. When accounting for both age (CYP3A4 maturation) and body weight (allometric scaling), the ticagrelor CL/F for a patient aged 2 months at a weight of 5 kg was predicted at 1.1 L/h. For patients aged 6 and 12 months, at weights 7.5 and 10 kg respectively, the predicted clearance was 3.2 L/h and 6.6 L/h, respectively.

2.2 PK-PD of ticagrelor and its active metabolite in pediatric patients with sickle cell disease of age 2 to < 18 years of age (HESTIA3)

HESTIA3 is a multinational, randomized (1:1), double-blind, double-dummy, parallel-group, placebo-controlled efficacy, and safety study to evaluate the effect of ticagrelor versus placebo in reducing the rate of VOCs in pediatric patients with SCD (193 pediatric patients) aged ≥ 2 to < 18 years and body weight ≥ 12 kg. The study was designed to demonstrate superiority of ticagrelor compared with placebo. Patients were to be followed until a common study end date, defined as 12 months after last patient randomized, or up to 24 months. In total, 451 VOC events were collected. The observed yearly rate of VOCs was 2.74 in the ticagrelor group and 2.60 in the placebo group. The study did not meet its primary objective. Ticagrelor was not superior to placebo in reducing the rate of VOCs: the incidence rate ratio was 1.06 (95% CI: 0.75, 1.50), p = 0.7597. The results of the primary efficacy analysis were consistent across the pre-defined subgroups (based on age, number of VOCs within the previous 12 months, baseline hydroxyurea use, sickle cell genotype, geographic region, gender, and race). The study included exploratory objectives to assess the PK of ticagrelor and its active metabolite using a population PK model, and to assess the effect of ticagrelor on platelet aggregation. Pharmacokinetic samples were to be collected at 0 hours (pre-dose) and 2 hours post-dose at specified visits. Collection of PK and PD samples was time matched. Assessment of platelet inhibition was based on the Platelet Reactivity Index (PRI) change from baseline measured using the VASP test. The study drug dose was body weight dependent:

≥ 12 to ≤ 24 kg: ticagrelor 15 mg or matching placebo, bid
> 24 to ≤ 48 kg: ticagrelor 30 mg or matching placebo, bid
> 48 kg: ticagrelor 45 mg or matching placebo, bid

Overall, 69 patients (35.8%) were in the weight group ≥ 12 to ≤ 24 kg, 101 (52.3%) were in the weight group > 24 to ≤ 48 kg, and 23 (11.9%) were in the group > 48 kg at baseline. For any patient having a weight gain during the study period clearly exceeding the upper weight limit of the band (≥ 27 kg and ≥ 54 kg, respectively), the dose was to be increased according to the next weight band.

The ticagrelor doses for HESTIA3 were selected using PKPD modelling targeting similar exposure across the 3 weight bands. The aim of the PKPD modelling and simulation was based on pooled data from the HESTIA1 and HESTIA2 studies. HESTIA1 (D5136C00007) is a multicenter, open-label, randomized, PK-PD dose-ranging phase II study of ticagrelor followed

by a double-blind, randomized, parallel-group, placebo-controlled 4 weeks extension phase in pediatric patients with sickle cell disease. HESTIA2 (D5136C00008) is a randomized, double-blind, double-dummy, parallel-group, multicenter, phase iib study to evaluate the effect of ticagrelor 10 mg and 45 mg BID versus placebo in reducing the number of days with pain in young adults with sickle cell disease. These doses were predicted to result in a platelet activity measured as P2Y12 reaction units ([PRU] as measured by VerifyNow®) of less than 180, corresponding to > 35% platelet inhibition in terms of reduction in PRU assuming a baseline PRU of 280 (which was based on the baseline PRU observed in HESTIA1 of 279, and similar to prasugrel Phase III DOVE study, but not associated with too high platelet inhibition (< 85 in absolute PRU), for an extended time period (> 6 hours) within a dosing interval. A body weight adjusted dosing algorithm of 15, 30, and 45 mg BID for children with body weight ≥ 12 to ≤ 24 kg, > 24 to ≤ 48 kg, and > 48 kg was proposed and used in HESTIA3.

Overall, ticagrelor plasma concentration reached the predicted level (Figure 1), and platelet inhibition in the ticagrelor group was majorly within the predicted range of 35% to 80% inhibition at the specified time points compared with baseline, except for Week 4 pre-dose, where the median platelet inhibition relative to baseline was ~25%. Plasma concentrations of ticagrelor pre-dose and 2 hours post-dose at steady state in the HESTIA3 study are summarized in Table 2. Overall, the geometric mean observed pre-dose plasma concentrations of ticagrelor were 38.5, 30.9, and 10.4 ng/mL at Week 4, Month 6, and Month 12, respectively. Geometric mean plasma concentrations of ticagrelor at 2 hours post-dose were 101, 127.4, 116.4, and 58.6 ng/mL at Day 0, Week 4, Month 6, and Month 12, respectively. The reason for the considerably lower pre- and post-dose plasma concentrations of ticagrelor at Month 12 compared to other sampling weeks is not clear. However, the number of patients with reported plasma concentrations was much lower at Month 12 (n = 15) compared to > 80 patients at Week 4 and Month 6. This lower number at Month 12 was attributed to the early study termination.

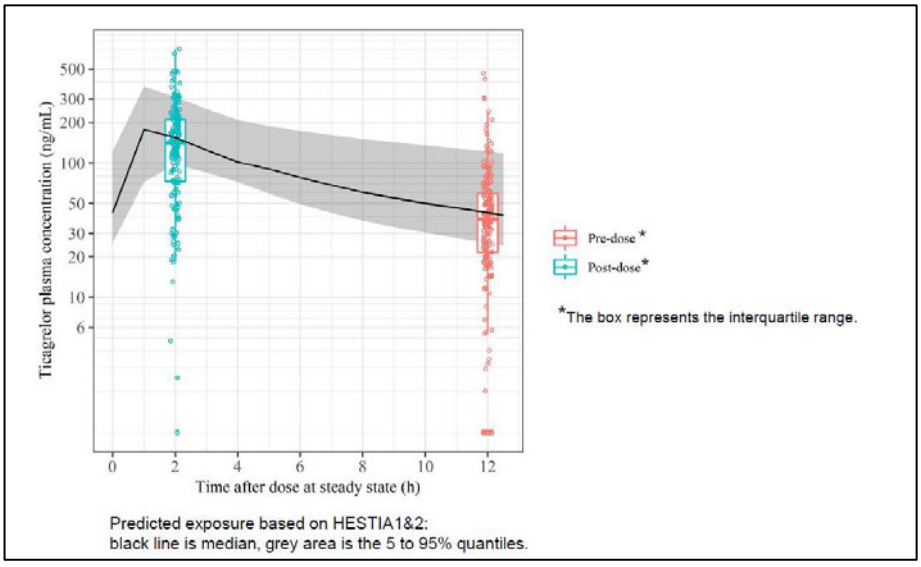

Figure 1. Observed steady state plasma concentration of ticagrelor in study HESTIA3 overlaying the population PK model predicted steady state concentration of ticagrelor.

Source: NDA022433 Type C meeting minutes (DARRTS 3/25/21)

Table 2. Summary of steady state plasma concentrations (ng/ml) of ticagrelor in pediatric patients with SCD and age ≥ 2 to < 18 years (HESTIA3) (Pharmacokinetic Analysis Set)

	HESTIA3			
	Ticagrelor 15/30/45 mg bid (N = 98)	**Ticagrelor 15 mg bid (N = 40)**	**Ticagrelor 30 mg bid (N = 41)**	**Ticagrelor 45 mg bid (N = 17)**
Study population	**Pediatric patients with SCD aged ≥ 2 to < 18 years**			
Weight band for dosing in HESTIA3		**≥ 12 to ≤ 24 kg**	**> 24 to ≤ 48 kg**	**> 48 kg**
Pre-dose at steady state [a]:				
n	83	35	34	14
Geometric mean	30.93	36.08	27.15	28.86
Geometric CV (%)	179.58	81.04	286.63	255.36
Arithmetic mean	51.30	43.03	51.96	70.37
SD	60.27	22.27	48.28	122.95
Median (min, max)	40.48 (1.00, 465.39)	42.27 (2.02, 101.87)	36.43 (1.00, 209.10)	27.29 (1.00, 465.39)
2 hours post-dose at steady state [a]:				
n	84	35	35	14
Geometric mean	116.38	105.21	119.44	140.35
Geometric CV (%)	104.41	82.32	119.82	126.77
Arithmetic mean	153.37	133.12	156.05	197.27
SD	107.35	95.63	92.57	155.09
Median (min, max)	140.69 (2.53, 649.57)	114.70 (19.02, 480.47	139.57 (2.53, 404.57)	178.66 (20.46, 649.57)

[a] Steady state refers to Month 6 in HESTIA3 (6 months after start of dosing). BID: twice daily; CSR, clinical study report; CV, coefficient of variance; max, maximum; min, minimum; N, number of patients in each treatment group; n, number of patients included in analysis; SD, standard deviation. Source: Table 3 in Clinical Pharmacology Summary (Derived from HESTIA2 CSR, Table 11.2.9.1 and HESTIA3 CSR Table 14.2.3.1.)

Assessment of platelet inhibition in HESTIA3 was based on the PRI (Platelet Reactivity Index) change from baseline. PRI (%) over time and PRI change from baseline for all ticagrelor dose levels combined is summarized in Table 3 and Table 4, respectively. At baseline the median PRI value was 84.8%. Two hours after the first dose of ticagrelor the median platelet inhibition was 43.9% compared to baseline. At Week 4, the median platelet inhibition was 25.1% at pre-dose and 54.1% at 2 hours post-dose compared to baseline. At Month 6, the pre- and post-dose median platelet inhibition was 34.9% and 55.7%, respectively compared to baseline.

Table 3. PRI (%) over time (PD Analysis Set, N = 68)

Visit	Time point	Result			
		n	aMean	SD	Median
Baseline	Pre-dose	68	76.6	23.2	84.8
Day 0	2 hours post-dose	67	47.0	27.7	41.1
Week 4	Pre-dose	50	53.7	28.1	56.3
	2 hours post-dose	50	43.6	24.7	40.0
Month 6	Pre-dose	45	48.9	23.5	47.2
	2 hours post-dose	45	34.1	22.1	29.2

PRI (%): Measured by VASP assay. VASP planned sampling: Collected while patient is on study treatment administration. Timepoints of collection: Pre-dose and 2 hours post-dose at specified visits or at time of change in dose level due to weight gain. aMean, Arithmetic mean; BID, Twice daily; N, Total number of patients in treatment group; n Number of patients included in analysis; PD, Pharmacodynamics; PRI, Platelet Reactivity Index; SD, Standard deviation; VASP, Vasodilator-stimulated phosphoprotein (assay).

Source: derived from HESTIA3 CSR Table 26

Table 4. Change from baseline in platelet inhibition (%PRI) following ticagrelor 15/30/45 mg BID dosing in HESTIA3 (Pharmacodynamic Analysis Set, N = 68)

Visit	Time point	Change from baseline				Platelet inhibition relative to the observed baseline median (%) [a]
		n	aMean	SD	Median	
Day 0	2 hours post-dose	67	-30.8	31.5	-37.2	43.9
Week 4	Pre-dose	50	-22.0	31.5	-21.3	25.1
	2 hours post-dose	50	-31.0	36.5	-45.9	54.1
Month 6	Pre-dose	45	-28.7	25.0	-29.6	34.9
	2 hours post-dose	45	-41.4	29.6	-47.2	55.7

[a] Manually derived as: median change from baseline (%) / median PRI (%) at baseline * 100, where median PRI (%) at baseline is 84.8. aMean, Arithmetic mean; BID, Twice daily; N, Total number of patients in treatment group; n, Number of patients included in analysis; PD, Pharmacodynamics; PRI, Platelet Reactivity Index; SD, Standard deviation; Source HESTIA3 CSR Table 27.

Overall, the achieved median platelet inhibition compared with baseline in HESTIA3 agreed with that predicted based on previous studies (HESTIA1 and HESTIA2) (Figure 2). Exposure-response analysis for PRI (%) and PRI inhibition from baseline shows a similar relationship for platelet inhibition (Figure 3).

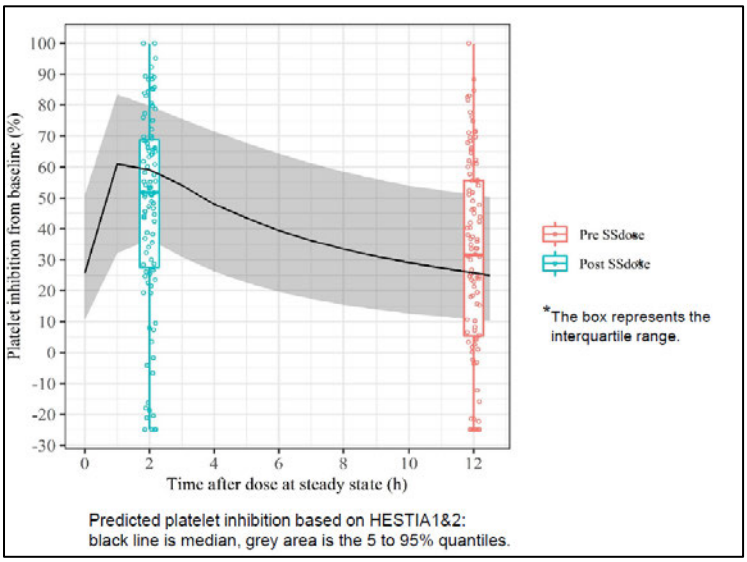

Figure 2. Observed PRI (%) change from baseline overlaying the model prediction for HESTIA3

Source: NDA022433 Type C meeting minutes (DARRTS 3/25/21)

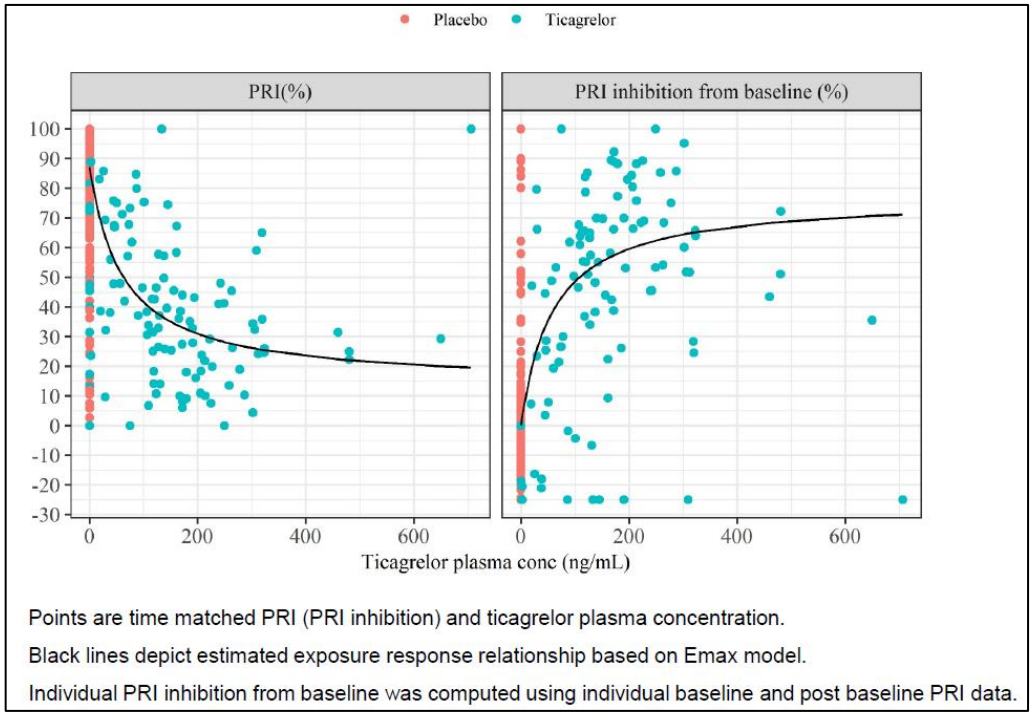

Figure 3. Observed PRI (%) (left panel) and PRI (%) change from baseline versus plasma concentration of ticagrelor (HESTIA3)

Source: NDA022433 Type C meeting minutes (DARRTS 3/25/21)

2.3 Relative bioavailability data in adults to support the pediatric formulation (HESTIA BA)

Pediatric table of 15 mg strength to be swallowed as whole or dispersed in water was administered in the Phase 3 study. Most patients took the formulation as a whole tablet. The absolute bioavailability of ticagrelor from the commercial 90 mg tablet is 36%. The applicant conducted an open-label, randomized, 4-period, 4-treatment, cross-over, single-center, single-dose study (HESTIA BA , D5136C00011) to assess the relative bioavailability of ticagrelor when administered as granule for oral suspension, pediatric ticagrelor tablet, pediatric ticagrelor tablet suspended in water and commercial ticagrelor tablet in healthy adult subjects.

Subjects were randomly assigned to 1 of 4 treatment sequences and received 4 different formulations of ticagrelor under fasted conditions. There was a minimum 7-day washout period between each dose administration. Study treatments were as follows:

- Treatment A: Ticagrelor granule for oral suspension (suspension equal to 90 mg ticagrelor [2 × 45 mg]).
- Treatment B: Ticagrelor pediatric tablets (6 × 15 mg tablets).
- Treatment C: Ticagrelor pediatric tablets suspended in water (suspension equal to 90 mg ticagrelor [6 × 15 mg]).
- Treatment D: Ticagrelor commercial tablet (1 × 90 mg tablet).

The AUC and C_{max} were similar following administration of the granule for oral suspension and the pediatric tablets taken whole compared to the ticagrelor commercial tablet, with geometric mean ratios (90% CI) of 106% (102.11, 109.97) and 101% (96.90, 104.42) respectively for AUC, and 105% (98.35, 113.04) and 99% (92.44, 106.39) respectively, for C_{max}. Similar results were observed for AR-C124910XX. Ticagrelor pediatric tablets administered whole were bioequivalent to ticagrelor pediatric tablets suspended in water, with geometric mean ratios of 104% and 109% for AUC and C_{max} respectively, and 90% CIs contained within the bioequivalence limit of 80% to 125%: 90% CI: 100.06, 107.83 for AUC, and 90% CI: 101.28, 116.53 for C_{max}. Similarly, relative bioavailability of the active metabolite AR-C124910XX pediatric tablets compared to the pediatric tablets suspended in water was 105% (98.19, 112.51) for C_{max} and 101% (97.41, 104.94) for AUC. Ticagrelor was rapidly absorbed with median t_{max} occurring between 2.0 to 2.5 hours post-dose (individuals ranging from 1 to 4 hours) and rapid formation of the metabolite AR-C124910XX was detected with median t_{max} of 2.5 to 3.0 hours post-dose (individuals ranging from 1.5 to 6.0 hours).

Table 5. Statistical comparison of key pharmacokinetic parameters of ticagrelor (PK Analysis Set)

Pair (Test/Reference)	Parameter (unit)	Geometric LS Mean$^{\Psi}$ (n)			Pairwise Comparison§	
		Test	Reference		Ratio#	90%CI#
A / D	C_{max} (ng/mL)	577.6 (43)	547.8 (42)		105.44	(98.35, 113.04)
	AUC (h*ng/mL)	3656 (43)	3450 (42)		105.97	(102.11, 109.97)
B / D	C_{max} (ng/mL)	543.2 (41)	547.8 (42)		99.17	(92.44, 106.39)
	AUC (h*ng/mL)	3471 (41)	3450 (42)		100.59	(96.90, 104.42)
B / A	C_{max} (ng/mL)	543.2 (41)	577.6 (43)		94.05	(87.68, 100.89)
	AUC (h*ng/mL)	3471 (41)	3656 (43)		94.93	(91.45, 98.54)
C / A	C_{max} (ng/mL)	500.0 (43)	577.6 (43)		86.57	(80.76, 92.80)
	AUC (h*ng/mL)	3341 (43)	3656 (43)		91.39	(88.07, 94.84)
B / C	C_{max} (ng/mL)	543.2 (41)	500.0 (43)		108.64	(101.28, 116.53)
	AUC (h*ng/mL)	3471 (41)	3341 (43)		103.87	(100.06, 107.83)

CI = confidence interval; LS = least-squares; n = number of subjects included in the statistical comparison analysis. A = Ticagrelor granule for oral suspension (a total of 90 mg) administered as a single oral dose. B = Ticagrelor pediatric tablets (a total of 90 mg) administered as a single oral dose. C = Ticagrelor pediatric tablets suspended in water (a total of 90 mg) administered as a single oral dose. D = Ticagrelor commercial ticagrelor tablet (1 x 90 mg) tablet administered as a single oral dose. $^{\Psi}$Based on pairwise balanced comparisons and were back-transformed. #Geometric mean ratio and 90% CI were back-transformed and presented as percentage. §Result based on ANOVA of log-transformed PK parameter with sequence, period and treatment as fixed effects and subject within sequence as a random effect.

Source: D5136C00011 CSR, Table 11-3

Plasma concentration-time profiles for ticagrelor and AR-C124910XX were similar across all treatments showing rapid absorption of ticagrelor (median time to reach t_{max}] ranged from 2.0-2.5 hours) and rapid formation of its metabolite AR-C124910XX (median t_{max} ranged from 2.5-3.0 hours) with a steady decline in plasma concentrations after reaching C_{max} (mean terminal elimination half-life [$t1/2\lambda z$] for ticagrelor ranged from 8.2-8.3 hours), similar metabolite to parent AUC and C_{max} ratios (geometric means of 46-49% for AUC and 32-35% for C_{max}) and moderate between-subject variability for ticagrelor (geometric CV% for AUC and C_{max} ranged from 26-38%). No specific food effect study has been performed for the ticagrelor pediatric tablet. In the Phase 3 study, ticagrelor pediatric tablets were administered without regards to food. The ticagrelor adult commercial tablet does not show any clinically relevant effect of food.

Table 6. Statistical comparison of key pharmacokinetic parameters of active metabolite AR-C124910XX (PK Analysis Set)

Pair (Test/Reference)	Parameter (unit)	Geometric LS Mean* (n)			Pairwise Comparison§	
		Test	Reference		Ratio#	90%CI#
A / D	C_{max} (ng/mL)	178.3 (43)	173.8 (42)		102.57	(95.87, 109.74)
	AUC (h*ng/mL)	1611 (43)	1550 (42)		103.96	(100.19, 107.87)
B / D	C_{max} (ng/mL)	158.0 (41)	173.8 (42)		90.91	(84.92, 97.33)
	AUC (h*ng/mL)	1470 (41)	1550 (42)		94.85	(91.38, 98.44)
B / A	C_{max} (ng/mL)	158.0 (41)	178.3 (43)		88.63	(82.80, 94.87)
	AUC (h*ng/mL)	1470 (41)	1611 (43)		91.23	(87.90, 94.69)
C / A	C_{max} (ng/mL)	150.4 (43)	178.3 (43)		84.32	(78.83, 90.20)
	AUC (h*ng/mL)	1454 (43)	1611 (43)		90.24	(86.97, 93.63)
B / C	C_{max} (ng/mL)	158.0 (41)	150.4 (43)		105.11	(98.19, 112.51)
	AUC (h*ng/mL)	1470 (41)	1454 (43)		101.11	(97.41, 104.94)

CI = confidence interval; LS = least-squares; n = number of subjects included in the statistical comparison analysis. A = Ticagrelor granule for oral suspension (a total of 90 mg) administered as a single oral dose. B = Ticagrelor pediatric tablets (a total of 90 mg) administered as a single oral dose. C = Ticagrelor pediatric tablets suspended in water (a total of 90 mg) administered as a single oral dose. D = Ticagrelor commercial ticagrelor tablet (1 x 90 mg) tablet administered as a single oral dose. *Based on pairwise balanced comparisons and were back-transformed. #Geometric mean ratio and 90% CI were back-transformed and presented as percentage. §Result based on ANOVA of log-transformed PK parameter with sequence, period and treatment as fixed effects and subject within sequence as a random effect.

Source: D5136C00011 CSR, Table 11-4

3. LABELING RECOMMENDATION

None

4. APPENDIX

4.1 Summary of Bioanalytical Method Validation and Performance

Determination of ticagrelor and AR-C124910XX in human plasma by HPLC with MS/MS detection for study D5136C00009

The bioanalytical method validation and performance is acceptable.

Analytes	Ticagrelor and AR-C124910XX
Analytical matrix	Lithium Heparin Plasma
Internal standards (ISTD)	[d-7]AZD6140
Validated range	Ticagrelor: 1.00 (LLOQ) to 2000 (ULOQ) ng/mL (1.00, 2.00, 1.00, 50.00, 1250, 1700, 2000 ng/mL) AR-C124910XX: 2.50 (LLOQ) to 1000 (ULOQ) ng/mL
Quality Control (QC) levels	Ticagrelor: 3.00 ng/mL, 60.0 ng/mL, and 1600 ng/mL AR-C124910XX: 7.50 ng/mL, 80.0 ng/mL, and 800 ng/mL
Analytical technique / method of detection	Protein precipitation / HPLC-MS/MS
Number of Runs	9 of 9 runs met acceptance criteria
Total number of samples analyzed	980
Total number of samples re-assayed	Ticagrelor: 1 (0.1% of total number of samples analyzed) AR-C124910XX: 1 (0.1% of total number of samples analyzed)
Sample storage conditions	-10 to -30°C
Incurred sample reanalysis	Ticagrelor: 49 of 50, 98.0% met acceptance criteria AR-C124910XX: 49 of 50, 98.0% met acceptance criteria 5.1% of total number of samples analyzed
Accuracy (%Bias)	Calibration standard (ticagrelor): -3.0 to 2.4 Calibration standard (AR-C124910XX): -1.3 to 1.4 QC (ticagrelor): -12.7 to 13.3 QC (AR-C124910XX): -12.6 to 8.9
Precision	Calibration standard (ticagrelor): 1.3 to 4.9 Calibration standard (AR-C124910XX): 1.5 to 4.6 QC (ticagrelor): 3.2 to 7.8 QC (AR-C124910XX): 4.0 to 4.6
Samples analyzed within known stability	Yes

4.2 Summary of Applicant's Population PK Analysis

The Applicant performed the following population PK (PopPK) analyses to characterize PK in pediatric patients: 1) PopPK analysis of ticagrelor and its active metabolite (AR-C124910XX) in

patients with sickle cell disease aged 0 to 17 years based on HESTIA 1 and HESTIA4, and 2) PopPK analysis of ticagrelor and its active metabolite (AR-C124910XX) in pediatric patients with sickle cell disease based on HESTIA3. Each analysis is briefly summarized in the following sections:

4.2.1 A Population Pharmacokinetic (PK) Analysis of Ticagrelor and its Active Metabolite (AR-C124910XX) in Patients with Sickle Cell Disease Aged 0 to 17 Years

Objectives: The aims of the analysis were 1) to describe the time course of ticagrelor and AR-C124910XX plasma concentrations, and 2) to evaluate the potential impact of relevant demographic covariates, including body weight and age.

Data: The analysis included data from studies HESTIA1 and HESTIA4 in children with sickle cell disease (SCD). HESTIA1 included 45 patients ages 3 to 17 years old, that were administered ticagrelor (dose range: 0.125 to 2.25 mg/kg) as two single oral doses separated by 1 week, followed by a 1 week twice-daily repeated dosing period. Sparse PK samples were taken during the repeated dosing periods, and with a denser sampling schedule during the single dose visits. HESTIA4 included 21 patients ages 3 to 21 months old, that were administered ticagrelor as single oral dose (0.1 or 0.2 mg/kg) with PK samples taken at 1, 2, 4, and 6 hours after dose.

The single doses ranged from 0.69 to 140 mg (0.07 to 2.5 mg/kg) and the repeated BID doses ranged from 2 to 45 mg (0.07 to 0.86 mg/kg). A total of 7% (83/1114) were below LLOQ and excluded from the PopPK analysis. The PopPK dataset consisted of 1031 ticagrelor and AR-C124910XX PK samples from 66 patients with SCD. The mean (range) age was 8 (0.25-17) years old. The mean (range) body weight was 29 (6.9-82.2) kg. A total of 73% of the PopPK analysis population were black or African American.

Methods: The data were analyzed using a non-linear mixed effect modeling approach. Model selection was based upon goodness of fit (GOF) criteria including the objective function value (OFV), diagnostic plots, parameter estimates, standard error, and correlation of the parameter estimates. Covariate analysis evaluated the following: sex, age, body weight, race, and a medical history of cholecystectomy. A visual predictive check (VPC) was used for model evaluation and informed on the predictive properties of the final model.

Results: The structural model for the final ticagrelor PopPK model was a two-compartment disposition model with absorption characterized using an absorption model with a fixed number of absorption transit compartments (n = 5) and first order transfer-rate constant (Ktr). The fraction of ticagrelor metabolized to the active metabolite AR-C124910XX (f_m) was fixed to 0.22, a mean value derived from the [^{14}C]-ticagrelor human mass balance study. The ratio was assumed to be similar between children and adults, as the observed metabolite to ticagrelor ratio (43% based on steady state data) in pediatrics was consistent with what was observed in adults (40%). The metabolite PK model was described by a two-compartment disposition model. Clearance and volume parameters were scaled allometrically to individual baseline body weight normalized by 35 kg and with the exponent fixed to 0.75 and 1 for clearance and volume parameters, respectively. The following ontogeny function describing maturation of the CYP3A4 enzyme was included:

$$CL_{35kg}*(weight/35)^{0.75}*PMA^{3.9}/(71^{3.9}+PMA^{3.9}), \text{ with } PMA= 52*age+40$$

A covariate modelling identified sex as significant predictors of PK variability and included in the final model. Parameter estimates are presented below.

Table 1. Parameter estimates for PopPK model of ticagrelor and AR-C124910XX (HESTIA1 and HESTIA4)

Parameter	Parameter Estimate (%RSE) [Bootstrap CI][a]
Mean transit time (MTT) (hr)	0.749 (12%) [0.621,0.88]
Ticagrelor oral clearance (CL/F (L/hr))	23.3 (4.3%) [21.1,26]
Ticagrelor central volume of distribution (Vc/F (L))	135 (7.1%) [113,155]
Ticagrelor inter-compartmental clearance (Q/F (L/hr))	12.2 (22%) [8.58,20.1]
Ticagrelor peripheral volume of distribution (Vp/F (L))	200 (14%) [124,291]
AR-C124910XX oral clearance (CLm/F (L/hr))	10.1 (5.7%) [8.95,11.4]
AR-C124910XX central volume of distribution (Vcm/F (L))	7.57 (11%) [6.25,9.18]
AR-C124910XX inter-compartmental clearance (Qm/F (L/hr))	5.72 (7%) [4.66,6.82]
AR-C124910XX peripheral volume of distribution (Vpm/F (L))	22.8 (17%) [17.3,28.7]
Inter individual variability on CL/F (IIV, CV%)	22 (18%) [15.2,28.1]
Inter individual variability on Q/F (IIV, CV%)	86 (21%) [50,118]
Inter individual variability on Vc/F (IIV, CV%)	25 (23%) [12,35.6]
Inter individual variability on CLm/F (IIV, CV%)	10 (49%) [0.101,16.4]
Inter individual variability on Frel (IIV, CV%)	29 (10%) [22.8,32.6]
Inter individual variability on MTT (IIV, CV%)	63 (13%) [48.2,78.4]
Covariate: Frel % in males relative to females	0.756 (6.6%) [0.658,0.864]
Ticagrelor proportional residual error (%)	37.4 (5.1%) [0.343,0.402]
AR-C124910XX proportional residual error (%)	34.3 (5.6%) [0.312,0.371]
[a] 90% CI: Confidence intervals were obtained from 1000 bootstrap replicates using the quantile function in R (with the type = 6 algorithm).	

Source: Adapted from Applicant's PopPK analysis based on HESTIA1 and HESTIA4, Table 3, page 22.

Oral clearance was estimated to 23.3 L/h for ticagrelor and 10.1 L/h for AR-C124910XX for a patient weighing 35 kg. Patients at age 6 and 12 months are predicted to have 57%, and 27% reduced clearance in addition to the reduction due to lower body weight, compared to patients with full maturation of the CYP3A4 enzyme. The oral ticagrelor clearance for a patient aged 6 months at a weight of 7.6 kg was predicted at 3.2 L/h, and the oral ticagrelor clearance for a patient aged 12 months at a weight of 10 kg was predicted at 6.6 L/h. Sex was a significant covariate for the relative ticagrelor bioavailability with male patients estimated to have 24% lower bioavailability compared to female patients. Race, medical history of cholecystectomy, and study were also evaluated but were not found to significantly affect the PK of ticagrelor or AR-C124910XX.

4.2.2 A Population Pharmacokinetic Report of Ticagrelor and its Active Metabolite (AR-C124910XX) in Pediatric Patients with Sickle Cell Disease (HESTIA3)

Objectives: The aims of this PopPK analysis were to 1) characterize the PK of ticagrelor and its active metabolite (AR-C124910XX) in HESTIA3 consisting of pediatric patients ages 2 to17 years old with SCD using the PopPK model previously developed using data from studies HESTIA1 and HESTIA4, and 2) characterize potential impact of relevant demographic covariates on the PK of ticagrelor and AR-C124910XX.

Data: The PopPK analysis was conducted based on ticagrelor and AR-C124910XX plasma concentrations from HESTIA 3, where the patients received twice daily dose of ticagrelor or matching placebo based on body weight; ≥12 to ≤24kg: ticagrelor 15 mg or matching placebo, >24 to ≤48 kg: ticagrelor 30 mg or matching placebo, and >48 kg: ticagrelor 45 mg or matching placebo. A total of 459 ticagrelor plasma concentrations and 452 AR-C124910XX plasma

concentrations from 98 patients treated with ticagrelor were used in the analysis. A total of 14 (3%) ticagrelor PK samples and 21 (4%) of AR-C124910XX PK samples were below LLOQ and excluded from the analysis. The mean [range] age was 10 (3 – 17) years old and the mean [range] body weight was 33 (12 – 76) kg.

Methods: The PopPK model previously developed based on HESTIA1 and HESTIA4 was used as the basis for this analysis. Model discrimination was based on the inspection of graphical diagnostics and changes in the OFV. Model evaluation included graphical analysis of goodness of fit (GOF) plots, relative standard errors (RSEs) and visual predictive checks (VPCs).

Results: From the base PopPK model, the ontogeny model was removed as it is not supported by HESTIA3 data (ages 3 years and older). Estimation of all model parameters in the previous PopPK model resulted in an unstable estimation with poor precision of the parameter estimates. Removing the peripheral compartments for both ticagrelor and AR-C124910XX resulted in an increase in OFV but a more stable parameter estimation and accurate precision of parameter estimates. Therefore, the final PopPK model was a one-compartmental model for both ticagrelor and ARC124910XX with transit absorption compartments for ticagrelor, including fixed exponents of 0.75 and 1 for clearance and volume related parameters, respectively. Parameter estimates are presented below.

Table 2. Parameter estimates for the PopPK model based on HESTIA3

Parameter	Parameter Estimate	RSE (%)
Ticagrelor oral clearance (CL/F (L/h))	18.9	7.7
Ticagrelor volume of distribution (Vc/F (L))	231.8	11.7
Mean transit time (MTT (h))	1.2	11.7
AR-C124910XX oral clearance (CLm/F (L/h))	7.5	7.2
AR-C124910XX volume of distribution (Vcm/F (L))	12.6	11.5
Covariate: Age (years) on Ticagrelor volume of distribution (Vc/F (L))	-0.1	20.9
Interindividual variability on Vc/F (IIV, CV%)	52.8	11.0
Interindividual variability on Frel (IIV, CV%)	41.5	8.2
Ticagrelor proportional residual error (%)	51.1	3.9
AR-C124910XX proportional residual error (%)	46.6	4.0

Source: Applicant's PopPK analysis for HESTIA3, Table 4, page 38.

The apparent oral clearance and volume of distribution were estimated to 18.9 L/h and 231.8 L for ticagrelor and 7.5 L/h and 12.6 L for AR-C124910XX for a patent with a 29 kg body weight. Age was in addition to body weight identified as a covariate on the volume of distribution of ticagrelor (lower volume of distribution with higher age). Race and sex did not have a statistically significant effect of the PK of ticagrelor or AR-C124910XX. The Applicant concluded that the PK characteristics of ticagrelor and AR-C124610XX in the HESTIA3 study was similar to that observed in previous studies.

Reviewer's comments: In this submission, the Applicant utilized a PopPK approach to estimate

PK parameters (e.g., oral clearance [CL/F]) for HESTIA4 patient population. For this purpose, the PopPK analysis based on HESTIA1 and HESTIA4 is acceptable: the PK parameters were estimated with acceptable precision (RSE <25%) and the goodness of fit plots including visual predictive check plots do not indicate obvious model misspecification. The PopPK analysis based on HESTIA3 alone is considered exploratory. If a PopPK approach is used to characterize covariate effect (e.g., age, body weight, disease status) to support any labeling changes or to propose a new dosing regimen for future submission, the Applicant should conduct PopPK analysis based on the pooled data including HESTIA1, HESTIA3 and HESTIA4 and the adequacy of the PopPK analysis should be re-assessed based on the model utility.

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