U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA #:	022433
Supplement #:	2366
Drug Name:	Brilinta (Ticagrelor)
Indication(s):	Vaso-occlusive crises for pediatric patients with sickle cell disease
Applicant:	AstraZeneca Pharmaceuticals LP
Receipt Date:	Nov 19, 2021
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Review Priority:	Priority
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1. EXECUTIVE SUMMARY

The NDA 22433 for BRILINTA® (ticagrelor) tablets was originally approved on 20 July 2011 for the indication of reducing the rate of heart attack and cardiovascular death in adult patients with acute coronary syndrome. On 18 March 2014, the Applicant submitted an Investigational New Drug Application (IND 120366) to evaluate ticagrelor in pediatric patients with sickle cell disease (SCD). The Agency issued the original Written Request (WR) for pediatric studies for ticagrelor on 20 June 2019 and the WR Amendment 1 on 12 August 2021.

In this submission, the Applicant submitted the sNDA for ticagrelor to fulfill the WR requirement for pediatric exclusivity. As specified in the WR Amendment 1, this sNDA contains the study report of Study 1 (D5136C00010, i.e., HESTIA4), a Phase I study investigating the pharmacokinetic properties of ticagrelor in pediatric patients from 0 to less than 24 months with SCD, and also Study 2 (D5136C00009, i.e., HESTIA3), a Phase III study evaluating the effect of ticagrelor versus placebo in reducing the rate of vaso-occlusive crises (VOCs) for pediatric patients with SCD.

The pivotal Phase III study HESTIA3 was an international, double-blind, randomized, parallel-group, placebo-controlled study. On 15 June 2020, the Applicant received a recommendation from the Data Monitoring Committee (DMC) to terminate the HESTIA3 study, on the grounds that "the risks to patients of continuing the study outweigh any possibility that ticagrelor may show a beneficial effect if the study was completed". The Applicant agreed with this recommendation of the premature termination, and the end of study visit was defined by a common study end date (18 June 2020). The study was fully recruited at the time of the DMC recommendation, with 193 patients randomized at 53 sites across 16 countries in Africa and Asia, Europe, and North and South America.

In the HESTIA3 study, a higher incidence rate is shown in the ticagrelor group (2.74 per year) than in the placebo group (2.60 per year) with an incidence rate ratio of 1.06 (95% CI: 0.75, 1.50; P-value = 0.7597) for the primary efficacy endpoint (i.e., number of VOCs) which suggested that there is no sufficient evidence to show that ticagrelor was superior to placebo in reducing the rate of VOCs.

Subgroup analyses were also conducted for the primary efficacy endpoint. The results of the efficacy analysis in all pre-specified subgroups were consistent with the results of the primary analysis based on all randomized patients.

2. REGULATORY BACKGROUND

On 20 July 2011, the FDA approved NDA 22433 for BRILINTA® (ticagrelor) indicated to reduce the rate of heart attack and cardiovascular death in adult patients with acute coronary syndrome.

On 15 January 2014, the pre-IND meeting was held to evaluate ticagrelor in pediatric patients with SCD and the FDA agreed key aspects of the initial study (Phase II study HESTIA1).

On 18 March 2014, the Applicant submitted an Investigational New Drug Application (IND 120366) for evaluating ticagrelor in pediatric patients with SCD.

On 24 November 2015, a Type C Meeting was held in which the FDA agreed modifications to inclusion criteria of HESTIA1 and agreed to make Part B of this study optional.

On 13 January 2017, a Type C meeting was held to discuss aspects of the design for the proposed Phase III Study HESTIA3 to support protocol development.

On 27 June 2017, an End of Phase II meeting was held in which the Applicant shared with the FDA results from two Phase II studies in patients with SCD, HESTIA1 (aged ≥ 2 to < 18 years) and HESTIA2 (aged ≥ 18 to 30 years). The FDA agreed the proposed design of Phase III Study HESTIA3 and requested that the Clinical Outcome Assessment strategy should be submitted and discussed at a future meeting.

On 10 January 2018, a Type C meeting was held in which the FDA agreed the Clinical Outcome Assessment strategy for HESTIA3.

On 20 June 2019, the FDA issued the Written Request detailed the requirement for 3 studies (HESTIA3, HESTIA4, and HESTIA5).

On 12 August 2021, the FDA agreed with the removal of the planned HESTIA5 study from the Written Request and issued the Written Request Amendment 1.

3. DATA SOURCES AND SUBMISSION LINKS

Data were provided electronically in standard data format. The data submitted were considered acceptable by the Agency. SAS programs used to create key efficacy and safety outputs for the study were submitted along with the data.

The link to the data from the pivotal HESTIA3 study is:
\\CDSESUB1\evsprod\NDA022433\0740\m5\datasets\d5136c00009

On 7 January 2022, the Agency sent an Information Request (IR) regarding the dependent SAS programs/macros for sensitivity analyses in the HESTIA3 study. The content of the IR and the response of the Applicant can be found at: \\CDSESUB1\evsprod\NDA022433\0834

On 8 February 2022, the Agency sent an IR to the Applicant regarding the sensitivity analysis results using different multiple imputation strategies for the missing values in the HESTIA3 study. The content of the IR and the response of the Applicant can be found at:
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4. STATISTICAL EVALUATION (HESTIA3 STUDY)

4.1 Data and Analysis Quality

Data of this submission, provided with SDTM and ADaM, are acceptable. The Applicant also provided clear definition file for datasets and, reviewer guide, and detailed analysis programs for assisting review.

4.2 Evaluation of Efficacy

4.2.1 Study Design

HESTIA3 was an international, multicenter, double-blind, randomized, parallel-group, placebo-controlled Phase III study to evaluate the effect of ticagrelor versus placebo in reducing the rate of VOC events in pediatric patients with SCD. Patients were monitored for occurrence of VOC events and other acute SCD complications.

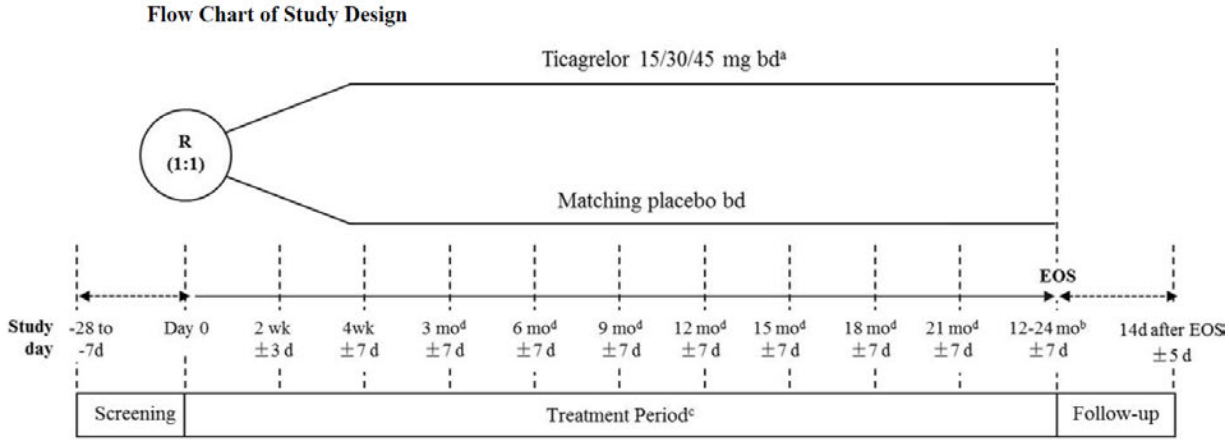
Patients were to receive standard of care for SCD adjusted to the individual patient at the discretion of the Investigator. In the treatment period, patients were to be followed for up to 24 months or until a common study end date (CSED) was reached, defined as 12 months after the last patient was randomized.

The double-blinded study drug dose was body weight dependent. Stratification for baseline hydroxyurea use by country was applied:

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

Figure 1 shows the design of the study and the sequence of study periods.

Figure 1: Design overview (HESTIA3 Study)



[a] Patients randomized to ticagrelor will receive doses based on weight band (at Screening): ≥ 12 to ≤ 24 kg = 15 mg, > 24 to ≤ 48 kg = 30 mg, > 48 kg = 45 mg.
[b] EOS = Patients were to be followed to a common study end date defined as 12 months after the last patient is randomized, or up to 24 months.
[c] See Table 3 for assessments during site visits and Table 4 for telephone visits that occurred monthly after Week 4 between site visits in the HESTIA3 clinical study report submitted by the Applicant.
[d] Interval was not to be more than 100 days to ensure tablet supply for all days.
Note: Only on-site visits are shown.
Note: bd = Twice daily; d = Day; EOS = End of study; mo = Month; R = Randomization; wk = Week
Source: Figure 1 in the HESTIA3 clinical study report submitted by the Applicant

4.2.2 Endpoints and Statistical Methodologies

Analysis Sets:

- Full analysis set (FAS): This analysis set includes all randomized patients.
- Safety analysis set (SAF): This analysis set includes all randomized patients who receive at least one dose of randomized study treatment, ticagrelor or placebo, and for whom any post-dose data are available.
- Per-protocol (PP) analysis set: This analysis set includes all randomized patients considered valid for safety, who comply with study course requirements and who, in addition, have no important protocol deviations/other factors impacting the efficacy outcome or treatment of the patient.

Reviewer's comment:
The SAF should not exclude patients for whom no post-dose data are available. In this study, the SAF has one fewer patient ([redacted] (b) (6)) than the FAS because there were no post-dose data for that patient. Because only one patient was excluded from FAS, the impact of excluding patients with no post-dose data was minimal.

Efficacy Variables:

- Primary efficacy variable: the number of VOC events during the treatment period

- Secondary efficacy variables:
    - Number of painful crises
    - Number of acute chest syndrome (ACS) events
    - Duration of painful crises
    - Number of VOC events requiring hospitalization or emergency department visits
    - Number of days hospitalized for VOC events
    - Number of acute SCD complications
    - Number of days hospitalized for acute SCD complications
    - Number of sickle cell-related red blood cell (RBC) transfusions
    - Health-related Quality of Life (HRQL) score
    - Proportion of days absent from school or work due to SCD
    - Intensity of worst daily VOC-related pain
    - Analgesics administered for VOC events
    - Swallowability and palatability

Analysis of Primary Efficacy Variables:
The primary efficacy variable is the number of VOC during the treatment period and the primary analysis is to compare the VOC event rate of ticagrelor with placebo based on the intent to treat (ITT) principle. The primary efficacy analysis was performed using FAS.

The null hypothesis is that the VOC event rate on ticagrelor is equal to the VOC event rate on placebo. The alternative hypothesis is that the VOC event rate on ticagrelor is not equal to the VOC event rate on the placebo. The significance level for the primary endpoint was 2-sided 5%.

The VOC event rate on ticagrelor was compared to the VOC event rate on placebo using a negative binomial model for the primary analysis. The response variable in the model was the number of VOC events experienced by a patient during the treatment period, regardless of premature discontinuation of study treatment. The model included covariates of treatment group and baseline hydroxyurea use (Yes/No) as covariates. The logarithm of the patient's follow-up time corresponding treatment period was used as an offset term in the model to adjust for patients having different follow-up times.

The estimated treatment effect (i.e., the rate ratio of ticagrelor versus placebo), the corresponding Wald 95% confidence interval (CI) and the p-value for the rate ratio were presented. In addition, the VOC event rate and the corresponding 95% CI within each treatment group were presented.

To examine the robustness of the primary efficacy analysis results, a number of sensitivity analyses were performed, including repeating the primary analysis on the PP analysis set, using alternative analysis models (Wilcoxon rank sum test, zero-inflated Poisson, and zero-inflated negative binomial models) and applying different multiple imputation methods for missing data (missing at random based (MAR), partial dropout reason-based (pDRMI), dropout reason-based (DRMI), and tipping point). The applied imputation methods were described in Keene et al [1].

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses were performed for the number of VOCs in pre-specified subgroups

(based on age, number of VOCs within the previous 12 months prior to study enrollment, baseline hydroxyurea use, sickle cell genotype, geographic region, gender, and race).

Analysis of Secondary Efficacy Variables:
The following secondary efficacy variables were analyzed using the same analysis method as the primary endpoint: number of painful crises, number of ACSs, duration of painful crises, number of VOCs requiring hospitalization or emergency department visits, number of days hospitalized for VOC, number of acute SCD complications, number of days hospitalized for acute SCD complications, and number of sickle cell-related red blood cell transfusions.

Descriptive statistics were presented for the HRQL score, proportion of days absent from school or work due to SCD, intensity of worst daily VOC-related pain, analgesics administered for VOC events, and swallowability and palatability.

Safety Variables:
The safety variables which address the safety of ticagrelor are AEs including serious adverse events (SAEs), deaths, bleeding events, overdose, blood product transfusions, laboratory variables, ECG and vital signs.

Safety Analyses:
No formal statistical analyses were performed on the safety data. The safety evaluation was primarily based on "on-treatment" summaries, which included AEs with onset date on or after the date of first dose of study treatment, and up to and including the date of last dose of study treatment + 7 days.

Sample Size Planning:
The number of VOCs was assumed to have a negative binomial distribution with shape parameter 0.8. The mean number of crises per year was assumed to be 2.0 in the placebo group with reduction of 50% in the ticagrelor group. Patients were randomized in a 1:1 ratio, and with minimum follow-up of 12 months and average follow-up of 18 months, 154 patients would provide about 90% power for a 2-sided test of the mean number of crises for ticagrelor versus placebo, at significance level 5%. Allowing for dropouts, the sample size was increased to 182. The calculations were based on simulation with 5000 repetitions.

Scenarios and simulations were evaluated to assess the risk with shorter and longer mean follow-up time. To ensure that the study was adequately powered the recruitment rate was monitored and the sample size could be adjusted to a maximum of 200 patients. With a mean follow-up time of 13 months, 200 patients would provide 90% power to detect a reduction of 50% in the ticagrelor group.

Interim Analysis:
A steering committee (SC) was appointed for this study and provided expert advice on the development of the protocol and protocol amendments. The SC monitored study conduct, results interpretation and reporting of the study.

A data monitoring committee (DMC) composed of independent SCD pediatric experts, including a platelet expert and a statistician, was appointed for this study and reported to the SC. The DMC was responsible for safeguarding the interests of the patients in the study by assessing the safety of the intervention during the study, and for reviewing the overall conduct of the clinical study. The DMC had regular predefined meetings according to the protocol and ad hoc meetings when needed. The DMC had access to unblinded individual data and were able to evaluate these while the study was ongoing.

A formal interim PD assessment was performed by the DMC when 60 patients had completed their PK/PD sampling after 4 weeks in the study.

Multiplicity Adjustment:
No multiplicity adjustment was included as no formal testing on secondary endpoints for statistical significance was carried out. Statistical testing of secondary efficacy endpoints was only for exploratory purposes.

4.2.3 Patient Disposition

A total of 193 patients were randomized at 53 sites across 16 countries: Africa and Asia (26 centers, 152 patients), Europe (16 centers, 25 patients) and North and South America (11 centers, 16 patients).

Seven patients discontinued the study due to withdrawal of consent: 2 (2.0%) in the ticagrelor group and 5 (5.4%) in the placebo group. Of these seven patients, 1 patient with ID (b) (6) in the ticagrelor group and 1 patient with ID (b) (6) in the placebo group completed follow-up of the primary endpoint because they withdrew consent after the common study end date of 18 June 2020. Furthermore, there was 1 patient (1.0%) lost to follow-up and 1 patient (1.0%) in withdrawn due to randomization in error, both in the ticagrelor group. The total number of missing data and dropouts was 7 (3.6%), where 3 (3.0%) in the ticagrelor group and 4 (4.3%) in the placebo group.

The disposition of the study population is summarized in Table 1. There were no notable differences in patient disposition between the two treatment groups.

Table 1: Treatment Disposition – FAS (HESTIA3 Study)

	Number (%) of patients		
	Ticagrelor 15/30/45 mg bd	**Placebo**	**Total**
Patients randomized	101	92	193
Patients who received study treatment	101 (100)	92 (100)	193 (100)
Patients withdrawn from study	101 (100)	92 (100)	193 (100)
Withdrawal by patient [a]	2 (2.0)	5 (5.4)	7 (3.6)
Death	3 (3.0)	1 (1.1)	4 (2.1)
Lost to follow-up	1 (1.0)	0	1 (0.5)
Other	95 (94.1)	86 (93.5)	181 (93.8)
Randomized in error	1 (1.0)	0	1 (0.5)
Study termination by the Applicant	94 (93.1)	86 (93.5)	180 (93.3)
Due to Covid-19 pandemic	0	0	0

[a] Patients (b) (6) in the ticagrelor group and (b) (6) in the placebo group withdrew consent after the common study end date (18 June 2020).
Source: FDA analysis

4.2.4 Baseline Demographic Characteristics

At baseline, the mean age of the 193 randomized patients was 10.3 years; 91 patients (41.0%) were female; 111 patients (57.5%) were Black or African American, 46 patients (23.8%) were White, 30 patients (15.5%) were Asian; 152 (78.8 %) patients were randomized in Africa & Asia, 25 (13.0 %) patients were randomized in Europe, 16 (8.3 %) patients were randomized in North & South America.

Comparisons of major patients' baseline demographic characteristics data between the treatment groups are shown in Table 2. In general, baseline demographic characteristics were balanced between the treatment groups.

Table 2: Demographic Characteristics – FAS (HESTIA3 Study)

	1 (N=101)	2 (N=92)	Overall (N=193)
Age (years) at randomization			
Mean (SD)	10.4 (± 4.1)	10.1 (± 3.8)	10.3 (± 4.0)
Age group (years) at randomization			
<12	61 (60.4 %)	54 (58.7 %)	115 (59.6 %)
>=12	40 (39.6 %)	38 (41.3 %)	78 (40.4 %)
Sex			
Female	48 (47.5 %)	43 (46.7 %)	91 (47.2 %)
Male	53 (52.5 %)	49 (53.3 %)	102 (52.8 %)
Race			
White	25 (24.8 %)	21 (22.8 %)	46 (23.8 %)
Black or African American	60 (59.4 %)	51 (55.4 %)	111 (57.5 %)
Asian	15 (14.9 %)	15 (16.3 %)	30 (15.5 %)
Other	1 (1.0 %)	5 (5.4 %)	6 (3.1 %)
Region			
Africa & Asia	78 (77.2 %)	74 (80.4 %)	152 (78.8 %)
Europe	14 (13.9 %)	11 (12.0 %)	25 (13.0 %)
North & South America	9 (8.9 %)	7 (7.6 %)	16 (8.3 %)
Number of prior VOCs			
<=1	0 (0.0 %)	1 (1.1 %)	1 (0.5 %)
>=2 to <=4	99 (98.0 %)	89 (96.7 %)	188 (97.4 %)
>4	2 (2.0 %)	2 (2.2 %)	4 (2.1 %)
Sickle cell disease genotype			
HbSS	87 (86.1 %)	83 (90.2 %)	170 (88.1 %)
HbS/β^0 thalassemia	13 (12.9 %)	9 (9.8 %)	22 (11.4 %)
Missing	1 (1.0%)	0 (0%)	1 (0.5%)
Baseline hydroxyurea use			
Yes	65 (64.4 %)	58 (63.0 %)	123 (63.7 %)
No	36 (35.6 %)	34 (37.0 %)	70 (36.3 %)

Source: FDA analysis

4.2.5 Efficacy Results

4.2.5.1 Primary Variable

Primary Analysis:

The primary analysis result showed that the primary efficacy variable (number of VOCs) had a higher incidence rate in the ticagrelor group (2.74 per year) than in the placebo group (2.60 per year) with an incidence rate ratio of 1.06 (95% CI: 0.75, 1.50; P-value = 0.7597). Analysis of the number of VOCs is presented in Table 3 below.

Table 3: Primary Analysis of the Primary Efficacy Variable (Number of VOCs) – FAS (HESTIA3 Study)

Treatment Group	Total Number of VOCs	Total Follow-Up Time (Years)	Results	Comparison between Ticagrelor and Placebo	
			Incidence Rate (Per Year) of VOCs (95% CI)	Incidence rate ratio (95% CI)	P-value
Ticagrelor 15/30/45 mg bd (N=101)	249	89.0	2.74 (2.16, 3.48)	1.06 (0.75, 1.50)	0.7597
Placebo (N=92)	202	80.0	2.60 (2.01, 3.34)		

Note: bd=twice daily; CI=confidence interval; N=total number of patients in treatment group; VOC=vaso-occlusive crisis

Note: Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and hydroxyurea use at randomization included in the model as covariates. Logarithm of each patient's corresponding follow-up time is used as an offset variable in the model to adjust for patients having different follow-up times during which the events occur.

Note: The number of VOCs is defined as the count of VOC events assessed throughout the treatment period from randomization to End of Study visit or date of premature study discontinuation. VOC events with an onset date ≤ 7 days of the previous event onset date are not counted as new events.

Source: FDA analysis

Reviewer's comment:

Following a recommendation from the DMC, the Applicant took the decision to terminate the study. However, with the early termination of the study 4 months ahead of the anticipated completion date, it did not appear to affect the ability to perform the pre-defined analyses and interpretability of the study results.

Sensitivity Analyses:

The results of sensitivity analyses were consistent with the primary analysis. Table 4 below presents the results of the sensitivity analysis by repeating the primary analysis on the PP analysis set.

Table 4: Sensitivity Analysis of the Primary Efficacy Variable (Number of VOCs) – PP Analysis Set (HESTIA3 Study)

Treatment Group	Total Number of VOCs	Total Follow-Up Time (Years)	Results	Comparison between Ticagrelor and Placebo	
			Incidence Rate (Per Year) of VOCs (95% CI)	Incidence rate ratio (95% CI)	P-value
Ticagrelor 15/30/45 mg bd (N=87)	224	77.0	2.86 (2.20, 3.73)	1.04 (0.71, 1.54)	0.8354
Placebo (N=76)	173	65.1	2.75 (2.06, 3.66)		

Note: bd=twice daily; CI=confidence interval; N=total number of patients in treatment group; VOC=vaso-occlusive crisis.
Note: Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and hydroxyurea use at randomization included in the model as covariates. Logarithm of each patient's corresponding follow-up time is used as an offset variable in the model to adjust for patients having different follow-up times during which the events occur.
Note: The number of VOCs is defined as the count of VOC events assessed throughout the treatment period from randomization to End of Study visit or date of premature study discontinuation. VOC events with an onset date ≤ 7 days of the previous event onset date are not counted as new events.
Source: FDA analysis

Table 5 below presents the results of sensitivity analyses using multiple imputation methods for missing data (MAR, pDRMI, DRMI, tipping point) and using alternative analysis models (Wilcoxon rank sum test, zero-inflated Poisson, and zero-inflated negative binomial models).

Table 5: Sensitivity Analyses of the Primary Efficacy Variable (Number of VOCs) – FAS (HESTIA3 Study)

	Estimate: Incidence Rate (Per Year) of VOCs (95% CI)		Comparison between Ticagrelor and Placebo	
	Ticagrelor 15/30/45 mg bd (N=101)	**Placebo (N=92)**	**Incidence rate ratio (95% CI)**	**P-value**
Multiple imputation - MAR analysis[a,b]	2.82 (2.15,3.48)	2.54 (2.01, 3.34)	1.06 (0.74, 1.50)	0.7618
Multiple imputation – pDRMI analysis[a,c]	2.82 (2.15, 3.48)	2.54 (2.01, 3.34)	1.06 (0.74, 1.50)	0.7618
Multiple imputation – DRMI analysis[a,d]	2.82 (2.15, 3.48)	2.54 (2.01, 3.34)	1.06 (0.74, 1.50)	0.7618
Multiple imputation – Tipping point analysis[a,e]	2.82 (2.16, 3.48)	2.54 (2.01, 3.34)	1.06 (0.75, 1.50)	0.7601
Wilcoxon rank sum test[f]	N/A	N/A	N/A	0.4461
Zero inflated negative binomial model[g]	3.24 (2.52, 4.16)	3.23 (2.41, 4.33)	1.00 (0.73, 1.39)	0.9802
Zero inflated Poisson model[h]	3.77 (3.31, 4.30)	3.92 (3.38, 4.54)	0.96 (0.79, 1.17)	0.7051

Note: bd=twice daily; CI=confidence interval; N=total number of patients in treatment group; VOC=vaso-occlusive crisis.

[a] The negative binomial model was used with treatment group and baseline hydroxyurea use as covariates and the logarithm of each patient's corresponding follow-up time as an offset variable.

[b] Missing at Random (MAR) based Multiple Imputation: Missing counts in each group are imputed assuming the expected event rate within that group.

[c] Partial Dropout Reason-based Multiple Imputation (pDRMI): Counts for patients in the Ticagrelor groups who dropped out for a study treatment-related reasons are imputed based on the expected VOC event rate in the placebo treatment group, whereas the remaining patients who have dropped out are imputed assuming MAR.

[d] Dropout Reason-based Multiple Imputation (DRMI): As for pDRMI with study treatment-related reasons and including "severe non-compliance with the protocol".

[e] Missing counts in each treatment group are imputed assuming the expected rate within that treatment group, and multiplied by a factor delta. Apply delta= 1 for placebo and increment by 0.025 for Ticagrelor group until an unfavorable primary efficacy result is obtained.

[f]The stratified Wilcoxon Rank Sum test was used with baseline hydroxurea use as the strata.

[g]The zero inflated negative binomial model was used with treatment group and baseline hydroxyurea use as covariates and the logarithm of each patient's corresponding follow-up time as an offset variable.

[h]The zero inflated Poisson model was used with treatment group and baseline hydroxyurea use as covariates and the logarithm of each patient's corresponding follow-up time as an offset variable.

Source: FDA analysis

Reviewer's comment:

There is only one treatment-related dropout in the ticagrelor group. This patient, (b) (6), withdrew consent after the common study end date and hence had complete follow-up of the primary endpoint. Therefore, the 3 imputation strategies (MAR, pDRMI, DRMI) yielded identical results.

The proportion of missing data and dropouts was low (3.6%), therefore the impact of missing data and dropouts with regards to the primary endpoint was minimal.

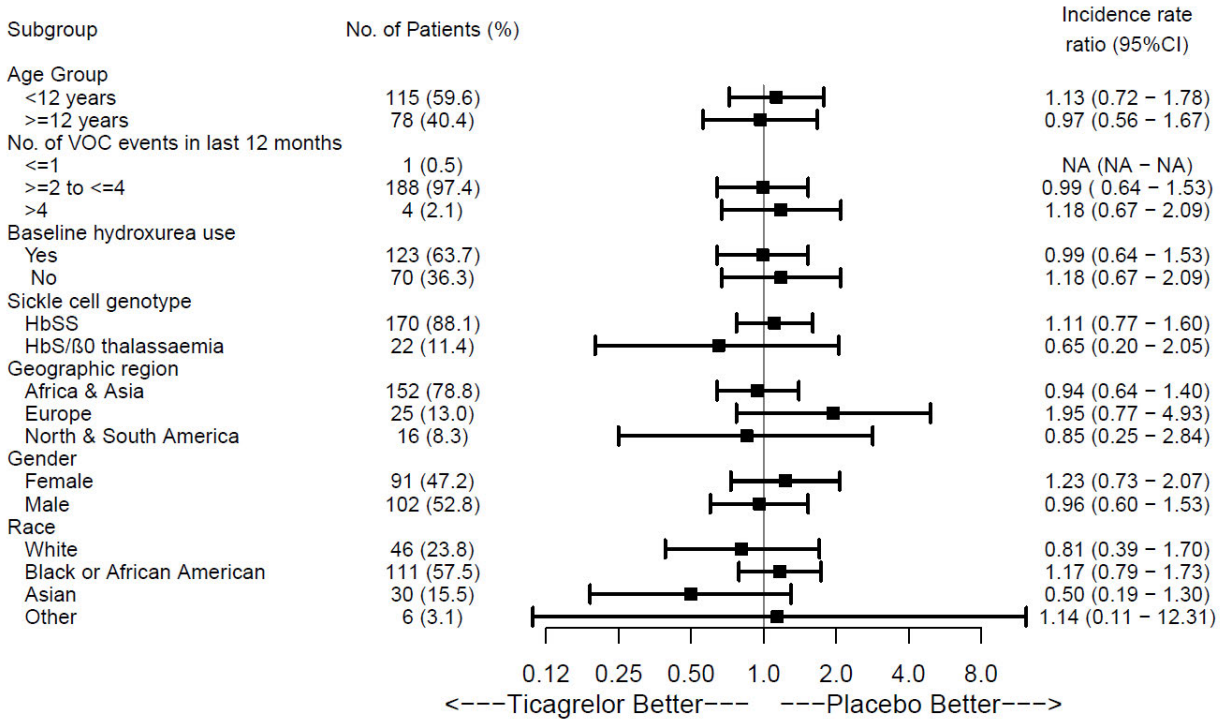
Subgroup Analyses:
The efficacy analysis results for all subgroups, including age, number of VOCs within the previous 12 months prior to study enrolment, baseline hydroxyurea use, sickle cell genotype, geographic region, gender, and race were consistent with the primary analysis result based on the FAS. The Applicant's subgroup analysis results for the number of VOCs in all pre-specified subgroups, confirmed by the statistical reviewer, are presented in Table 6 and visualized in Figure 2. The results of analysis appeared to be consistent across all subgroups (i.e., similar incidence rates in both treatment groups) without any outlier of subgroups.

Table 6: Subgroup Analyses of the Primary Efficacy Variable (Number of VOCs) – FAS (HESTIA3 Study)

	N (%)	Estimate: Incidence Rate (Per Year) of VOCs (95% CI)		Comparison between Ticagrelor and Placebo		Subgroup-by-Treatment Interaction P-value
		Ticagrelor 15/30/45 mg bd	Placebo	Incidence Rate Ratio (95% CI)	P-value	
Age at Randomization						0.67
<12 years	115 (59.6)	2.80 (2.06, 3.82)	2.48 (1.78, 3.46)	1.13 (0.72, 1.78)	0.60	
>=12 years	78 (40.4)	2.69 (1.84, 3.92)	2.77 (1.87, 4.10)	0.97 (0.56, 1.67)	0.91	
No. of VOC Events in Last 12 Months						0.79
<=1	1 (0.5)	NA	1.31 (0.08, 22.11)	NA	NA	
>=2 to <=4	188 (97.4)	2.74 (2.15, 3.49)	2.57 (1.99, 3.33)	1.07 (0.75, 1.52)	0.72	
>4	4 (2.1)	3.36 (0.68, 16.54)	4.31 (0.90, 20.68)	0.78 (0.08, 7.29)	0.83	
Baseline Hydroxurea Use						0.63
Yes	123 (63.7)	2.48 (1.83, 3.35)	2.50 (1.82, 3.44)	0.99 (0.64, 1.53)	0.96	
No	70 (36.3)	3.26 (2.20, 4.83)	2.77 (1.82, 4.20)	1.18 (0.67, 2.09)	0.57	
Sickle Cell Genotype						0.38
HbSS	170 (88.1)	3.00 (2.33, 3.86)	2.70 (2.07, 3.50)	1.11 (0.77, 1.60)	0.57	
HbS/β^0 thalassaemia	22 (11.4)	1.12 (0.51, 2.44)	1.73 (0.74, 4.04)	0.65 (0.20, 2.05)	0.46	
Geographic Region						0.36
Africa & Asia	152 (78.8)	2.44 (1.86, 3.22)	2.59 (1.95, 3.42)	0.94 (0.64, 1.40)	0.78	
Europe	25 (13.0)	4.27 (2.38, 7.66)	2.19 (1.06, 4.51)	1.95 (0.77, 4.93)	0.16	
North & South America	16 (8.3)	2.91 (1.27, 6.64)	3.42 (1.42, 8.23)	0.85 (0.25, 2.84)	0.79	
Gender						0.48
Female	91 (47.2)	2.55 (1.80, 3.62)	2.07 (1.41, 3.04)	1.23 (0.73, 2.07)	0.43	
Male	102 (52.8)	2.93 (2.12, 4.05)	3.06 (2.18, 4.28)	0.96 (0.60, 1.53)	0.86	
Race						0.40
White	46 (23.8)	1.17 (0.70, 1.94)	1.43 (0.84, 2.45)	0.81 (0.39, 1.70)	0.59	
Black or African American	111 (57.5)	3.94 (3.04, 5.12)	3.38 (2.52, 4.52)	1.17 (0.79, 1.73)	0.44	
Asian	30 (15.5)	0.81 (0.39, 1.70)	1.63 (0.89, 2.99)	0.50 (0.19, 1.30)	0.15	
Other	6 (3.1)	2.94 (0.33, 26.45)	2.58 (1.03, 6.49)	1.14 (0.11, 12.31)	0.92	

Note: N=Total number of patients in the subgroup; CI=Confidence interval; HbSS=Homozygous sickle cell anaemia; HbS/β^0=Sickle beta-zero-thalassaemia; VOC=Vaso-occlusive crisis; bd=Twice a day
Note: Incidence rates, rate ratios and p-values are from a negative binomial model analysis for each subgroup separately, with treatment group, subgroup and subgroup-by-treatment interaction included in the model as covariates. Logarithm of each patient's corresponding follow-up time is used as an offset variable in the model to adjust for patients having different follow-up times during which the events occur.
Note: Number of VOCs is defined as the count of VOC events assessed throughout the treatment period from randomization to EOS visit or date of premature study discontinuation. VOC events with an onset date ≤ 7 days of the previous event onset date are not counted as new events.
Note: Subject (b) (6) is missing sickle cell genotype and is not shown in this subgroup analysis.
Source: FDA analysis

Figure 2: Forest plot for Subgroup Analyses Results of the Primary Efficacy Variable (Number of VOCs) – FAS (HESTIA3 Study)



Source: FDA analysis

4.2.5.2 Secondary Variables

The analysis results for the secondary efficacy endpoints analyzed by the same analysis method as the primary endpoint (negative binomial model) are summarized in Table 7. There was no evidence of efficacy results favoring ticagrelor across any of these secondary endpoints. There was also no evidence that the efficacy outcome favored ticagrelor across other secondary endpoints analyzed with descriptive statistics.

Table 7: Analyses of the Secondary Efficacy Variables – FAS (HESTIA3 Study)

	Estimate: Incidence Rate (Per Year) of VOCs (95% CI)		**Comparison between Ticagrelor and Placebo**	
	Ticagrelor 15/30/45 mg bd (N=101)	**Placebo (N=92)**	**Incidence Rate Ratio (95% CI)**	**P-value**
Number of painful crises[a,b]	2.73 (2.14,3.48)	2.67 (2.07,3.45)	1.02 (0.72,1.45)	0.9037
Number of individual painful crises[a,c]	2.92 (2.28,3.74)	2.82 (2.17,3.67)	1.03 (0.72,1.48)	0.8573
Number of ACS events[a,b]	0.05 (0.01,0.15)	0.06 (0.02,0.19)	0.76 (0.17,3.30)	0.7136
Number of individual ACS events[a,c]	0.05 (0.01,0.15)	0.06 (0.02,0.19)	0.76 (0.17,3.30)	0.7136
Duration of painful crises (days)[d]	16.09 (11.35,22.81)	19.20 (13.33, 27.64)	0.84 (0.50,1.40)	0.4970
Number of VOCs requiring hospitalization or emergency department visits[a,b]	0.87 (0.62,1.21)	0.61 (0.41,0.89)	1.43 (0.87,2.36)	0.1636
Number of days hospitalized for VOCs[d]	5.07 (2.93,8.79)	3.01 (1.69,5.38)	1.68 (0.76,3.75)	0.2011
Number of acute SCD complications[a]	The model did not converge			
Number of days hospitalized for acute SCD complications[d]	0.00 (0.00, ∞)	0.00 (0.00, ∞)	0.00 (0.00, ∞)	0.9940
Number of sickle cell-related red blood cell transfusions[a,e]	0.41 (0.25, 0.68)	0.53 (0.32, 0.88)	0.77(0.38, 1.58)	0.4822

Note: bd=twice daily; CI=confidence interval; N=total number of patients in treatment group; VOC=vaso-occlusive crisis

Note: Incidence rates, incidence rate ratios, and p-values are from a negative binomial model analysis, with treatment group and hydroxyurea use at randomization included in the model as covariates. Logarithm of each patient's corresponding follow-up time is used as an offset variable in the model to adjust for patients having different follow-up times during which the events occur.

[a] Number of secondary endpoint events as assessed throughout the treatment period from randomization (Visit 2) to EOS visit or date of premature study discontinuation (observed follow-up).

[b] Events with an onset date ≤ 7 days of the previous event onset date are not counted as new events.

[c] Individual painful crisis and ACS events with an onset date ≤ 7 days of the previous event onset date are counted as new events.

[d] For patients not experiencing a secondary endpoint event in the defined treatment period, duration of defined event is set to 0 days.

[e] Sickle cell-related red blood cell transfusions as identified by study physician review.

Source: FDA analysis

4.3 Evaluation of Safety

Please refer to the clinical review on the safety issues for this study.

5. STATISTICAL ISSUES

After thorough evaluation, the statistical review team determined that the Applicant had successfully addressed the following statistical related issues or requirements by the FDA.

First, the WR required the Applicant to impute missing data using the following multiple imputation method: 1) all treatment-related missing data are multiply imputed using data from the placebo arm; 2) other missing data are multiply imputed under missing at random assumption. The Applicant followed the Agency's request. In addition, the Applicant also conducted several analyses, including multiply imputing missing data in both arms using the missing at random assumption and tipping point analysis to assess the impact of the missing data and to ensure the robustness of the results. All results from different methods for dealing with missing data are consistent.

Second, the WR required the Applicant to adjust in the model for the multiple imputation by treatment group, study site, baseline hydroxyurea use, age, and baseline crisis count. The Applicant indeed tried to perform the multiple imputation by adjusting the suggested covariates. However, because using all the recommended covariates could have resulted in sparse data and the failure of the model, the Applicant’s final multiple imputation analyses only adjusted for some (i.e., treatment group, baseline hydroxyurea use), but not all, of the suggested covariates in WR. The statistical review team determined that the Applicant’s revised analysis model is appropriate.

Third, the WR required the Applicant to pre-specify the primary analysis model from one of negative binomial regression model, Wilcoxon rank sum test, and Poisson regression model prior to study unblinding and to use the remaining models as sensitivity analyses. The Applicant met this requirement by pre-specifying the negative binomial regression model as the primary analysis model and used the other two models for sensitivity analyses. The results of the sensitivity analyses of the alternative models are consistent with the results of the primary analysis model.

6. CONCLUSIONS

The Applicant submitted a Phase I study (HESTIA4) to investigate the pharmacokinetic properties of ticagrelor in pediatric patients from 0 to less than 24 months with SCD and a Phase III study (HESTIA3) to evaluate the effect of ticagrelor versus placebo in reducing the rate of vaso-occlusive crises (VOCs) for pediatric patients with SCD.

In the pivotal HESTIA3, the primary analysis showed that the primary efficacy variable (number of VOCs) had a higher incidence rate in the ticagrelor group (2.74 per year) than in the placebo group (2.60 per year) with an incidence rate ratio of 1.06 (95% CI: 0.75, 1.50; P-value = 0.7597). The results of sensitivity analyses and subgroup analyses were consistent with the primary analysis. In addition, there was no evidence of efficacy results favoring ticagrelor across any secondary endpoints. Therefore, the statistical review team determined that the pivotal trial (HESTIA3) is negative, where the superiority of ticagrelor to placebo was not demonstrated.

7. LABELING RECOMMENDATIONS

The Agency recommended the Applicant revise the conclusions from the pediatric study in Section 8.4 in the label as follows and the Applicant agreed:

The safety and effectiveness of BRILINTA have not been established in pediatric patients. Effectiveness was not demonstrated in an adequate and well-controlled study conducted in (b) (4) *BRILINTA-treated pediatric patients, aged 2 to <18 for reducing the rate of vaso-occlusive crises in sickle cell disease.*

8. REFERNCES

1. Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical Statistics. 2014 Jul;13(4):258-64.

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