IND 120366/NDA 022433

WRITTEN REQUEST – AMENDMENT 1

AstraZeneca Pharmaceuticals LP
Attention: Robert Griffin
Sr. Director, Regulatory Affairs
1800 Concord Pike
Wilmington, DE 19803

Dear Mr. Griffin:

Please refer to your correspondence dated April 14, 2021, requesting changes to FDA's June 20, 2019, Written Request for pediatric studies for Brilinta (ticagrelor).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on June 20, 2019, remain the same. (Text added is underlined. Text deleted is strikethrough.)

BACKGROUND:

These studies investigate the potential use of ticagrelor for the reduction in occurrence of vaso-occlusive crises (VOCs) in pediatric patients with sickle cell disease (SCD).

SCD is a progressive multisystem disorder which can be chronic and debilitating. A VOC is a severe, acute, painful episode that occurs when sickle-shaped red blood cells obstruct the microcirculation and restrict blood flow to an organ or tissue, resulting in ischemia, necrosis, and organ damage. The rationale for the use of antiplatelet therapies in management of SCD is based on the evidence that platelets participate in the vaso-occlusive process and that platelet activation correlates with the frequency of pain episodes.

To obtain needed pediatric information on ticagrelor, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below. Given the persistence of fetal hemoglobin in newborns, documentation of VOCs may be limited in pediatric patients less than 6 months. Therefore, the evaluation of VOCs in pediatric patients less than 6 months of age will not be assessed.

The unfavorable benefit-risk profile (b) (4) of ticagrelor in pediatric patients (aged ≥2 years to <18 years) with sickle cell disease in Study 2: D5136C00009 (HESTIA3)

resulted in the termination of this study. This study was modified for the purposes of the Written Request to account for the early termination. Furthermore, Study 3: D5136C00013 (HESTIA5) in pediatric patients with sickle cell disease (aged 6 months to <18 years) is being removed from the Written Request because it would be inappropriate and unethical to initiate this study given the early termination of Study 2. The Agency agrees that the continuation of clinical studies evaluating ticagrelor in pediatric patients with sickle cell disease would be inappropriate and unethical.

- Nonclinical study(ies):

Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- Clinical studies:

Study 1: D5136C00010 (HESTIA4)
This is a phase 1, multicenter, multinational, open-label PK study where at least 20 pediatric patients with SCD age <24 months will receive a single oral dose of ticagrelor granules. Samples for pharmacokinetics (PK) assessment will be taken at specific timepoints (e.g., 1, 2, 4, and 6 hours post dose) up to 6 hours post dose as defined in the protocol.

Study 2: D5136C00009 (HESTIA3)
This is a phase 3, multicenter, double-blind, randomized, parallel-group, placebo-controlled study evaluating the effect of ticagrelor versus placebo in reducing the number of VOCs in pediatric patients with SCD aged ≥2 years to <18 years. The study will randomizepatients (1:1) to receive ticagrelor or matching placebo at least 12 months. Hydroxyurea and L-glutamine as background treatment will be allowed. This study was terminated early (b) (4).

~~Study 3: D5136C00013 (HESTIA5)~~
~~This is a phase 3, multicenter, double-blind, randomized, parallel-group, placebo-controlled study to evaluate the effect of ticagrelor versus placebo in reducing the number of VOCs in pediatric patients with SCD aged 6 months to <18 years. The study will randomize at least 182 patients (1:1) to receive ticagrelor or matching placebo for at least 12 months. Prior to randomization, patients aged 6 to <24 months will undergo a 14-day open-label run-in period in which they will receive open-label ticagrelor 5, 10, or 15 mg depending on body weight. Hydroxyurea and L-glutamine as background treatment will be allowed.~~

- Objective of each study:

Study 1: D5136C00010 (HESTIA4)

The primary objective is to determine PK properties of ticagrelor after a single oral dose.

Study 2: D5136C00009 (HESTIA3)
The primary objective is to compare the effect of ticagrelor versus placebo for the reduction of VOCs which is a composite of painful crisis and/or acute chest syndrome (ACS), in pediatric patients with SCD. This study was terminated early (b) (4)

~~Study 3: D5136C00013 (HESTIA5)~~
~~The primary objective is the same as in Study 2 but in patients aged 6 months to <18 years.~~

- Patients to be Studied:

Study 1: D5136C00010 (HESTIA4)
Age group in which study(ies) will be performed: Pediatric patients with SCD from age <24 months. The following age groups and number of patients will be evaluated:

- 6 months to <12 months: A minimum of 3 evaluable patients will be enrolled.
- 12 months to <24 months: A minimum of 5 evaluable patients will be enrolled.

Study 2: D5136C00009 (HESTIA3)
Age group in which study(ies) will be performed: Pediatric patients with SCD from age ≥2 years to <18 years. ~~The following two age groups and number of patients will be studied:~~

- ~~≥2 years to <12 years: At least 50 evaluable patients will be enrolled.~~
- ~~≥12 years to <18 years: At least 50 evaluable patients will be enrolled.~~

This study was terminated early (b) (4). Therefore, there will be no minimum number of patients to be enrolled. The sponsor should submit data from all subjects enrolled.

~~Study 3: D5136C00013 (HESTIA5)~~
~~Age group in which study(ies) will be performed: Pediatric patients with SCD from age 6 months to < 18 years. The following three age groups and number of patients will be studied:~~

- ~~6 months to <24 months: At least 20 patients will be enrolled.~~
- ~~≥2 to <12 years: At least 50 randomized patients will be enrolled.~~
- ~~≥12 to <18 years: At least 50 randomized patients will be enrolled.~~

- Number of patients to be studied:

Study 1: D5136C00010 (HESTIA4)
At least 20 evaluable patients will be studied.

Study 2: D5136C00009 (HESTIA3)
~~At least 182 randomized patients will be studied.~~
This study was terminated early [redacted] (b) (4). Therefore, there will be no minimum number of patients to be enrolled. The sponsor should submit data from all subjects enrolled.

~~Study 3: D5136C00013 (HESTIA5)~~
~~At least 182 randomized patients will be studied.~~

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- Study endpoints:

Study 1: D5136C00010 (HESTIA4)
The primary endpoint will be assessment of PK properties of ticagrelor after a single dose, including observed plasma concentrations as well as PK parameters obtained using a population PK analysis approach, e.g., CL/F (oral clearance), Cmax, and AUCinf.

Secondary endpoints should include PK properties of the active metabolite (AR-C124910XX) after a single oral dose, including observed plasma concentrations as well as PK parameters obtained using a population PK analysis approach, e.g., Cmax, and AUCinf, as well as the acceptability and the palatability of a single oral dose of ticagrelor.

Study 2: D5136C00009 (HESTIA3)
The primary efficacy endpoint will be reduction in the number of VOCs which is a composite of painful crisis and/or ACS. Each component is defined as follows: painful crisis is an onset of worsening of pain that lasts at least 2 hours for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids, parenteral non-steroidal anti-inflammatory drugs, or other analgesics prescribed by a health care provider in a medical setting (such as hospital, clinic, emergency room visit or at home). An ACS is an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray.

Secondary efficacy endpoints include the following: reduction in number of painful crisis, reduction of ACS, duration of painful crisis, number of VOCs requiring

hospitalization or emergency department visits, number of acute SCD complications, number of days hospitalized for acute SCD complications, additional health-related quality of life assessments, and the effect of ticagrelor on platelet aggregation.

~~Study 3: D5136C00013 (HESTIA5)~~
~~The primary efficacy endpoint will be reduction in the number of VOCs which is a composite of painful crisis and/or ACS.~~

~~Secondary efficacy endpoints are the same as for Study 2 except for the number of VOC in patients aged 2 to <18 years.~~

- Safety Assessments:

Study 1 D5136C00010 (HESTIA4): To assess the safety and tolerability of a single oral dose of ticagrelor.

Study 2 D5136C00009 (HESTIA3): To assess the long-term safety and tolerability of therapy with ticagrelor versus placebo. This study was terminated early (b) (4)

~~Study 3 D5136C00013 (HESTIA5): To assess the long-term safety and tolerability of therapy with ticagrelor versus placebo.~~

- Safety Endpoints for Study 1 and Study 2:

Safety outcomes must include adverse events and serious adverse events, including bleeding from randomization throughout the treatment period and including the follow-up period.

Adverse events will be collected from the run-in open label treatment for patients in the age range of 6 to <24 months.

A Data Monitoring Committee (DMC) should ~~confirm model based predictions on ticagrelor exposure levels in patients aged 6 to <24 months in Study D5136C00013 before randomization~~, conduct a formal interim PD assessment when 60 patients (32%) have undergone their first PKPD sampling after 4 weeks in Study D5136C00009 while also reviewing the unblinded treatment data regularly.

- Known Drug Safety concerns and monitoring:

Bleeding is the most important safety concern for all antiplatelet medications; inherent to their pharmacodynamic (PD) effects, antiplatelet agents increase the risk of bleeding. Based on previous studies in adult patients with cardiovascular disease, many of whom were taking dual antiplatelet therapy, there is a risk of bleeding across all degrees of severity from minimal nuisance bleeding to life-

threatening and fatal bleeding that may occur related to surgical or other procedures, as well as during long-term out of hospital use. The studies will incorporate appropriate inclusion and exclusion criteria at entry and discontinuation criteria during the study to minimize the bleeding risk, by excluding patients who may be predisposed to clinically significant bleeding.

- Extraordinary results:

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment. Study 2 was terminated early (b) (4). The Written Request was amended based on this result.

- Drug information:

- Dosage form

Study 1: D5136C00010 (HESTIA4)
- Ticagrelor (b) (4) suspension of 1 mg/mL ticagrelor.

Study 2: D5136C00009 (HESTIA3)
- Ticagrelor tablet of 15 mg and its matching placebo

~~Study 3: D5136C00013 (HESTIA5)~~
- ~~Ticagrelor tablet of 5 mg or 15 mg and its matching placebo.~~

- Route of administration

~~Tablets to be administered orally, either swallowed whole or dispersed in water, other suitable liquids, based on age and/or ability to swallow study drugs.~~
The formulation activities will be stopped.

- Regimen

Study 1: D5136C00010 (HESTIA4)
The selected doses are based on:
- Age group ≥6 months but <24 months: 0.2 mg/kg single dose.

Study 2: D5136C00009 (HESTIA3)
The selected doses are based on 3 body weight bands:

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

This study was terminated early [redacted] (b) (4).

~~Study 3: D5136C00013 (HESTIA5)~~
~~Run-in period: Patients aged 6 to <24 months only will receive ticagrelor based on 3 weight bands:~~

- ~~≥6 kg to ≤9 kg body weight: 5 mg twice daily.~~
- ~~9 kg to ≤12 kg body weight: 10 mg twice daily.~~
- ~~12 kg to ≤24 kg body weight: 15 mg twice daily.~~

~~The doses selected for patients aged 6 months to <24 months in the 14-day run-in period should be agreed upon by the Division. The doses for patients >24 kg are below:~~

- ~~>24 kg to ≤48 kg: 30 mg twice daily.~~
- ~~>48 kg: 45 mg twice daily.~~

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

The Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a

commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

As the results from the clinical studies do not support a pediatric indication for ticagrelor in SCD, these related formulation activities will be stopped.

- Statistical information, including power of study(ies) and statistical assessments:

  Study~~ies~~ ~~1 and 2~~ ~~2 and 3~~: D5136C00009 (HESTIA3) ~~and D5136C000010 (HESTIA4) D5136C00013 (HESTIA5)~~

  ~~Your sample size for the study must be adequate to ensure a power of 80% to detect a 50% reduction in the event rate for the ticagrelor group compared to the placebo group, assuming a mean number of two VOC crises per year.~~

  Your primary analysis for the primary efficacy endpoint, i.e., the number of VOCs, must target the treatment policy estimand where patients are analyzed as randomized regardless of adherence. Your primary analysis must 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 multiple imputation should be adjusted for treatment group, study site, baseline hydroxyurea use, age, and baseline crisis count. Missing data sensitivity analyses must include a tipping analysis that varies assumptions about the missing outcomes on the two treatment arms.

  You must specify your intended primary analysis methodology prior to study unblinding. This may be either a negative binomial regression model, a Wilcoxon rank sum test or a Poisson regression model. The remaining analyses can be used as sensitivity analyses.

- Labeling that may result from the study(ies): You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that ticagrelor is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the

results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

For Study 1 and Study 2, case report forms, case report tabulations, study data, and full clinical study reports, which include the analyses from Study 1 and formal statistical analyses from Study 2, should be submitted to the Agency.

- Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain Agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry, E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

- Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before May 3, 2022. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity

that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated June 20, 2019, as amended by this letter must be submitted to the Agency on or before May 3, 2022 ~~July 31, 2023~~, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Carleveva Thompson, Regulatory Project Manager, at 301-796-1403.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, MD,
Deputy Director (Acting)
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE:

- Complete Copy of Written Request as Amended

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

IND 120366/NDA 022433

WRITTEN REQUEST – AMENDMENT 1

BACKGROUND:

These studies investigate the potential use of ticagrelor for the reduction in occurrence of vaso-occlusive crises (VOCs) in pediatric patients with sickle cell disease (SCD).

SCD is a progressive multisystem disorder which can be chronic and debilitating. A VOC is a severe, acute, painful episode that occurs when sickle-shaped red blood cells obstruct the microcirculation and restrict blood flow to an organ or tissue, resulting in ischemia, necrosis, and organ damage. The rationale for the use of antiplatelet therapies in management of SCD is based on the evidence that platelets participate in the vaso-occlusive process and that platelet activation correlates with the frequency of pain episodes.

To obtain needed pediatric information on ticagrelor, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below. Given the persistence of fetal hemoglobin in newborns, documentation of VOCs may be limited in pediatric patients less than 6 months. Therefore, the evaluation of VOCs in pediatric patients less than 6 months of age will not be assessed.

The unfavorable benefit-risk profile (b) (4) of ticagrelor in pediatric patients (aged ≥2 years to <18 years) with sickle cell disease in Study 2: D5136C00009 (HESTIA3) resulted in the termination of this study. This study was modified for the purposes of the Written Request to account for the early termination. Furthermore, Study 3: D5136C00013 (HESTIA5) in pediatric patients with sickle cell disease (aged 6 months to <18 years) is being removed from the Written Request because it would be inappropriate and unethical to initiate this study given the early termination of Study 2. The Agency agrees that the continuation of clinical studies evaluating ticagrelor in pediatric patients with sickle cell disease would be inappropriate and unethical.

- Nonclinical study(ies):

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- Clinical studies:

Study 1: D5136C00010 (HESTIA4)
This is a phase 1, multicenter, multinational, open-label PK study where at least 20 pediatric patients with SCD age <24 months will receive a single oral dose of ticagrelor granules. Samples for pharmacokinetics (PK) assessment will be taken at specific timepoints (e.g., 1, 2, 4, and 6 hours post dose) up to 6 hours post dose as defined in the protocol.

Study 2: D5136C00009 (HESTIA3)
This is a phase 3, multicenter, double-blind, randomized, parallel-group, placebo-controlled study evaluating the effect of ticagrelor versus placebo in reducing the number of VOCs in pediatric patients with SCD aged ≥2 years to <18 years. The study will randomizepatients (1:1) to receive ticagrelor or matching placebo at least 12 months. Hydroxyurea and L-glutamine as background treatment will be allowed. This study was terminated early (b) (4).

- Objective of each study:

Study 1: D5136C00010 (HESTIA4)
The primary objective is to determine PK properties of ticagrelor after a single oral dose.

Study 2: D5136C00009 (HESTIA3)
The primary objective is to compare the effect of ticagrelor versus placebo for the reduction of VOCs which is a composite of painful crisis and/or acute chest syndrome (ACS), in pediatric patients with SCD. This study was terminated early (b) (4)

- Patients to be Studied:

Study 1: D5136C00010 (HESTIA4)
Age group in which study(ies) will be performed: Pediatric patients with SCD from age <24 months. The following age groups and number of patients will be evaluated:

  - 6 months to <12 months: A minimum of 3 evaluable patients will be enrolled.
  - 12 months to <24 months: A minimum of 5 evaluable patients will be enrolled.

Study 2: D5136C00009 (HESTIA3)
Age group in which study(ies) will be performed: Pediatric patients with SCD from age ≥2 years to <18 years.

This study was terminated early (b) (4) Therefore, there will be no minimum number of patients to be enrolled. The Sponsor should submit data from all subjects enrolled.

- Number of patients to be studied:

Study 1: D5136C00010 (HESTIA4)
At least 20 evaluable patients will be studied.

Study 2: D5136C00009 (HESTIA3)
This study was terminated early (b) (4). Therefore, there will be no minimum number of patients to be enrolled. The Sponsor should submit data from all subjects enrolled.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- Study endpoints:

Study 1: D5136C00010 (HESTIA4)
The primary endpoint will be assessment of PK properties of ticagrelor after a single dose, including observed plasma concentrations as well as PK parameters obtained using a population PK analysis approach, e.g., CL/F (oral clearance), Cmax, and AUCinf.

Secondary endpoints should include PK properties of the active metabolite (AR-C124910XX) after a single oral dose, including observed plasma concentrations as well as PK parameters obtained using a population PK analysis approach, e.g., Cmax, and AUCinf, as well as the acceptability and the palatability of a single oral dose of ticagrelor.

Study 2: D5136C00009 (HESTIA3)
The primary efficacy endpoint will be reduction in the number of VOCs which is a composite of painful crisis and/or ACS. Each component is defined as follows: painful crisis is an onset of worsening of pain that lasts at least 2 hours for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids, parenteral non-steroidal anti-inflammatory drugs, or other analgesics prescribed by a health care provider in a medical setting (such as hospital, clinic, emergency room visit or at home). An ACS is an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray.

Secondary efficacy endpoints include the following: reduction in number of painful crisis, reduction of ACS, duration of painful crisis, number of VOCs requiring hospitalization or emergency department visits, number of acute SCD complications, number of days hospitalized for acute SCD complications, additional health-related quality of life assessments, and the effect of ticagrelor on platelet aggregation.

- Safety Assessments:

Study 1 D5136C00010 (HESTIA4): To assess the safety and tolerability of a single oral dose of ticagrelor.

Study 2 D5136C00009 (HESTIA3): To assess the long-term safety and tolerability of therapy with ticagrelor versus placebo. This study was terminated early (b) (4)

- Safety Endpoints for Study 1 and Study 2:

Safety outcomes must include adverse events and serious adverse events, including bleeding from randomization throughout the treatment period and including the follow-up period.

Adverse events will be collected from the run-in open label treatment for patients in the age range of 6 to <24 months.

A Data Monitoring Committee (DMC) should conduct a formal interim PD assessment when 60 patients (32%) have undergone their first PKPD sampling after 4 weeks in Study D5136C00009 while also reviewing the unblinded treatment data regularly.

- Known Drug Safety concerns and monitoring:

Bleeding is the most important safety concern for all antiplatelet medications; inherent to their pharmacodynamic (PD) effects, antiplatelet agents increase the risk of bleeding. Based on previous studies in adult patients with cardiovascular disease, many of whom were taking dual antiplatelet therapy, there is a risk of bleeding across all degrees of severity from minimal nuisance bleeding to life-threatening and fatal bleeding that may occur related to surgical or other procedures, as well as during long-term out of hospital use. The studies will incorporate appropriate inclusion and exclusion criteria at entry and discontinuation criteria during the study to minimize the bleeding risk, by excluding patients who may be predisposed to clinically significant bleeding.

- Extraordinary results:

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an

amendment. Study 2 was terminated early [redacted] (b) (4). The Written Request was amended based on this result.

- Drug information:

- Dosage form

Study 1: D5136C00010 (HESTIA4)
- Ticagrelor [redacted] (b) (4) suspension of 1 mg/mL ticagrelor.

Study 2: D5136C00009 (HESTIA3)
- Ticagrelor tablet of 15 mg and its matching placebo

- Route of administration

The formulation activities will be stopped.

- Regimen

Study 1: D5136C00010 (HESTIA4)
The selected doses are based on:
- Age group ≥6 months but <24 months: 0.2 mg/kg single dose.

Study 2: D5136C00009 (HESTIA3)
The selected doses are based on 3 body weight bands:
- ≥12 kg to ≤24 kg body weight: 15 mg (1 tablet of ticagrelor 15 mg or 1 tablet of placebo to match ticagrelor 15 mg) twice daily.
- >24 kg to ≤48 kg body weight: 30 mg (2 tablets of ticagrelor 15 mg or 2 tablets of placebo to match ticagrelor 15 mg) 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.

This study was terminated early [redacted] (b) (4)

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

The Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

As the results from the clinical studies do not support a pediatric indication for ticagrelor in SCD, these related formulation activities will be stopped.

- Statistical information, including power of study(ies) and statistical assessments:

  Study 2: D5136C00009 (HESTIA3)

  Your primary analysis for the primary efficacy endpoint, i.e., the number of VOCs, must target the treatment policy estimand where patients are analyzed as randomized regardless of adherence. Your primary analysis must 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 multiple imputation should be adjusted for treatment group, study site, baseline hydroxyurea use, age, and baseline crisis count. Missing data sensitivity analyses must include a tipping analysis that varies assumptions about the missing outcomes on the two treatment arms.

You must specify your intended primary analysis methodology prior to study unblinding. This may be either a negative binomial regression model, a Wilcoxon rank sum test or a Poisson regression model. The remaining analyses can be used as sensitivity analyses.

- Labeling that may result from the study(ies): You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that ticagrelor is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

  For Study 1 and Study 2, case report forms, case report tabulations, study data, and full clinical study reports, which include the analyses from Study 1 and formal statistical analyses from Study 2, should be submitted to the Agency.

- Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain Agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry, E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the

https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

- Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before May 3, 2022. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
08/12/2021 02:24:01 PM