DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022433

WRITTEN REQUEST

AstraZeneca LP
Attention: Robert Griffin
Senior Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Griffin:

Reference is made to your February 21, 2019, Proposed Pediatric Study Request for Brilinta (ticagrelor).

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.

- *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 I, 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 up to 6 hours post dose (1, 2, 4, and 6 hours post dose) from each patient.

Study 2: D5136C00009 (HESTIA3)

This is a Phase III, 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 randomize at least 182 patients (1:1) to receive ticagrelor or matching placebo at least 12 months. Hydroxyurea and L-glutamine as background treatment will be allowed.

Study 3: D5136C00013 (HESTIA5)

This is a Phase III, 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.

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.

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.

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 AUC_{inf}.

Secondary endpoints are 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 AUC_{inf}, 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.

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

- *Safety Endpoints:*

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) will 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 for both Phase III studies.

- *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.

- *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 (approximately 6 mm in diameter).

  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.

- *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.

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.

Randomization period: Patients aged 6 months to < 18 years will receive ticagrelor doses with dose selection for patients < 24 kg will be determined based upon information from the PK study for all patients in Study D5136C0010. 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.

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

Studies 2 and 3: D5136C00009 (HESTIA3) and D5136C00013 (HESTIA5)

Your sample size for each 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.

You must adequately control the study-wise type I error rate for any secondary endpoints intended for inclusion in labeling using appropriate pre-specified methods.

- *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).

- *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 July 2023. 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 study(ies), 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.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please 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, *Dissemination of Pediatric Information*, 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 circumstances:

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

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Beatrice Kallungal, Senior Regulatory Health Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

Greg Reaman, MD
Associate Director for Oncology Services
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/

GREGORY H REAMAN
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