DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207620

WRITTEN REQUEST – AMENDMENT 1

Novartis Pharmaceuticals Corp.
Attention: Amol Parekh, PharmD
Sr. Global Program Regulatory Manager
One Health Plaza
Building 315, Room 5250A
East Hanover, NJ 07936

Dear Dr. Parekh:

Please refer to your correspondence dated May 29, 2018, requesting changes to FDA's March 2, 2017 Written Request for pediatric studies for sacubitril/valsartan.

We have reviewed your proposed changes and are amending several sections of the Written Request as noted in the attached document (see red-lined version).

All other terms stated in our Written Request issued on March 2, 2017 remain the same.

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 March 2, 2017, as amended by this letter, must be submitted to the Agency on or before April 29, 2022, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved 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- the status of the application (i.e., withdrawn after the supplement has been filed or pending);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 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

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, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Modifications to Written Request (red-lined version)
Complete Copy of Written Request as Amended (clean version)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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NDA 207620

WRITTEN REQUEST – AMENDMENT 1

Novartis Pharmaceuticals Corp.
Attention: Amol Parekh, PharmD
Sr. Global Program Regulatory Manager
One Health Plaza
Building ~~100~~315, Room ~~130A~~5250A
East Hanover, NJ 07936

Dear Dr. Parekh:

Reference is made to your August 19, 2016 Proposed Pediatric Study Request for ENTRESTO (sacubitril/valsartan) Tablets.

BACKGROUND:
This two-part study investigates the potential use of sacubitril/valsartan in the treatment of pediatric patients from 1 ~~month~~ to <18 years of age with heart failure due to systemic left ventricular systolic dysfunction~~–~~, consistent with dilated cardiomyopathy (DCM).

Pediatric heart failure (HF) is associated with significant morbidity and mortality and poor quality of life. Approximately 12,000 to 35,000 children below 19 years of age are diagnosed with HF in the United States (US) each year, with congenital heart disease and cardiomyopathy being the two most common causes. For patients with congenital heart disease, corrective surgery can have a major impact on the clinical course, although HF can still develop for a number of reasons. Patients with severe HF can undergo heart transplant; however, cardiac transplantation is usually a last resort given the limited availability of donor organs and the associated morbidity and mortality. To date, few clinical trials have been conducted in pediatric patients with heart failure, and no trial has demonstrated a clear benefit of any pharmacotherapy. As a result, there are no approved therapies for pediatric HF and there remains significant unmet medical need.

~~The common causes and mechanisms of heart failure are different in children (congenital malformations and cardiomyopathy) compared with adults (ischemic heart disease). Hence, efficacy in pediatric patients from 1 month to <18 years of age cannot be extrapolated and will be determined by the studies outlined in the Written Request.~~ Adults with heart failure due to reduced ejection fraction (HFrEF) and DCM, not due to etiologies such as hypertension, diabetes mellitus, and coronary artery disease, demonstrate similarity to pediatric HF patients with left ventricular systolic dysfunction in the context of DCM. This disease similarity, in conjunction with data supporting the use of NT-proBNP to bridge the clinical efficacy of sacubitril/valsartan in adults to pediatric patients, allows for a partial extrapolation approach to determine sacubitril/valsartan's efficacy in pediatric patients from 1 to <18

years of age using NT-proBNP as a bridging biomarker. Infants <1 year old are not required because of the rarity of pediatric HF diagnosis in this age group. Because of concerns with the potential impact of renin-angiotensin system blockade on kidney development, studies are not requested in ~~children~~ <neonates (< 1 month of age~~.~~).

To obtain needed pediatric information on sacubitril/valsartan, 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. Patients enrolled in Part 2 of the study will continue in their assigned treatment arms for 52 weeks to characterize the treatment effect on an agreed-upon global rank endpoint, derived from five categories including clinical events and functional status, and to capture longer-term safety data on known and/or unexpected adverse reactions. Submission of the 52-week study data would not be needed to fulfill the Written Request. However, the study would need to be initiated and an interim clinical study report with datasets containing at least 12 weeks of evaluable safety and efficacy data must be submitted to fulfill the Written Request.

- *Nonclinical study(ies)*:

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

- *Clinical study:*

  Part 1: A multi-center, open~~-~~-label study in pediatric patients with heart failure due to systemic left ventricular systolic dysfunction, consistent with DCM to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of more than one dose strength of sacubitril/valsartan.

  Part 2: A double-blind, randomized, multi-center, active-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of sacubitril/valsartan compared to enalapril in pediatric patients with heart failure due to systemic left ventricular systolic dysfunction, consistent with DCM.

  The eldest age group will be the first cohort of Part 1. Results for each age cohort in Part 1 must be reviewed and doses for each age cohort in Part 2 must be agreed upon by the Agency before enrollment may begin for that age cohort into Part 2. Enrollment into the successive younger cohorts in Part 1 may continue in parallel with FDA review.

  In Part 2 of the study, clinical efficacy in pediatric patients is to be evaluated by NT-proBNP change from baseline to Week 12, relative to control. Follow-up for safety is to continue until at least 100 enrolled subjects have completed the Week 12 assessment.

- *Objective of study:*

The primary objective of Part 1 is to determine the PK and PD of sacubitril/valsartan in pediatric heart failure patients due to systemic left ventricular systolic dysfunction, consistent with DCM.

The ~~primary~~ objective of a bridging biomarker interim analysis in Part 2 is to ~~determine whether~~ evaluate efficacy by determining the NT-proBNP change from baseline at Week 12 of sacubitril/valsartan ~~is superior to~~versus enalapril for the treatment of heart failure in pediatric heart failure patients due to systemic left ventricular systolic dysfunction, consistent with DCM.

- *Patients to be Studied:*

  - *Age group in which study will be performed*:

    The study must enroll pediatric patients aged 1 ~~month~~ to ~~less than~~< 18 years.

  - *Number of patients to be studied:*

    Part 1 must enroll a minimum of 16 subjects with at least six subjects in Group 1~~,~~ and six subjects in Group 2~~, and four subjects in Group 3.~~. Half of the minimum required subjects in Group 1 must be 6 to 11 years of age.

    Group 1: 6 to < 18 years
    Group 2: 1 to < 6 years
    ~~Group 3: 1 month to <1 year~~

    For Part 1, enrollment must be staggered starting with Group 1. Results from Part 1 must be reported to and reviewed by the Agency and agreement must be reached with the Agency on doses to be used in Part 2 before sequential initiation of each successively younger age group in Part 2. If the information from an age group in Part 1 is insufficient to inform dosing for Part 2, additional subjects from that age group must be enrolled in Part 1.

    Part 2 must enroll ~~a minimum of 360~~at least 100 subjects (1 to < 18 years old) with ~~at least 72 subjects (20%) per age group.~~balanced distribution in each treatment arm.

    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:*
  - *Pharmacokinetic/Pharmacodynamic Endpoints:*

    For Part 1, the pharmacokinetic and pharmacodynamic endpoints after single dose treatment will include:
    - PK: C_{max} (ng/mL); T_{max}(h); AUC_{last}, AUC_{inf} (h▪ng/mL); Cl/F (L/h); $T_{1/2}$ (h)

- PD: plasma cyclic guanosine monophosphate (cGMP), urine cGMP, plasma B-type natriuretic peptide (BNP), plasma N-terminal pro B-type natriuretic peptide (NT-proBNP)

- *Efficacy Endpoints;*

  For Part 2, the ~~primary~~biomarker interim analysis efficacy endpoint will be ~~a global ranked endpoint based~~NT-proBNP change from baseline at Week 12. Descriptive efficacy, including data on the following events: death; UNOS Status 1A listing for heart transplant or equivalent; ventricular assist device (VAD)/extracorporeal membrane oxygenation (ECMO)/mechanical ventilation/intra-aortic balloon pump requirement for life support ~~at end of study~~; worsening heart failure; and measures of functional status ~~and quality of life.~~ will be provided.

- *Safety Endpoints:*

  The study must be well-designed to actively monitor for and capture safety outcomes of interest including hypotension, hyperkalemia, renal impairment, angioedema, and liver toxicity.

  A Data Monitoring Committee (DMC) must be included because findings at an interim analysis may require termination of the study before its planned completion ~~for reasons of ethics.~~. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees ~~http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf~~http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *Known Drug Safety concerns and monitoring:*

  Based on the safety concerns identified in studies of sacubitril/valsartan in adults, subjects must be monitored for hypotension, hyperkalemia, renal impairment, and angioedema.

  Based on potential safety concerns identified in studies of valsartan in children, subjects must be monitored for liver toxicity.

- *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*

The dosage form must include an age-appropriate formulation.

- *route of administration*

  The route of administration will be oral.

- *regimen*

  The regimen will be agreed upon in the protocol.

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation 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., it 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.

  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:*

  In Part 1 of the study, descriptive statistics will be provided for the specified pharmacokinetic and pharmacodynamic endpoints.

  ~~In Part 2 of the study, the primary analysis method will be a stratified Wilcoxon rank-sum test on the fully ranked data for the primary endpoint. The trial should be designed with at least 80% power with a type 1 error rate of 0.05 (two-sided) for the global rank endpoint assuming the Mann-Whitney odds is 0.65. The study must continue until a minimum of 80 subjects experience a Category 1 (death; UNOS Status 1A listing for heart transplant or equivalent; VAD/ECMO/ mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study) or Category 2 (worsening heart failure) event. The protocol should clearly state how subjects with missing data will be analyzed. You must conduct a penalty-free interim analysis near the end of the study to determine the number of tied ranks and the number of Category 1 and 2 events and adjust the sample size and/or duration of follow-up accordingly.~~

~~A detailed statistical analysis plan must be submitted prior to initiating Part 2 and agreement must be obtained with the Agency prior to 25% enrollment in Part 2.~~
In Part 2 of the study, the NT-proBNP interim analysis method must be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance of the NT-proBNP change from baseline to Week 12, relative to control. The interim analysis is designed with at least 80% statistical power with a Type 1 error rate of 0.05 (two-sided), if the true effect size is 30%. The statistical analysis plan (SAP) must be submitted to the FDA for review and agreement prior to the interim analysis. The SAP must prespecify methods to handle missing data for the biomarker interim analysis efficacy endpoint.

- *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 sacubitril/valsartan 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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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 http://www.fda.gov/Cder/guidance/7087rev.htmhttp://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before April 29, 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 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

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, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
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Novartis Pharmaceuticals Corp.
Attention: Amol Parekh, PharmD
Sr. Global Program Regulatory Manager
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Dear Dr. Parekh:

Reference is made to your August 19, 2016 Proposed Pediatric Study Request for ENTRESTO (sacubitril/valsartan) Tablets.

BACKGROUND:
This two-part study investigates the potential use of sacubitril/valsartan in the treatment of pediatric patients from 1 to <18 years of age with heart failure due to systemic left ventricular systolic dysfunction, consistent with dilated cardiomyopathy (DCM).

Pediatric heart failure (HF) is associated with significant morbidity and mortality and poor quality of life. Approximately 12,000 to 35,000 children below 19 years of age are diagnosed with HF in the United States (US) each year, with congenital heart disease and cardiomyopathy being the two most common causes. For patients with congenital heart disease, corrective surgery can have a major impact on the clinical course, although HF can still develop for a number of reasons. Patients with severe HF can undergo heart transplant; however, cardiac transplantation is usually a last resort given the limited availability of donor organs and the associated morbidity and mortality. To date, few clinical trials have been conducted in pediatric patients with heart failure, and no trial has demonstrated a clear benefit of any pharmacotherapy. As a result, there are no approved therapies for pediatric HF and there remains significant unmet medical need.

Adults with heart failure due to reduced ejection fraction (HFrEF) and DCM, not due to etiologies such as hypertension, diabetes mellitus, and coronary artery disease, demonstrate similarity to pediatric HF patients with left ventricular systolic dysfunction in the context of DCM. This disease similarity, in conjunction with data supporting the use of NT-proBNP to bridge the clinical efficacy of sacubitril/valsartan in adults to pediatric patients, allows for a partial extrapolation approach to determine sacubitril/valsartan's efficacy in pediatric patients from 1 to <18 years of age using NT-proBNP as a bridging biomarker. Infants <1 year old are not required because of the rarity of pediatric HF diagnosis in this age group. Because of concerns with the potential impact of renin-angiotensin system blockade on kidney development, studies are not requested in neonates (< 1 month of age).

To obtain needed pediatric information on sacubitril/valsartan, 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. Patients enrolled in Part 2 of the study will continue in their assigned treatment arms for 52 weeks to characterize the treatment effect on an agreed-upon global rank endpoint, derived from five categories including clinical events and functional status, and to capture longer-term safety data on known and/or unexpected adverse reactions. Submission of the 52-week study data would not be needed to fulfill the Written Request. However, the study would need to be initiated and an interim clinical study report with datasets containing at least 12 weeks of evaluable safety and efficacy data must be submitted to fulfill the Written Request.

- *Nonclinical study(ies)*:

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

- *Clinical study:*

  Part 1: A multi-center, open-label study in pediatric patients with heart failure due to systemic left ventricular systolic dysfunction, consistent with DCM to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of more than one dose strength of sacubitril/valsartan.

  Part 2: A double-blind, randomized, multi-center, active-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of sacubitril/valsartan compared to enalapril in pediatric patients with heart failure due to systemic left ventricular systolic dysfunction, consistent with DCM.

  The eldest age group will be the first cohort of Part 1. Results for each age cohort in Part 1 must be reviewed and doses for each age cohort in Part 2 must be agreed upon by the Agency before enrollment may begin for that age cohort into Part 2. Enrollment into the successive younger cohorts in Part 1 may continue in parallel with FDA review.

  In Part 2 of the study, clinical efficacy in pediatric patients is to be evaluated by NT-proBNP change from baseline to Week 12, relative to control. Follow-up for safety is to continue until at least 100 enrolled subjects have completed the Week 12 assessment.

- *Objective of study:*

  The primary objective of Part 1 is to determine the PK and PD of sacubitril/valsartan in pediatric heart failure patients due to systemic left ventricular systolic dysfunction, consistent with DCM.

  The objective of a bridging biomarker interim analysis in Part 2 is to evaluate efficacy by determining the NT-proBNP change from baseline at Week 12 of sacubitril/valsartan versus

enalapril for the treatment of heart failure in pediatric heart failure patients due to systemic left ventricular systolic dysfunction, consistent with DCM.

- *Patients to be Studied:*

  - *Age group in which study will be performed*:

    The study must enroll pediatric patients aged 1 to < 18 years.

  - *Number of patients to be studied:*

    Part 1 must enroll a minimum of 16 subjects with at least six subjects in Group 1 and six subjects in Group 2. Half of the minimum required subjects in Group 1 must be 6 to 11 years of age.

    Group 1: 6 to < 18 years
    Group 2: 1 to < 6 years

    For Part 1, enrollment must be staggered starting with Group 1. Results from Part 1 must be reported to and reviewed by the Agency and agreement must be reached with the Agency on doses to be used in Part 2 before sequential initiation of each successively younger age group in Part 2. If the information from an age group in Part 1 is insufficient to inform dosing for Part 2, additional subjects from that age group must be enrolled in Part 1.

    Part 2 must enroll at least 100 subjects (1 to < 18 years old) with balanced distribution in each treatment arm.

    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:*
  - *Pharmacokinetic/Pharmacodynamic Endpoints:*

    For Part 1, the pharmacokinetic and pharmacodynamic endpoints after single dose treatment will include:
    - PK: C_{max} (ng/mL); T_{max}(h); AUC_{last}, AUC_{inf} (h▪ng/mL); Cl/F (L/h); $T_{1/2}$ (h)
    - PD: plasma cyclic guanosine monophosphate (cGMP), urine cGMP, plasma B-type natriuretic peptide (BNP), plasma N-terminal pro B-type natriuretic peptide (NT-proBNP)

  - *Efficacy Endpoints;*

    For Part 2, the biomarker interim analysis efficacy endpoint will be NT-proBNP change from baseline at Week 12. Descriptive efficacy, including data on the following events:

death; UNOS Status 1A listing for heart transplant or equivalent; ventricular assist device (VAD)/extracorporeal membrane oxygenation (ECMO)/mechanical ventilation/intra-aortic balloon pump requirement for life support; worsening heart failure; and measures of functional status will be provided.

- *Safety Endpoints:*

  The study must be well-designed to actively monitor for and capture safety outcomes of interest including hypotension, hyperkalemia, renal impairment, angioedema, and liver toxicity.

  A Data Monitoring Committee (DMC) must be included because findings at an interim analysis may require termination of the study before its planned completion. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *Known Drug Safety concerns and monitoring:*

  Based on the safety concerns identified in studies of sacubitril/valsartan in adults, subjects must be monitored for hypotension, hyperkalemia, renal impairment, and angioedema.

  Based on potential safety concerns identified in studies of valsartan in children, subjects must be monitored for liver toxicity.

- *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*

    The dosage form must include an age-appropriate formulation.

  - *route of administration*

    The route of administration will be oral.

  - *regimen*

    The regimen will be agreed upon in the protocol.

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation 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., it 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.

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:*

  In Part 1 of the study, descriptive statistics will be provided for the specified pharmacokinetic and pharmacodynamic endpoints.

  In Part 2 of the study, the NT-proBNP interim analysis method must be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance of the NT-proBNP change from baseline to Week 12, relative to control. The interim analysis is designed with at least 80% statistical power with a Type 1 error rate of 0.05 (two-sided), if the true effect size is 30%. The statistical analysis plan (SAP) must be submitted to the FDA for review and agreement prior to the interim analysis. The SAP must prespecify methods to handle missing data for the biomarker interim analysis efficacy endpoint.

- *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 sacubitril/valsartan 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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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 http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before April 29, 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 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

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, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, MD
Director
Office of Drug Evaluation I
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/

ELLIS F UNGER
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