DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206143
(b) (4)

WRITTEN REQUEST – AMENDMENT 1

Amgen, Inc.
Attention: Christine Kubik
Senior Manager, Regulatory Affairs
601 13th St., NW, 12th Floor
Washington, DC 20005

Dear Ms. Kubik:

Please refer to your correspondence dated December 20, 2017, requesting changes to FDA's September 27, 2017 Written Request for pediatric studies for ivabradine.

We have reviewed your proposed changes and are amending the below-listed section of the Written Request. All other terms stated in our Written Request issued on September 27, 2017 remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

Timeframe for submitting reports of the study:
Reports of the above studies must be submitted to the Agency on or before ~~March 31, 2018~~ January 15, 2019. 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.

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 September 27, 2017 as amended by this letter, must be submitted to the Agency on or before January 15, 2019 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 addition, send a copy of the cover letter of your submission via fax (240-276-9327) or messenger, to:

Director, Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773

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 Ms. Meg Pease-Fye, MS, RAC (US), Senior Regulatory Project Manager, at (301) 796 1130.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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WRITTEN REQUEST

Amgen Inc.
Attention: Christine Kubik
Senior Manager, Regulatory Affairs
601 13th St, NW
12th floor
Washington, DC 20005

Dear Ms. Kubik:

Reference is made to your correspondence dated May 12, 2017, requesting changes to FDA's February 12, 2016 Written Request for pediatric studies for ivabradine. Because this correspondence was received after the study submission date of December 30, 2016, a new Written Request is being issued that extends the timeframe for reporting these studies to March 31, 2018. Please refer to your correspondence dated December 20, 2017, requesting changes to FDA's September 27, 2017 Written Request for pediatric studies for ivabradine.

While the majority of heart failure in pediatric patients is caused by congenital heart disease, the Division acknowledges the uncommon occurrence of dilated cardiomyopathy (DCM) in children that likely shares phenotypic, and in some cases genotypic overlap with non-ischemic heart failure with reduced ejection fraction (HFrEF) in adults. The SHIFT trial demonstrated clinical benefits to adult patients with non-ischemic HFrEF, and the Division agrees that some children with DCM may benefit from this therapy as well. Accordingly, it is in the interest of US public health that your recently completed clinical trial in children with DCM be submitted for the review of this agency for the purpose of potentially making this therapy available to US pediatric DCM patients.

To obtain needed pediatric information for ivabradine, 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 following study (protocol and final study report):

- Determination of the efficacious and safe dose of ivabradine in pediatric patients with dilated cardiomyopathy and symptomatic chronic heart failure aged from 6 months to less than 18 years. A randomized, double-blind, multicenter, placebo controlled, phase II/III dose-finding study with a PK/PD characterization and a 1 year efficacy/safety evaluation.

Background

The PK/PD trial that you have recently completed outside of the United States investigates the potential use of ivabradine in the treatment of pediatric DCM, according to the Pediatric Investigational Plan (PIP) for the EU, and incorporates a pediatric formulation (b) (4) that was assessed for relative bioavailability.

Dilated cardiomyopathy (DCM) in children is a serious intrinsic disease of the heart muscle that results in systolic dysfunction. In children without congenital heart defect, dilated cardiomyopathy (DCM) is the most prevalent cause of heart failure (HF), but the overall incidence of DCM is uncommon at 44 per million per year in North American infants younger than 1 year and 3.4 per million per year in children between 1 and 18 years of age.[1] Pediatric DCM results in 1- and 5-year rates of death or transplantation of 31% and 46% respectively. Despite the best available therapies including diuretics, angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, DCM remains the primary reason for cardiac transplantation in children. The Division agrees that there is a substantial unmet medical need in this population to delay the time to hospitalization for worsening heart failure and the time to transplant.

Ivabradine is an inhibitor of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarization in the sinus node resulting in a heart rate (HR) lowering effect. It is approved in Europe for adults with angina or heart failure with reduced ejection fraction (HFrEF). The HFrEF indication was supported by the SHIFT trial, in adult patients with stable moderate to severe symptoms of CHF (class II to IV NYHA), LV systolic dysfunction (left ventricular ejection fraction [LVEF] $\leq$ 35%), HR $\geq$ 70 bpm and receiving a therapeutic regimen for CHF based on current guidelines, including beta-blockers. The primary endpoint was the composite of cardiovascular death or hospital admission for worsening heart failure (HF).

Relevant to the pediatric DCM population, approximately 32% of the adult patients in SHIFT had non-ischemic HFrEF. Though multiple etiologies may produce the non-ischemic HFrEF/DCM phenotypes in adults and children, in the absence of toxic drug effects or alcohol-induced myopathy, non-ischemic HFrEF/DCM in adults and DCM in children share many pathophysiologic and phenotypic similarities. Thus, we accept your hypothesis that if children with DCM have the same reduction in heart rate with ivabradine treatment as demonstrated in adults, it is reasonable to extrapolate efficacy to the pediatric population supported with a pediatric study demonstrating safety and effectiveness. The Division agrees that adult data from SHIFT should not be extrapolated to neonates and young infants (< 6 months) because this subset of patients may be disproportionately dependent on heart rate to maintain cardiac output (small stroke volume, immature sympathetic nervous system, low proportion of contractile myocardium).

Required Study

To obtain needed pediatric information on ivabradine, 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

[1] Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006;296:1867-1876.

of 2007, that you submit information from the study described below. Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- Clinical study:
  A randomized, double-blind, placebo-controlled, multicenter PK/PD and dose-finding study in pediatric patients 6 months to less than 18 years of age to demonstrate effectiveness and obtain safety information.
  - *Objectives of study*

    Primary objectives are to determine the optimal dose of ivabradine to reach the target heart rate reduction of 20%, without inducing bradycardia (i.e., heart rate should be greater than a predefined heart rate threshold by age subset) and/or signs or symptoms related to bradycardia, to assess the pharmacokinetic parameters of ivabradine and its active metabolite S 18982 after repeated oral administrations, and to assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship of ivabradine and its active metabolite S 18982 using heart rate as the evaluation criterion, as well as obtaining information on safety.

    Secondary objectives are to compare to placebo the effects of ivabradine at target dose on LVEF, left ventricular (LV) shortening fraction, LV end-systolic volume, LV end-diastolic volume, heart rate, HF functional classification (NYHA or Ross), global clinical status, growth (weight and height), cardiovascular biomarker NT-proBNP, and long-term (1 year) safety of ivabradine. An additional objective of an ancillary substudy is to assess quality of life.
  - *Patients Studied:*

    Pediatric subjects age 6 months to less than 18 years divided into three age groups:

    6 – <12 months
    1 – <3 years
    3 – <18 years
  - *Number of patients studied:*

    At least 90 patients (randomized 2:1for ivabradine:placebo), with the following minimums per age group:
    - At least 10 patients in age-subset 6 months to less than 12 months
    - At least 30 patients in age-subset 1 to less than 3 years
    - At least 30 patients in age-subset 3 to less than 18 years
  - *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:*
  - Primary endpoints:
    - Characterization of PK parameters of ivabradine (S 16257) and S 18982 (active metabolite) plasma concentrations and corresponding heart rate values
    - Target heart rate achieved - achievement of a heart rate reduction from baseline of at least 20% without inducing a bradycardia and/or signs or symptoms related to bradycardia.
  - Secondary endpoints of efficacy:
    - Echocardiographic parameters (LVEF, left ventricular shortening fraction, left ventricular end-systolic volume, left ventricular end-diastolic volume)
    - Heart failure symptoms severity assessed by the NYHA or Ross classification
    - Global clinical status evaluated by the investigator/parents
    - Weight and height
    - Cardiovascular biomarker NT- proBNP
  - Secondary endpoints of safety
    - Long-term (at least 1 year) safety of ivabradine in each age group and for the trial overall, to include analyses of all-cause mortality, CV mortality, Arrhythmic mortality, heart failure mortality, all-cause hospitalization, CV hospitalization, arrhythmic hospitalization, hospitalization for worsening heart failure, and the composite endpoint that was used in SHIFT (CV mortality and hospitalization for worsening heart failure).
    - Occurrence of bradycardia
    - 12-lead ECG parameters
    - Vital signs and adverse events
    - Clinical laboratory examination

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

  In this study , six subjects ages 6 to 12 months, 20 subjects ages 1 to 3 years, and 20 subjects ages 3 to <18 years treated with ivabradine were considered to be sufficient to assess the primary endpoint, the PK/PD characteristics in the pediatric population. Taking into account a randomization ratio of 2:1 for ivabradine:placebo, stratified by each age subset, at least 90 evaluable children were planned to be enrolled in the study (n= 60 for ivabradine group, n=30 for placebo group), including ≥ 10 infants ages 6 to 12 months, ≥ 30 infants and children ages 1 to 3 years, and ≥ 30 children and adolescents ages 3 to <18 years. Descriptive statistics of plasma concentration-time data of ivabradine and its active metabolite as well as descriptive statistics of heart rate at rest should be presented at each time point for the entire study population and by age subgroup. The safety analyses should be performed on all subjects who received ≥ 1 dose of investigational product and by age subgroup. Treatment-emergent adverse events, ECG parameters, blood pressures, and laboratory parameters should be summarized using descriptive statistics.

A detailed analysis of the electrocardiographic findings in each age group, and for the overall pediatric population, must be included with the final study report and datasets that you submit. Age-specific effects of ivabradine on the QT and the QTc should be described in detail.

A detailed analysis of mortality and hospitalization should be included, as described above.

Known Drug Safety concerns and monitoring:
Carefully monitor for bradycardia, QT/QTc prolongation, and the occurrence of worsening heart failure.

Extraordinary results:
In the course of conducting this study, 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:
(b) (4)

Pediatric Formulation:
If the pediatric formulation that you are tested in your clinical PK/PD study is found safe and effective in the studied pediatric population, 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 compounded 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 compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding 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.

***Labeling that may result from the study*:**
You must submit proposed pediatric labeling to incorporate the findings of the above-noted studies. Under section 505A(j) of the Act, regardless of whether the clinical study demonstrates that ivabradine 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 studies. 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.

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 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 FDA website at: 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:
Reports of the above studies must be submitted to the Agency on or before ~~March 31, 2018~~ January 15, 2019. 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, call Meg Pease-Fye, MSc., RAC (U.S.), Sr. Regulatory Project Manager, at (301) 796-1130.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
01/31/2018