DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22527

WRITTEN REQUEST – AMENDMENT #1

Novartis Pharmaceutical Corporation
Attention: Mara Stiles
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to your correspondence dated November 6, 2015, requesting changes to FDA's March 20, 2013, Written Request for pediatric studies for Gilenya (fingolimod).

In summary, we agree with your plan to introduce a flexible duration into your pediatric study design for study D2311. We agree that, based on your blinded assessment of relapses in the current trial, you can reduce the amount of time certain subjects are in the trial, but maintain the required power of 80% to detect a 50% relative treatment effect on the annualized relapse rate. We also agree with your plan to conduct another blinded assessment of relapses in the first half of 2017, and if the blinded sample size re-estimation based on the relapse units observed is below what is needed to maintain 80% power for the primary analysis, the trial will not stop in June, 2017, but instead will continue so that all patients are enrolled for a minimum of 2 years, as originally planned.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 20, 2013, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

- Reference is made to your July 23, 2012, Proposed Pediatric Study Request for Gilenya (fingolimod), our Written Request issued March 20, 2013, and your November 6, 2015, Formal request to amend the Gilenya Written Request.~~.~~

  Multiple sclerosis (MS) is an illness that affects approximately 2.5 million individuals worldwide. Although MS generally affects young adults, it can present in childhood and adolescence. The true incidence of pediatric MS is unknown, yet it is estimated that 2-5% of patients diagnosed with MS present in childhood and that most of these cases occur at or after the age of 10. For this reason, neonates and pediatric patients less than 10 years will not be studied. Although other products approved for the treatment of MS in adults are used off label in pediatric patients, to date there has been no prospective controlled clinical study evaluating the efficacy and safety of these products in pediatric MS patients. An adequate and well controlled ~~two year~~ trial evaluating the safety and

efficacy of fingolimod in pediatric MS would provide much needed data about the risks and benefits associated with the use of fingolimod in pediatric patients. It is premature to extrapolate efficacy from the adult experience with fingolimod to pediatric MS patients, as there are phenotypic differences between pediatric MS and adult MS, as well as differences in immune responses between pediatric and adult patients. Standard medical practice includes using off-label beta interferons as first line therapy in pediatric MS patients, therefore, the use of this active comparator is appropriate. Because fingolimod is an oral product and interferon beta-1a must be given by injection, children randomized to fingolimod in the proposed trial would receive weekly placebo injections to maintain blinding. Because there is no prospect of direct (medical) benefit to children enrolled in the placebo arm, the repeated placebo injections would need to be considered a minor increase over minimal risk under 21 CFR 50.53 for the study to be approved by local institutional review boards.

- Study 1: Pediatric efficacy and safety trial: A ~~two year~~ multicenter, randomized, double-blind, double-dummy, active-controlled study to evaluate the efficacy and safety of fingolimod administered orally once daily versus interferon (IFN) beta-1a administered once weekly in pediatric patients with MS. This study must be designed to show superiority of fingolimod over the active comparator.

  Pharmacokinetic sampling must take place in all patients weighing 40 kg or less. ~~There must be a minimum of six patients weighing less than 40kg with evaluable PK data.~~

- *Patients to be studied*

  Male and female patients age 10 to 17 years. ~~Pediatric patients must be approximately evenly distributed across ages.~~ A sufficient number of both sexes of pediatric patients with at least 25% males need to be enrolled. ~~At~~ Approximately ~~least~~ 10%~~20%~~ of patients enrolled should be ~~pre-pubertal~~12 and under.

- *Study endpoints*

  Efficacy Endpoints:
  - The primary efficacy endpoint must be the annualized relapse rate, defined as the average number of confirmed clinical relapses per year.
  - Secondary endpoints must include:
    - ~~number~~ annualized rate (number of lesions per year) of new or newly enlarged T2 lesions ~~over 24 months~~ on MRI.
    - number of T1 gadolinium-enhancing lesions ~~over 24 months~~per scan on MRI.
    - time to first relapse.
  - proportion of patients relapse-free.
  - Measures of compliance must include capsule counts or counts of syringes at each visit.

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

  The trial must enroll a sufficient number of patients to have at least 80% power to detect a 50% reduction in the primary endpoint assuming a two-sided type 1 error rate of 5%. A minimum of 60 patients will be exposed for at least one year in the controlled portion of the trial. The primary analysis population will consist of the set of patients who are randomized and have taken at least one dose of their randomized treatment. You must pre-specify one or more methods for the treatment of missing data for patients who do not complete the trial. Randomization should be stratified by pubertal status. If the randomization is stratified by pubertal status, the analysis of the primary endpoint should incorporate pubertal status as a fixed effect in the statistical model if possible (i.e. if both strata are sufficiently populated).~~.~~

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 20, 2013, as amended by this letter must be submitted to the Agency on or before November 15, 2017, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission [**DRUGS**], via fax (240-276-9327) or messenger, to the 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, call Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I, HFD-120
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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WRITTEN REQUEST

Novartis Pharmaceutical Corporation
Attention: Mara Stiles
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Reference is made to your July 23, 2012, Proposed Pediatric Study Request for Gilenya (fingolimod), our Written Request issued March 20, 2013, and your November 6, 2015, Formal request to amend the Gilenya Written Request.

Multiple sclerosis (MS) is an illness that affects approximately 2.5 million individuals worldwide. Although MS generally affects young adults, it can present in childhood and adolescence. The true incidence of pediatric MS is unknown, yet it is estimated that 2-5% of patients diagnosed with MS present in childhood and that most of these cases occur at or after the age of 10. For this reason, neonates and pediatric patients less than 10 years will not be studied. Although other products approved for the treatment of MS in adults are used off label in pediatric patients, to date there has been no prospective controlled clinical study evaluating the efficacy and safety of these products in pediatric MS patients. An adequate and well controlled trial evaluating the safety and efficacy of fingolimod in pediatric MS would provide much needed data about the risks and benefits associated with the use of fingolimod in pediatric patients. It is premature to extrapolate efficacy from the adult experience with fingolimod to pediatric MS patients, as there are phenotypic differences between pediatric MS and adult MS, as well as differences in immune responses between pediatric and adult patients. Standard medical practice includes using off-label beta interferons as first line therapy in pediatric MS patients, therefore, the use of this active comparator is appropriate. Because fingolimod is an oral product and interferon beta-1a must be given by injection, children randomized to fingolimod in the proposed trial would receive weekly placebo injections to maintain blinding. Because there is no prospect of direct (medical) benefit to children enrolled in the placebo arm, the repeated placebo injections would need to be considered a minor increase over minimal risk under 21 CFR 50.53 for the study to be approved by local institutional review boards.

To obtain needed pediatric information on fingolimod, the Food and Drug Administration (FDA) is hereby making a formal Written Request (WR), 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.

Nonclinical study:

A juvenile animal toxicology study in rat has been submitted; therefore, no additional animal studies are required at this time to support the clinical studies described in this written request.

Clinical studies:

Study 1: Pediatric efficacy and safety trial: A multicenter, randomized, double-blind, double-dummy, active-controlled study to evaluate the efficacy and safety of fingolimod administered orally once daily versus interferon (IFN) beta-1a administered once weekly in pediatric patients with MS. This study must be designed to show superiority of fingolimod over the active comparator.

Pharmacokinetic sampling must take place in all patients weighing 40 kg or less.

- *Objective of each study*

  Study 1: To evaluate the efficacy of fingolimod, relative to IFN beta-1a, in reducing the frequency of relapses in pediatric MS patients age 10 to 17 years.

- *Secondary objectives*

  1) To evaluate the safety of fingolimod in pediatric MS patients.
  2) To evaluate the effect of fingolimod on the time to first relapse and the proportion of patients relapse free in pediatric MS patients.
  3) To evaluate the effect of fingolimod on T1 gadolinium-enhancing lesions on brain MRI in pediatric MS patients.
  4) To study the pharmacokinetics of fingolimod in pediatric MS patients.

- *Patients to be studied*

  Male and female patients age 10 to 17 years. A sufficient number of both sexes of pediatric patients with at least 25% males need to be enrolled. Approximately 10% of patients enrolled should be 12 and under.

- *Representation of Ethnic and Racial Minorities*

  The studies must take into account an adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.

- *Study endpoints*

  Efficacy Endpoints:
  - The primary efficacy endpoint must be the annualized relapse rate, defined as the average number of confirmed clinical relapses per year.
  - Secondary endpoints must include:
    - annualized rate (number of lesions per year) of new or newly enlarged T2 lesions on MRI.
    - number of T1 gadolinium-enhancing lesions per scan on MRI.
    - time to first relapse.
  - proportion of patients relapse-free.
  - Measures of compliance must include capsule counts or counts of syringes at each visit.

  Safety Endpoints:
  - Safety monitoring must include: adverse events, concomitant medications, ECG, vital signs, hematology, blood chemistry, urinalysis, growth parameters and development (Tanner stage) and serum pregnancy tests in all menarchal females.
  - The following adverse events must be actively monitored: bradycardia and/or AV block with the first dose, pulmonary function abnormalities, impaired vision (macular edema), and hepatic dysfunction. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
  - A Data Monitoring Committee (DMC) must be included to oversee the study and perform ongoing review of safety specifically in terms of cardiac events, pulmonary events, infection, macular edema, lymphopenia, hepatic dysfunction, or any other unexpected adverse events.

    See Guidance: *Establishment and Operation of Clinical Trial Data Monitoring Committees,* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

- *Known drug safety concerns and monitoring*

  Bradycardia with the first dose, AV block, diminished pulmonary function, increased lower respiratory infections, macular edema, lymphopenia, and hepatic effects.

- *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: capsule
    - Route of administration: oral
    - Regimen: 0.5 mg capsule once daily for patients weighing 40 kg or over, and 0.25 mg capsule once daily for patients weighing under 40 kg.

Use an age-appropriate formulation in the study 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 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.

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

The trial must enroll a sufficient number of patients to have at least 80% power to detect a 50% reduction in the primary endpoint assuming a two-sided type 1 error rate of 5%. A

minimum of 60 patients will be exposed for at least one year in the controlled portion of the trial. The primary analysis population will consist of the set of patients who are randomized and have taken at least one dose of their randomized treatment. You must pre-specify one or more methods for the treatment of missing data for patients who do not complete the trial. Randomization should be stratified by pubertal status. If the randomization is stratified by pubertal status, the analysis of the primary endpoint should incorporate pubertal status as a fixed effect in the statistical model if possible (i.e. if both strata are sufficiently populated).

- *Labeling that may result from the study*

  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 fingolimod 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.

- *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 FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf.

- *Timeframe for submitting reports of the study*

  Reports of the above study must be submitted to the Agency on or before 11/15/2017. 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 study 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 study will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study. 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, 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 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 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, HFD-600, Metro Park North IV, 7519 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 LCDR Hamet Touré, PharmD MPH, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I, HFD-120
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/

ROBERT TEMPLE
03/08/2016