DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202992

WRITTEN REQUEST

Sanofi-aventis U.S. Inc.
Attention: Cynthia Psaras, Ph.D.
Director, Global Regulatory Affairs
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Psaras:

Reference is made to your August 8, 2012, Proposed Pediatric Study Request for Aubagio (teriflunomide).

Multiple sclerosis (MS) is an illness that affects approximately 2.5 million individuals worldwide. MS generally affects young adults, but it can present in infancy, childhood, and adolescence. Although the true incidence of pediatric MS is unknown, for those from birth through early childhood, the incidence is thought to be between 0.2-0.7% of new cases. Only 2-5% of patients diagnosed with MS present before age 18 and the majority 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 in pediatric MS evaluating the safety and efficacy of teriflunomide would provide much needed data about the risk/benefit of teriflunomide in pediatric patients. It is premature to fully extrapolate efficacy from the adult experience with teriflunomide 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. A placebo arm in this clinical trial is acceptable as presenting no more than a minor increase over minimal risk (21 CFR 50.53) to the enrolled children because a child who experiences a relapse of symptoms of MS will be removed from the trial and treated by the child's physician.

To obtain needed pediatric information on teriflunomide, 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:

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 two year, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of teriflunomide administered orally once daily in pediatric patients with relapsing forms of MS. This study must be designed to show superiority of teriflunomide over placebo control. Pharmacokinetic sampling must take place in each patient in an initial run-in phase of the study to determine dosing for the remainder of the study in a manner that protects the blind.

- *Objective of each study*

Study 1: To evaluate the efficacy and safety of teriflunomide administered orally once a day in pediatric patients age 10 to 17 years with relapsing forms of MS.

- *Patients to be studied*

Male and female patients age 10 to 17 year old. At least 20% of patients enrolled must be pre-pubertal. A minimum of 100 patients must be randomized to receive study drug. Pediatric patients must be approximately evenly distributed across ages. A sufficient number of both sexes of pediatric patients with at least 25% males must be enrolled.

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

- *Study endpoints*

Efficacy Endpoints:

- The primary efficacy endpoint must be the time to first clinical relapse after randomization.
- Secondary endpoints must include:
  - Number of new/newly enlarged T2 lesions on MRI.
  - Number of T1 Gd-enhancing lesions on MRI
  - Proportion of patients relapse-free.
- Measures of compliance must include tablet count at each visit.

Safety Endpoints:

- Safety monitoring must include adverse events, concomitant medications, ECG, vital signs, hematology, blood chemistry, urinalysis, usage of rapid

elimination procedure, growth parameters and development (Tanner stages), and serum pregnancy tests in all menarchal females.

- The following adverse events must be actively monitored: pancreatitis, peripheral neuropathy, infection, transaminase elevations, renal dysfunction, blood pressure elevation, and skin reactions such as toxic epidermal necrolysis or Stevens Johnson syndrome. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- A Data Monitoring Committee (DMC) must be included. Oversight of the study is needed, with ongoing review of hepatic dysfunction, infection, neutropenia, lymphopenia, reversible acute renal failure, hyperkalemia, elevated blood pressure, changes in pulmonary status, new skin rashes, 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*

  No safety issues are currently being tracked.

- *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 to the Written Request.

- *Drug information*

  - Dosage form: tablet
  - Route of administration: oral
  - Regimen: Starting dose for the run-in phase of the study is either 3.5 mg or 7 mg once daily based on body weight below and above 40 kg, respectively. The final dose for the remainder of the study will be determined based on the PK results from the run-in phase.
  - If the trough concentration of teriflunomide at 7 mg dose is confirmed to be within the adult trough concentration range, the dose will be increased individually to the equivalent of the 14 mg dose until the end of treatment.

  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 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 hazard ratio of 0.5 with a two-sided α of 0.05. Randomization should be stratified by patient's pubertal status.

- *Labeling that may result from the study*

  You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrate that teriflunomide 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. 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/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 studies must be submitted to the Agency on or before June 30, 2016. 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. 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
03/07/2013