IND 100593/BLA 761053

WRITTEN REQUEST – AMENDMENT 1

Genentech, Inc.
Attention: Isa Samuels
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Isa:[1]

Please refer to your correspondence dated April 3, 2023, requesting changes to FDA's April 11, 2022, Written Request for pediatric studies for Ocrevus (ocrelizumab).

We have reviewed your proposed changes and are amending the Written Request as follows. Note that we are also amending the Written Request due to evolution of the Agency's thinking regarding dose selection for the pediatric multiple sclerosis population, and to align studied weight categories across therapies approved for relapsing forms of multiple sclerosis. Other revisions were recommended by the Agency's Pediatric Review Committee to facilitate future potential Pediatric Exclusivity Board review and are not intended to change the nature of the Written Request. All other terms stated in our Written Request issued on April 11, 2022, remain the same. Edited text is shown in red (text added is underlined, text deleted is strikethrough).

BACKGROUND:

MS affects approximately 2.8 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 before 18 years of age, and that most of these cases occur in patients at least 10 years of age. For this reason, neonates and pediatric patients less than 10 years of age will not be studied. Gilenya (fingolimod) is the only approved therapy for patients less than 18 years of age with MS. Although other products approved for the treatment of MS in adults are used off-label in pediatric patients, there have been few controlled clinical studies evaluating the efficacy and safety of these products in pediatric MS patients. An adequate and well-controlled trial evaluating the safety and efficacy of ocrelizumab in pediatric MS would provide important data about the risks and benefits associated with the use of ocrelizumab in this population. It is premature to extrapolate efficacy from the adult experience with ocrelizumab to pediatric patients with MS because there are phenotypic differences between pediatric MS and adult MS, there are differences in immune responses between pediatric and adult patients, and evidence

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from clinical trials indicates that the safety and efficacy reported for therapies approved in adults to treat MS may be significantly different in pediatric patients with MS. After approval, as a highly effective oral treatment, fingolimod became the standard of care for pediatric MS leading to a reduced acceptability for placebo treatment in pediatric MS trials by many patients and institutional review boards. A non-inferiority trial design comparing ocrelizumab to fingolimod is an acceptable trial design for pediatric MS because all enrolled patients will receive active treatment, the standard of care treatment (fingolimod) is the comparator arm treatment option, and there is a reasonable prospect of benefit for pediatric patients randomized to treatment with ocrelizumab given its performance in treating adults with relapsing forms of MS.

Additionally, pediatric MS is rare, with an estimated 1500 individuals with pediatric MS in the United States, and the proposed non-inferiority trial with ocrelizumab has features intended to minimize the necessary enrollment.

To obtain needed pediatric information on ocrelizumab, 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(ies)*:

No additional nonclinical studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

Study 1: An open-label, parallel-group, dose-finding study to evaluate safety and tolerability, pharmacokinetics, and pharmacodynamic effects of ocrelizumab in children and adolescents with relapsing-remitting MS (RRMS) weighing 40 kg or less.

Study 2: A randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison with fingolimod in children and adolescents with RRMS.

- *Study Objectives:*

  - Study 1 Objectives: ~~Pediatric patients in this study must be allocated to receive 600 mg or 300 mg of ocrelizumab (for patients weighing 40 kg or greater, and for patients weighing 40 kg or less, respectively).~~ Safety and tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) (B-cell depletion) data ~~from the respective cohorts~~ must be assessed in order to select the appropriate dose for children and adolescents weighing 40 kg or less for Study 2.

- Study 2 Objectives:
  - Primary objective: To demonstrate the non-inferiority of ocrelizumab as compared to fingolimod on protocol-defined annualized relapse rates (ARR). The primary endpoint will be assessed in all RRMS patients.
  - Key secondary objective: To demonstrate the non-inferiority of ocrelizumab compared with fingolimod on the number of new or enlarging T2 hyperintense lesions (T2 lesions) as detected by brain magnetic resonance imaging (MRI) during the double-blind period.

- *Patients to be Studied:*
  - Age groups to be studied: For studies 1 and 2 – children and adolescents 10 to less than 18 years of age with RRMS ~~at screening~~.
  - Number of patients to be studied:
    - Study 1: The sample size ~~for each age/weight cohort (i.e., patients weighing 40 kg or greater, and patients weighing less than 40 kg)~~ must be adequate to characterize the PK and inform dose selection for Study 2.
    - Study 2: A minimum of 60 patients randomized to treatment with ocrelizumab must be enrolled.
  - Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportional to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*
  - Study 1: PK/PD endpoints – the timing of the PK sampling must be specified in the protocol. The protocol must also include a specific plan for collection of PK data in patients weighing 40 kg or less. The protocol must be agreed upon with the Agency before the study is initiated. PK endpoints must include AUC and C_{trough}, and PD endpoints must include B-cell depletion (extent and duration).
  - Study 2: Primary efficacy endpoint – the primary endpoint must be ARR.

- *Safety Endpoints/Monitoring:*

- For studies 1 and 2:
  - The protocol must include collection of the following safety information: adverse events, concomitant medications, vital signs, hematology, CD19+ B-lymphocytes, serum immunoglobulins, blood chemistry, urinalysis, growth parameters and development (Tanner stage), and serum pregnancy tests in all menarchal females.
  - The protocol must include a plan to actively monitor the following adverse events: infusion reactions, serious and opportunistic infections, and neutropenia.
  - The protocol must include plan for monitoring of all adverse events until symptom resolution, until the condition stabilizes, or until the laboratory abnormality resolves.
  - For each safety endpoint, the protocol must specify:
    - Definition of exposure time (time at risk)
    - Sample size requirements
    - Analysis considerations
  - A Data Monitoring Committee (DMC) must be included.
- Study 2: A minimum of 60 patients treated with ocrelizumab for at least 1 year must be enrolled for evaluation of safety.

- *Statistical information, including power of study(ies) and statistical assessments:*
  - Study 1:
    - Descriptive analysis will only be conducted.
  - Study 2:
    - The study must have a detailed statistical analysis plan (SAP) agreed-upon with the Agency before the unblinding of study data.
    - The study must be designed with adequate power to demonstrate that ocrelizumab is not substantially inferior to fingolimod, assuming a non-inferiority margin no greater than 3.
    - The SAP must include an agreed-upon prespecified decision rule for deciding whether the trial demonstrates the non-inferiority of ocrelizumab.

- The SAP must include the following elements and be agreed upon with the Agency:
  - For each primary efficacy endpoint and each key secondary efficacy endpoint the SAP must specify:
    - Sample size requirements
    - Analysis considerations

The following information pertains to all clinical studies in the Written Request.

- *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: injection*
  - *route of administration: intravenous*
  - *regimen: must be agreed upon in Study 2*

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  (3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for

preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *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 ocrelizumab 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 pediatric 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.[2] You are encouraged to contact the reviewing Division for further guidance. For studies started after December 17, 2017, study data must be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange

[2] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before ~~January 31, 2024~~November 30, 2025. 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.

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 April 11, 2022, as amended by this letter and must be submitted to the Agency on or before ~~January 31, 2024~~November 30, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a biologics license application (BLA) / supplement to an approved BLA 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);
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FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[3]

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 Kristen Haslam, Regulatory Health Project Manager, at (240) 402-4246.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD
Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

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

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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- *Study Objectives:*
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  - Age groups to be studied: For studies 1 and 2 – children and adolescents 10 to less than 18 years of age with RRMS.

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information: adverse events, concomitant medications, vital signs, hematology, CD19+ B-lymphocytes, serum immunoglobulins, blood chemistry, urinalysis, growth parameters and development (Tanner stage), and serum pregnancy tests in all menarchal females.

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- A Data Monitoring Committee (DMC) must be included.

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

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    - Descriptive analysis will only be conducted.

  - Study 2:

    - The study must have a detailed statistical analysis plan (SAP) agreed-upon with the Agency before the unblinding of study data.
    - The study must be designed with adequate power to demonstrate that ocrelizumab is not substantially inferior to fingolimod, assuming a non-inferiority margin no greater than 3.
    - The SAP must include an agreed-upon prespecified decision rule for deciding whether the trial demonstrates the non-inferiority of ocrelizumab.
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- For each primary efficacy endpoint and each key secondary efficacy endpoint the SAP must specify:
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The following information pertains to all clinical studies in the Written Request.

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- *Drug information:*

  - *dosage form: injection*
  - *route of administration: intravenous*
  - *regimen: must be agreed upon in Study 2*

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

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  (3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using

such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

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- *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.
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industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

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If you have any questions, please call Kristen Haslam, Regulatory Health Project Manager, at (240) 402-4246.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD
Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended (Clean Copy of the Amended WR Should Be Attached Here)

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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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/

PAUL R LEE
08/01/2023 05:56:24 PM